Exploring Mechanochemistry for Organic Synthesis

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This thesis is submitted for the degree of Doctor of Philosophy (PhD) at Cardiff University

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This thesis is dedicated to my grandad,

Robert Hilton Wake

(1926 - 2018)

who encouraged me from a young age to explore how the world works and inspired me to pursue chemistry.

Summary

This thesis describes an investigation into performing organic synthesis under mechanochemical conditions. Procedures were developed for the selective mono- and difluorination of 1,3-dicarbonyls and the one-pot, two-step synthesis of fluorinated pyrazolones under ball milling. Attempts to perform a two-step mechanochemical synthesis of difluoromethylthioethers led to exciting results demonstrating that ball milling can lead to alternative reactions occurring. Finally, some initial results into the generation and reaction of organomanganese reagents under mechanochemical conditions are reported.

Initial investigations into the use of mechanochemistry for organic synthesis focused on the mechanochemical formation of the C-F bond, with a particular focus on differences in selectivities observed under different milling conditions. It was found that electrophilic fluorination of 1,3-dicarbonyls could be achieved under ball milling conditions using Selectfluor. The selectivity of this process could be significantly enhanced using Liquid Assisted Grinding with acetonitrile as an additive. The possible causes of this observed change in selectivity were investigated.

Further work developing a one-pot, two-step mechanochemical process was performed. A procedure for the synthesis of fluorinated pyrazolones was developed and some of the key considerations when attempting one-pot mechanochemical procedures were established by a careful optimisation. Conditions compatible with both the heterocycle formation step and the fluorination step were found and a range of fluorinated pyrazolones successfully synthesised by this method.

It was observed that mechanochemistry could be used to alter the chemoselectivity of a reaction while attempting the synthesis of difluoromethylthioethers. After detailed study, a hypothesis to the origin of this alteration in selectivity was proposed. Finally, some initial results into the use of mechanochemical methods to activate manganese metal for applications in synthesis are presented.

Related publications

Some of the work presented in this thesis is also presented in the following papers:

[1] **Mechanochemistry as an emerging tool for molecular synthesis: what can it offer?**
J. L. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, **9**, 3080–3094.

[2] **Controlling reactivity through liquid assisted grinding: the curious case of mechanochemical fluorination**
J. L. Howard, Y. Sagatov, L. Repusseau, C. Schotten and D. L. Browne, *Green Chem.*, 2017, **19**, 2798–2802.

[3] **Mechanochemical electrophilic fluorination of liquid beta-ketoesters**
J. L. Howard, Y. Sagatov and D. L. Browne, *Tetrahedron*, 2018, **74**, 3118–3123.

[4] **One-pot multistep mechanochemical synthesis of fluorinated pyrazolones**
J. L. Howard, W. Nicholson, Y. Sagatov and D. L. Browne, *Beilstein J. Org. Chem.*, 2017, **13**, 1950–1956.

[5] **Switching chemoselectivity: Using mechanochemistry to alter reaction kinetics**
J. L. Howard, M. C. Brand and D. L. Browne, *Angew. Chem. Int. Ed.*, 2018, DOI: 10.1002/anie.201810141

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The other members of the DLB group also deserve a mention here, both as colleagues in the lab and friends in the pub. Christiane, you were my first friend in Cardiff and we toughed out PhD life together for just over three years. You helped and supported me when times were challenging and celebrated with me when hard work paid off, as well as keeping me on the straight and narrow with constant, unrelenting advice on how best to clean every single piece of lab equipment in the group. The next members to join the group also became friends and are (or are in the process of becoming) great chemists, so to Yerbol, Qun, Roddy, Tom, Will and Yin I would also like to say thank you. You have all helped me at various times, from talking through a difficult purification to finding glassware for me when I'm looking straight at it.

I would also like to thank members of other research groups in the department, who have also been supportive, so to the LCM, DB and TW groups: Thanks. In particular, I should mention James Ayres (for the ice cream), Alexandre Rossignon (for the beer) and Micol Santi, who have become close friends.

Several students have directly contributed to the work presented in this thesis and must also be thanked for their hard work and for putting up with me as their lab supervisor. In particular, Yerbol Sagatov (then MPhil student) contributed to the later stages of the work presented in chapter 2, with Laura Repusseau (Erasmus student) contributing to the very early investigations. William Nicholson (then an MChem student) performed the optimization experiments in chapter 3 and Michael Brand (MChem student) performed various experiments presented in chapter 4. Although their work is not presented in this thesis, I would also like to thank other students who worked hard with me. So thanks also to Robert Bowen, Emilie Wheatley and Tom McBride.

Finally, a huge thanks to my family and friends outside of Cardiff, especially to my parents, Clare and David Howard. I could not have achieved anything like this without your support.

Abbreviations

Ac	Acetate
Bn	Benzyl
Cp*	Pentamethylcyclopentadienyl
Cy	Cylohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DoE	Design of experiment
dppf	Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
ee	Enantiomeric excess
equiv.	Equivalents
GC	Gas chromatography
GC-MS	Gas chromatography - mass spectrometry
GP	General procedure
h	Hours
HRMS	High resolution mass spectrometry
IR	Infrared
LAG	Liquid assisted grinding
min	Minutes
mol%	Mole percent
mp	Melting point
N.D.	Not determined
NHC	N Heterocyclic carbene
NIS	N-Iodosuccinamide
NMP	N-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
PET	Positron emission tomography

RSM	Remaining starting material
RT	Room temperature
TBAB	Tetrabutylammonium bromide
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
Tf	Trifluoromethanesulfonate
THF	Tetrahydrofuran
wt%	Weight percent

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1 Mechanochemistry for organic synthesis

1.1 Chemical reactions and energy input

In order for any chemical reaction to occur, the system needs to absorb energy equal to or greater than the activation energy required for the transformation. When performing reactions for synthesis, this energy is most commonly delivered by controlled heating of the reaction mixture. Alongside heating, which was defined as thermochemistry, in 1890 Ostwald categorised chemical reactions by energy input as photochemistry, electrochemistry and mechanochemistry.[1] In more recent times, photochemistry[2-6] and electrochemistry[7-12] have been pursued significantly as techniques to improve synthetic methods. Mechanochemistry remains less utilised and studied for organic synthesis, despite recent progress establishing that fundamental organic transformations are possible under mechanochemical conditions.[13-21]

1.2 Mechanochemistry

A mechanochemical reaction is defined as "a chemical reaction that is induced by the direct absorption of mechanical energy". [22] Mechanochemistry therefore complements the conventional methods of energy input discussed above.

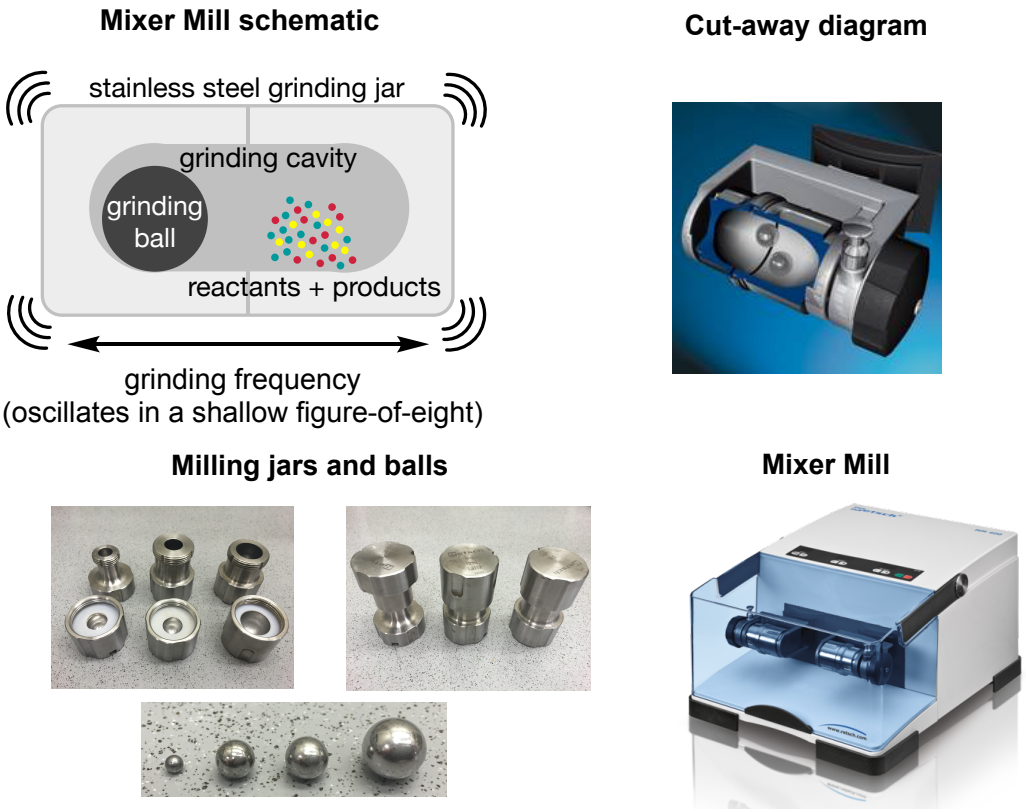
It is well known that chemical reactions initiated differently often lead to different products, and that altering the reaction environment in this way can be used to control the reaction pathway. For example, pericyclic reactions proceed differently depending on whether they are induced by light or heat. This is well understood and explained by the Woodward-Hoffman rules.[23, 24] However, products have been observed using ultrasound that do not obey these rules and it has been suggested that they should not be applied to mechanochemical pericyclic reactions.[25, 26] Mechanochemistry therefore presents an opportunity to explore a potentially novel space of chemical reactivity.

1.3 Equipment

The earliest mechanochemical reactions were carried out using a pestle and mortar.[27] However, how these reactions behave is highly operator dependent, as each individual may impart different levels of energy. Running reactions for longer than a few minutes also becomes challenging, and depends on the operator's stamina. Therefore, automatic milling devices are commonly used for mechanochemical reactions. These mills were initially developed as a reliable method for the production of fine powders

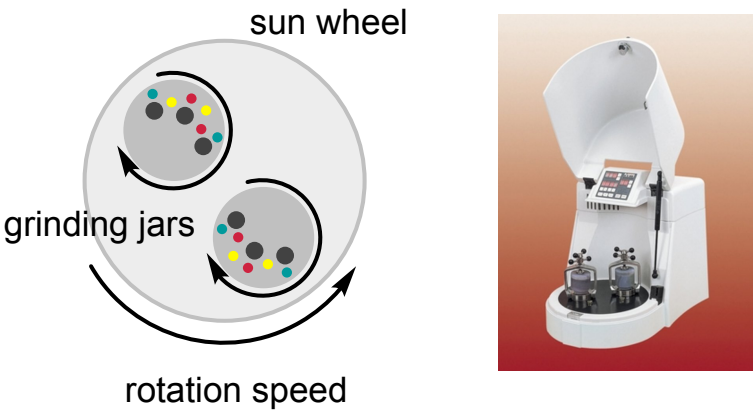
with a desired particle size.[28] However, they have subsequently been adopted for mechanochemical reactions.

The mixer mill is one type of ball milling machine, which uses the movement of ball bearings to apply mechanical force to the reagents. In this case, reagents are loaded into jars and one or more balls are added. The jars are then mounted horizontally and shaken at the desired frequency (Scheme 1.1). The main mechanical energy applied to the reagents is impact force.



Scheme 1.1 Operation of a mixer mill and examples of equipment available.

The other most common type of ball mill is a planetary mill. In this case, the reagents and ball(s) are loaded as before, but the motion is different. The jars are spun around a central axis analogous to planets orbiting around the sun. In both cases, the material and size of the jars and balls can be altered (Scheme 1.2). The main type of force applied is shear force.



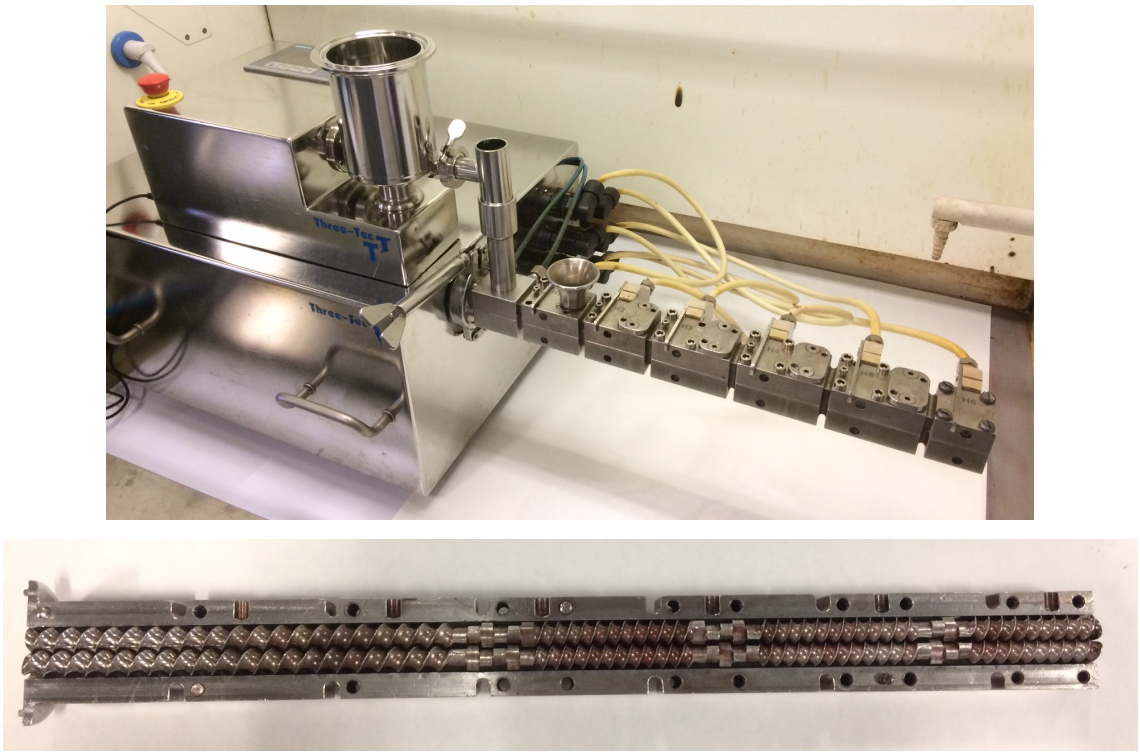
Scheme 1.2 Movement of a planetary mill and example of mill available.

Stirred media ball mills are also available, in which the reagents and balls are stirred together. This type of mill is commonly used to create very fine powders, such as of coal.[29, 30] However, it has found limited application in the lab for mechanochemistry.

1.4 Scale Up

If any synthetic procedure is to be useful to society (eg in drug discovery or manufacture) it must be achievable on different scales. For mechanochemistry, each type of milling device can achieve different scales. The mixer mill can achieve gram scales, which are suitable for lab investigations. However, for anything larger, other types of mill must be used, and different sizes of planetary mill are available. However, for pilot and manufacture scales, stirred media ball mills are used. For example, the Outotec HIGMill has a volume of 30000 litres and can be used at >1000 kg scales.[31]

Stolle et al. demonstrated the scalability of the mechanochemical Knoevenagel condensation between vanillin and barbituric acid, scaling up from 20 to 300 mmol scales, and state that it should be possible to achieve this reaction in a stirred media ball mill.[32]



Scheme 1.3 Top: A fully assembled twin-screw extruder. Bottom: Twin screws, showing conveying and kneading sections.

A different approach to scalability can be attempted if the process is modified from batch to continuous. This can be achieved by using extruders instead of mills. Extruders continuously force material through confined spaces and apply shear and compression forces (Scheme 1.3). They are commonly used in the pharmaceutical industry for drug formulation. The twin-screw extruder moves material along the barrel by turning two screws. It can be fitted with different sections, such as kneading or reverse sections. In the typical setup, a combination of screw sections (used to convey material) and kneading sections (used to compress the material) is employed. James and co-workers synthesised MOFs at rates of kilograms per hour making use of twin-screw extruders.[33]

1.5 Variables affecting reactions

As when performing any reaction, understanding and controlling the variables is important, but when using a ball mill it can be challenging to control or even measure the variables individually. There are three main variables that effect how mechanical energy is transferred to the reagents: the kinetic energy of the ball(s) prior to collision, how that energy is transferred to reagents and the frequency of collisions. If these

variables could be controlled individually and independently of each other, their effects on a reaction could be more easily understood.

The amount of kinetic energy that the ball(s) possess prior to collision is the maximum amount of energy that can be transferred to the reagents per collision. The kinetic energy the ball(s) can achieve prior to collision depends on their mass and velocity. Their mass can be controlled, but the velocity they possess just before a collision depends on their exact trajectory within the jar and therefore depends on several parameters. These include filling degree and size of the jar, the mass and number of the ball(s) and the frequency of the milling.

In a collision, how that energy is transferred can have an effect on whether a reaction occurs. This can be by direct impact, under which the material is locally compressed, or by shear force. It has been shown that these different types of energy absorption can lead to different outcomes.[34] Different types of ball mill achieve different ratios of impact and shear forces. How much energy is absorbed in a collision also depends how much is lost by physical deformation of the materials. This therefore also depends on the texture of the reaction mixture, including its Young's modulus.

The number of collisions per second is also an important variable. Clearly, the higher the number of collisions, the more energy can be transferred and therefore the faster the reaction. This depends on the frequency of the mill, the size and number of balls and the filling degree of the jar.

Differences in mixing, or mass transfer, can affect the outcome of any reaction. In solution, this is easily controlled by stirring, so provided all reagents are dissolved, mass transfer is rarely a problem and will be comparable for different mixtures. However, in milled reactions, this can be a difficult variable to characterise or control and can have a dramatic effect on the outcome of a reaction. It depends on almost every variable that can be controlled, and some that cannot (number and size of balls, jar filling degree and volume of jar, volume of reagents, type of mill, frequency of milling and texture of reagents to name a few).

Finally, variables that are usually changed in any reaction also apply, such as stoichiometry, reaction time and temperature. Temperature is not easily controlled, as the reaction vessel heats up due to the collisions, although the cryomill has been developed, which can apply external cooling.[35] Also, if the vessel heats up significantly,

it can be debatable whether the reaction is occurring mechanochemically or due to heat.

Of these variables that can affect how a reaction performs, few of them can be independently changed or controlled. However, there are a number of variables that can be controlled, which have multiple influences on the variables affecting reactivity.

1.6 Directly controllable variables

One of the first variables to be decided is what type of ball mill is to be used. As discussed previously, there are three main types: the mixer mill, the planetary mill and the stirred media mill. This decision may be based on the scale of the reaction, but otherwise the key differences are all related to the trajectory of the balls within the milling vessel. This leads to differences in the ratio of impact:shear forces, as well as the kinetic energy of the ball(s) and mixing. There have been relatively few studies comparing different ball mills, although different results have been observed using different mills.[36-39] Choosing which mill to use may depend on the scale of the proposed reaction, with planetary mills capable of handling larger scales than mixer mills. However, if any mill can be used, it is not easy to predict which will lead to the best outcomes, so early experiments in the optimisation of a process could be a comparison of different mills.

The next consideration is usually given to the filling degree. This is a measure of how full the jars are, considering the volumes occupied by the reagents and balls compared to the total volume of the jars. This has a significant effect on the trajectories of the balls, and therefore the energy transfer and mixing. The effect of the milling ball filling degree has been investigated for the Knoevenagel condensation of vanillin with barbituric acid in a planetary mill by changing the number of balls in the milling vessel.[32] When this parameter is low, the jar has a small number of balls, so the mixing and kinetic energy is low. When this parameter is high, the balls inhibit each other's motion, and they are not able to move freely, so their velocities (and therefore kinetic energy) will be limited. There is therefore an optimal value, which is a compromise between those two extremes.

The size of grinding balls can be controlled. This is usually decided based on the volume of the milling jar, with the most appropriate size being chosen. In general,

larger balls may not lead to good mixing and smaller balls can improve the mixing. This is because if the diameter of a ball is large and close to the diameter of the jar, the reagents cannot easily pass the ball and mix effectively. The mass of the grinding balls can also be controlled. The larger the mass, the more kinetic energy the balls can possess before a collision, so the larger the energy transferred each collision. As a larger ball will have a larger mass, this implies that when choosing the size of ball there is a compromise between best mixing and highest energy input. However, the material of the balls can also be controlled, and therefore balls of different density can be used, allowing the mass to be changed without changing the size.

The material of the grinding balls and jars is therefore important. Density has been discussed, but it is also important to consider other properties. Young's Modulus is an important parameter and is the ratio of stress to strain, and is a measure of to what extent a material deforms under pressure. It is therefore related to how much energy is absorbed on application of force. In a mechanochemical reaction, it is desirable to transfer as much energy as possible to the reagents. Therefore, using grinding balls and jars that will not absorb much energy (have a high Young's Modulus) is desirable. The other main consideration when deciding on a grinding material is chemical compatibility. Not only can this lead to deterioration of the grinding balls and jars, which would need to be replaced more frequently, but it can also affect the outcome of a reaction. However, the material of the balls can be chosen deliberately to cause chemical reactivity, and there are examples of catalysts being replaced by milling materials.[40]

The number of balls used can also influence mechanochemical reactions.[41] In general, by increasing the number of balls, the mixing can be improved and the frequency of collision can be increased. However, unless the material is changed, increasing the number of balls usually means decreasing their individual size and mass. This can lead to a decrease in their kinetic energy.

Probably the variables that are easiest to control are also the most easily understood. The milling frequency can be changed simply by adjusting the settings on the mill. When increased, this increases the velocities of the balls, and so increases their kinetic energy. This is a facile way to change the energy input into a reaction. Finally, variables that apply to any chemical reaction can also be easily controlled, such as stoichiometry and reaction time.

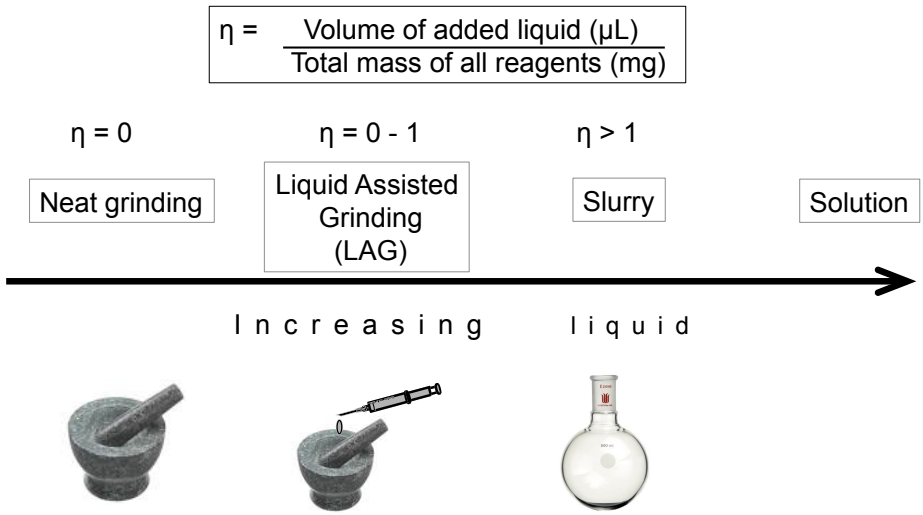
1.7 Grinding auxiliaries

The texture of the reaction mixture can also be important in how a mechanochemical reaction proceeds. This depends largely on the physical state of reagents and products. For example, liquids do not absorb mechanical energy efficiently as during an impact, they can freely move away from the position of impact.

To overcome these issues, a grinding auxiliary can be added to the reaction mixture. This is usually a solid that is inert to the reaction being performed and is often silica, sand, alumina or an inorganic salt, such as sodium chloride.[42-44] The liquid materials can then be adsorbed onto the surface of such solids, which can restrict the motion of the liquid and decrease its ability to move away from the position of an impact. The addition of a grinding auxiliary can therefore improve the energy transfer to liquid reagents. A reaction mixture composed of liquids and solids can also become a gum or paste, which can prevent efficient mixing. Under these circumstances, the mixing can also be overcome by use of a grinding auxiliary. This method is used in the formulation of pharmaceuticals in order to aid the passage of material through an extruder, where such additives are termed glidants or lubricants.[45] In practice, choosing which grinding auxiliary to add in order to improve mixing and energy transfer is often not straightforward and can be a trial and error process. In certain circumstances, some solid additives can also interfere with organic reactions. For example, silica is slightly acidic and can lead to degradation.

1.8 Liquid Assisted Grinding

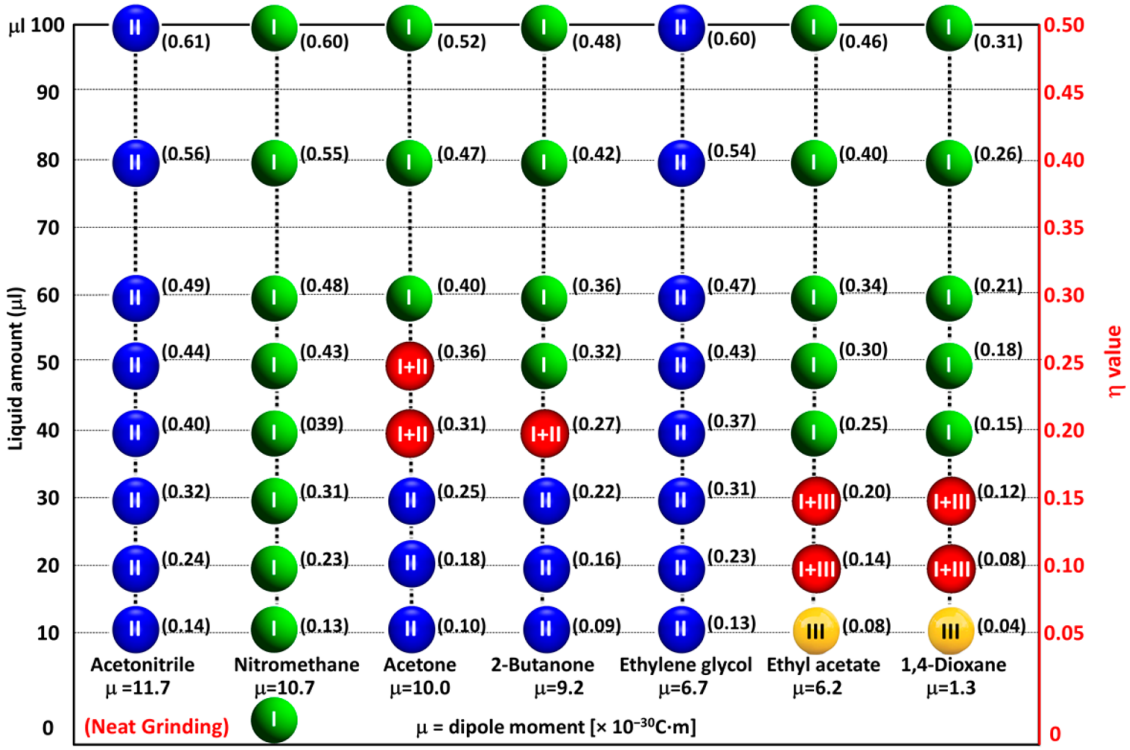
The mechanochemical reaction environment can be modified further by the addition of a small amount of liquid. This is termed “Liquid Assisted Grinding” (LAG). The amount of liquid has been characterised as a ratio compared to the mass of reagents by the parameter η.[46] This ratio can vary from grinding neat reagents together with no liquid, through to LAG, slurry reactions and eventually to solution reactions with increasing amounts of liquid (Scheme 1.4).



Scheme 1.4 Different reaction environments with different amounts of added liquid.

Liquid assisted grinding was originally used in mechanochemical cocrystallisation and it was found to speed up the cocrystallisation.[47] It has also been demonstrated that this reaction environment can lead to different results to slurry reactions and that the outcomes do not necessarily depend on the solubility of the starting materials in the liquid used.[46]

More recently, it has been shown that using different amounts and polarities of liquid can lead to the formation of different polymorphs under mechanochemical conditions, dispelling the commonly held belief that polymorphism depends on the solvent (Scheme 1.5).[48] This scheme depicts the polymorphic outcome of milling caffeine and anthranilic acid under different LAG conditions. This mixture forms cocrystals, in one of three different polymorphs. For example, it can be seen that on milling with any quantity of acetonitrile, polymorph II is formed and on milling with nitromethane, polymorph I is obtained. However, when milling with ethyl acetate, the polymorphic outcome observed depends on the quantity of added liquid. Overall, it was found that different polymorphs of a cocrystal were obtained depending on both the quantity and identity of which liquid was added.



Scheme 1.5 Polymorphic outcomes of cocrystal formation of caffeine and anthranilic acid (different polymorphs I, II and III). Grinding with different quantities and types of liquid additive leads to the formation of different polymorphs.[i]

The use of LAG could therefore speed up a reaction, or lead to different outcomes when compared with neat grinding or the reaction in solution. However, it is also possible to achieve different results by modifying the LAG conditions used, such as the polarity of the added liquid or the quantity of added liquid.

It is therefore another reaction environment worth exploring when applying mechanochemistry to organic synthesis.[49] However, although many studies to date use LAG, the role of the liquid remains unclear and is perhaps different in each case.

1.9 Reaction optimisation

Having discussed the variables that can be controlled, we see that each one of these has multiple influences on the reaction (Table 1.1). This can make reaction optimisation a daunting task. However, considering the number of mechanochemical transformations now known demonstrates that this challenge is not insurmountable.

[i] Scheme reproduced from ref. 48 with permission from the ACS. Further permissions for reproduction of this scheme should be directed to the ACS. Direct link to source: https://pubs.acs.org/doi/10.1021/acs.cgd.6b00682.

Variables affecting reactions	*Depends on…*	Directly controllable variables
• Kinetic energy of ball(s) prior to collision	• Number of balls • Size of balls • Ball material	• Size of jar • Filling Degree • Type of Mill • Milling frequency
• Mixing	• Number of balls • Size of balls • Size of jar • Filling Degree	• Type of Mill • LAG • grinding auxiliary • Milling frequency
• How Energy is transferred to reagents.	• Number of balls • Size of balls • Size of jar • Filling Degree	• Type of Mill • LAG • grinding auxiliary
• Frequency of collisions.	• Milling frequency	• Number of balls
• Stoichiometry	• Stoichiometry	
• Reaction time	• Milling time	

Table 1.1 Summary of variables affecting a mechanochemical reaction.

The most important factors investigated when optimising these reactions seem to be the choice of reagents, stoichiometries and reaction times.[16] However, once a reaction is found to proceed mechanochemically, the complex interdependence of the controllable variables often prevents further logical probing of conditions. It may be possible to attempt a full understanding of this interdependence, however this could be different for each individual case and would be challenging. Instead, it is simpler to investigate the effects of each variable and observe trends. This can lead to more optimal conditions via a “trial and error” method. A more sophisticated approach would be to use statistical methods, such as design of experiment (DoE), to probe the effect of the controllable variables and predict optimal conditions. Such approaches are frequently used with success in industrial processes.[50]

1.10 Reactions well-suited to mechanochemistry

As so many of the mechanisms operating mechanochemically remain elusive, it can be difficult to decide when to use mechanochemistry. Certainly, many of the examples that

exhibit different reactivity, are unlikely to have been predicted. However, there are a few cases where definite advantages over solution-based reactions can be expected.

Perhaps the most obvious advantage is that reactions can be performed under solvent-free conditions. This leads to several cases where it is worth attempting mechanochemical reactions. Firstly, reactions between solids that are not soluble (or not all components are soluble in the same solvent) are well suited to mechanochemistry. This class of reactions can otherwise be very challenging, or even impossible. Reactions in which the solvent can interfere are also interesting candidates for mechanochemical investigations. For example, many catalysts and reagents can be very sensitive towards water, or solvents with Lewis basic sites. Indeed, great lengths are often taken, with expense, to dry solvents. However, in the mill the solvent is not required. Finally, reactions that require hazardous solvents can be made safer by using solvent-free conditions, such as mechanochemistry.

1.11 Mechanochemical Organic Synthesis

Mechanochemistry is often chosen as a technique because it does not require solvents. Reactions between neat reagents in a solvent-free process have several advantages. They often occur faster, due to the higher concentration of reagents, and can make handling easier and the overall process more efficient.[51, 52] One of the most common reasons solvent-free methods are often chosen is because decreasing the use of solvents leads to “greener” processes.

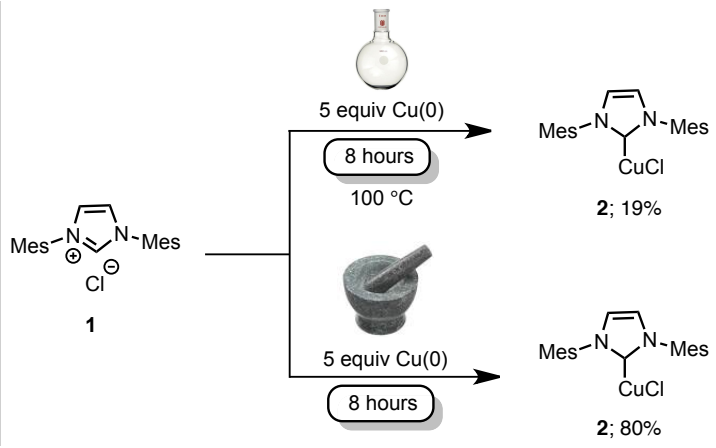
Although developing a solvent-free reaction is desirable, solvents used in other parts of the overall process are frequently not considered, despite the fact that the largest quantity of solvent is typically used during purification. Among the most common methods used for purification are chromatography, crystallisation, washing and filtering. All of these methods require the use of significant quantities of solvents.

Apart from enabling solvent free reactions, mechanochemistry can be used to improve known reactions and potentially to discover novel transformations. As discussed above, mechanochemistry has been used to access cocrystals and polymorphs different from those formed in solution, with LAG able to further modify the conditions to afford alternative polymorphs. As this has been established for non-covalent intermolecular processes, it can be envisaged that for covalent bond forming reactions, different reaction outcomes to those obtained in solution can be expected. It is these

possibilities that could lead to significant improvements over solution-based reactions. Some recent examples of mechanochemical reactions demonstrating interesting differences compared to the same reactions in solution are presented below.

1.12 Time Saving

One way in which mechanochemistry offers apparent advantages over solution based reactions is a reduction in reaction time. This could be due to a large increase in concentration. Several examples comparing reactions under mechanochemical conditions and in solution are described in this section, with a time saving achieved by using mechanochemistry.

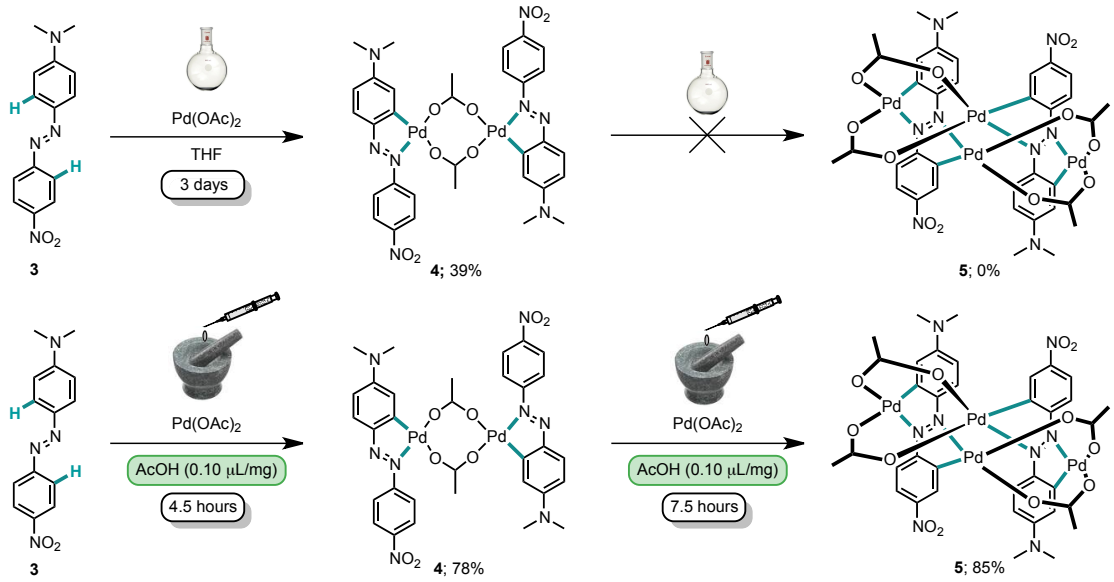


Scheme 1.6 Formation of Cu-NHC complexes.

An example of an inorganic reaction with increased reactivity is the synthesis of Cu-NHC complexes (NHC = N-heterocyclic carbene). These are used widely as organometallic catalysts for a variety of reactions and various methods have been developed for the synthesis of Cu-NHC complexes.[53] Under solvent-based conditions, Cu-NHC complexes can be synthesised by the reaction of metallic Cu(0) with imidazolium salts, although these reactions require a large excess of insoluble Cu(0) and long reaction times.[54] Recently, Lamaty and co-workers reported that Cu-NHC complexes (**2**) could be synthesised from imidazolium salts (**1**) and metallic copper using a planetary ball mill (Scheme 1.6).[55] The rate of reactions was enhanced due to the highly concentrated reagents and the highly efficient mixing under mechanochemical conditions. Using this novel method, five Cu-NHC complexes with different counter ions (Cl^-, BF_4^-, and PF_6^-) were successfully synthesised in improved yields compared to the analogous reactions in solution.

One of the most powerful tools for chemical synthesis is the selective functionalization of C-H bonds. Such methods allow the formation of C-C bonds without prefunctionalisation of the starting materials.[56] There are already several known methods for C-H activation and functionalisation using mechanochemical conditions, some of which provide a time saving against the analogous reactions in solution.[57]

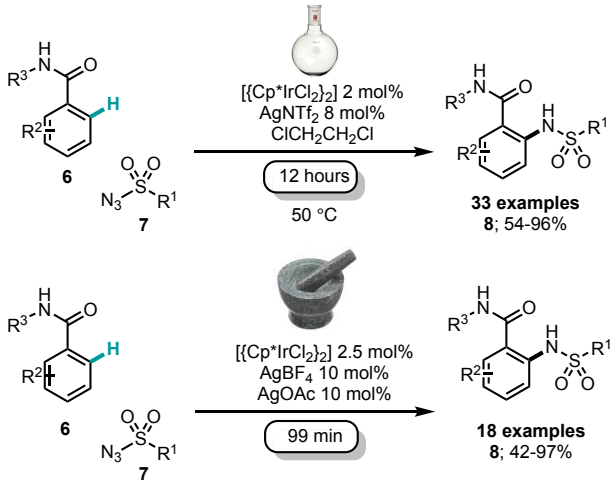
In 2014, Ćurić and co-workers achieved the first mechanochemical transition-metal-mediated C-H bond activation and monitored the transformation with in-situ solid-state Raman spectroscopy.[58] Using liquid-assisted grinding (LAG) with acetic acid, palladacycle **4** was synthesised from asymmetrically substituted azobenzene **3** and $Pd(OAc)_2$ in 78% yield after 4.5 hours (Scheme 1.7). When performed in solution, this reaction required 3 days and a significantly poorer yield was achieved. Further milling of **4** with $Pd(OAc)_2$ yielded dicyclopalladated complex **5**, which was not observed after multiple attempts at the same transformation in solution. In addition to saving time, this example demonstrates that using mechanochemistry can offer novel reaction pathways for the synthesis of organometallic compounds that could not be obtained using other methods.



Scheme 1.7 Palladacycle synthesis.

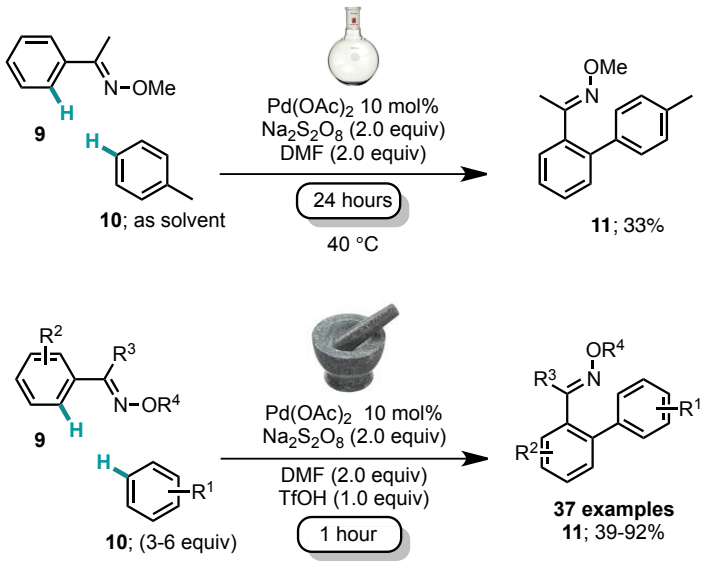
In 2016, Bolm and co-workers developed a mechanochemical Iridium(III)-catalyzed C-H bond amidation of benzamides **6** with sulfonyl azides **7** (Scheme 1.8).[59] In this study, it was demonstrated that the active cationic Ir(III) catalyst could be formed *in situ* in the mixer mill by reaction of $[\{Cp^*IrCl_2\}_2]$ with $AgNTf_2$. The corresponding amidated products could be obtained in high yields with shorter reaction times (99 min) than

those under a solvent-based protocol (12 hours) as reported by Chang and co-workers.[60]



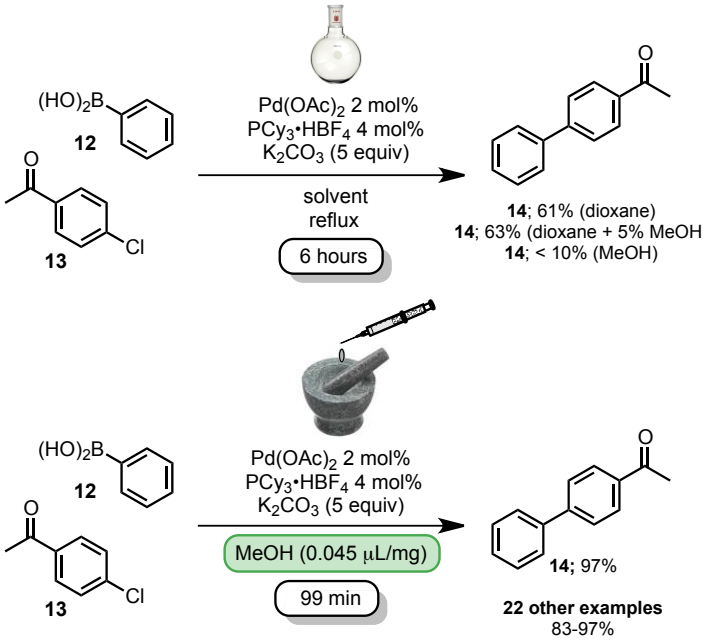
Scheme 1.8 Iridium catalysed amidation of benzamides with sulfonyl azides.

Oxidative C-H/C-H coupling has the potential to become a very powerful tool for sustainable chemical synthesis, as no starting material prefunctionalization is required for either coupling partner.[61] Ball-milling has also been used for dehydro-C-C coupling reactions with an illustrative example having been developed by Xu and co-workers.[62] Under mechanochemical conditions, biaryl products **11** could be obtained in both high selectivity and yield within a one hour reaction time. Specifically, electron-deficient oximes **9** were treated with a variety of arenes **10** in the presence of a palladium catalyst and oxidant (Scheme 1.9). The comparable reaction in solution, after stirring for 24 hours using toluene as both a solvent and reagent, achieved a poorer yield than any mechanochemical results. Similar solution based methods by Yu,[63a] Dong,[63b] and You[63c] also usually require more than 16 hours for the reaction to be complete. By employing ball milling, only 3-6 equiv. of simple arenes were required. It is also worth noting that electron-deficient arenes such as acetophenone and fluorobenzene were found reactive using this method, which were less studied in other C-H/C-H reports.[63]



Scheme 1.9 Palladium catalysed oxidative C-H / C-H coupling.

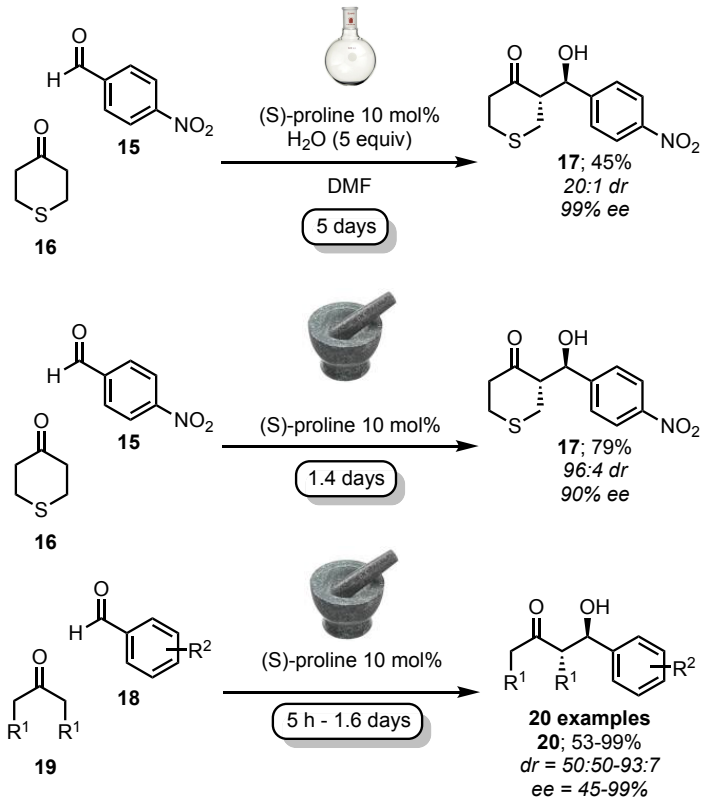
In 2016, Su and co-workers developed a LAG accelerated, palladium catalysed Suzuki-Miyaura coupling of aryl chlorides **13** with boronic acids **12** under ball-milling conditions (Scheme 1.10).[64] Compared to the solvent-based reaction, higher yields in shorter reaction times could be achieved. Adding solvents, which are commonly used in Suzuki-Miyaura reactions (THF, dioxane, DMF or MeCN), as LAG agents, did not lead to improved results.[65] However, protic solvents such as alcohols/H_2O led to improved reactivity. It was proposed that under these conditions alcohols form alkoxides *in situ*, which could participate in ligand exchange and boronic acid activation. This may explain the improved reactivity observed using LAG. In addition, it was also shown that much lower catalyst loading, 0.5 mol% Pd with 2.5 equiv K_2CO_3, could be used when the reaction was scaled up to gram scale.



Scheme 1.10 Suzuki reaction of aryl chlorides with boronic acids.

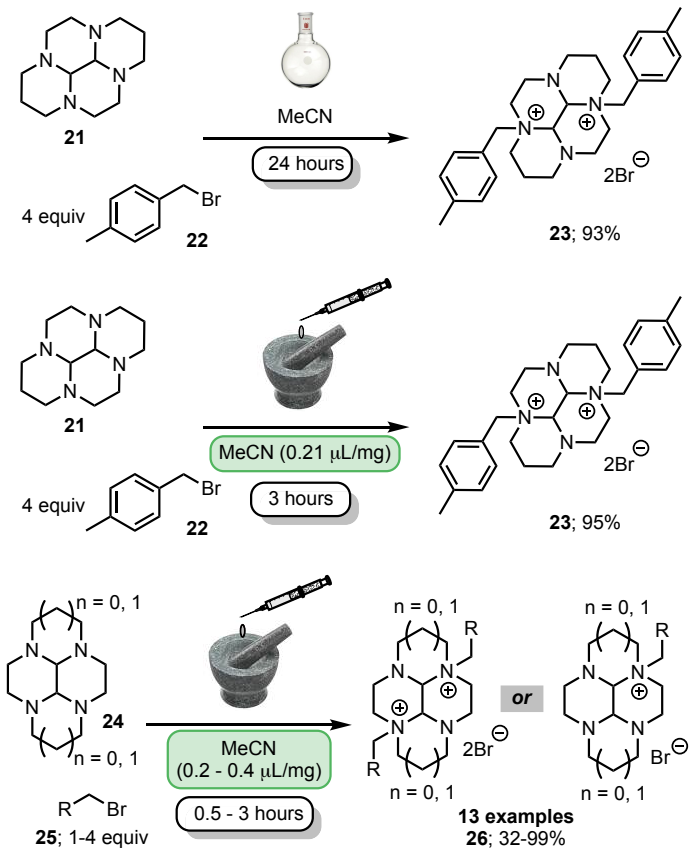
The use of organocatalysts negates the need for a metal catalyst, which can lead to greener synthetic processes.[66] However, there are still limitations such as high catalyst loadings (often 10-20 mol%), limited solvent choice (chlorinated solvents are commonly used), catalyst recovery and long reaction times, which restricts the industrial applications of organocatalysis. In the last decade, ball-milling has been used to improve the performance of organocatalysts under solvent free/LAG conditions, particularly in the area of secondary amine organocatalysis.

Pioneering investigations of mechanochemical (S)-proline-catalyzed asymmetric aldol reactions were carried out by Bolm and co-workers, affording *anti*-aldol products in high yield and with up to 99% ee (Scheme 1.11).[67] When comparing the reaction of 4-nitrobenzaldehyde **15** with tetrahydrothiopyran-4-one **16** to analogous solution reactions, a higher yield was achieved with shorter reaction time and similar ee.[68] Following this pioneering work, several other reports on secondary amine mechanochemical organocatalysis were published, reporting similar improvements in comparison to solution based reactions.[69]



Scheme 1.11 Proline catalysed enantioselective aldol reaction under milling.

Metal complexes containing macrocyclic polyamine ligands have a range of applications such as medical imaging agents, protein binding agents, antimalarial drugs and catalysis.[70] In 2016, Archibald and co-workers developed a novel method for N-alkylation of glyoxal-bridged bisaminal derivatives of cyclam (1,4,8,11-tetraazacyclotetradecane) **21** and cyclen (1,4,7,10-tetraazacyclododecane) **22** under mechanochemical LAG conditions (Scheme 1.12).[71] Most of the monofunctionalized quaternary ammonium salts could be formed in good to excellent yields by using stoichiometric amounts of alkyl bromides within 30 minutes. Yields of bis-N-alkylated products could be increased by increasing the relative quantity of bromide reagent or the reaction time. Compared to conventional solution methods, using mechanochemistry resulted in a five-fold reduction in the reaction time. It was further suggested that CB-TE2A, widely used to form stable ^{64}Cu complexes for PET imaging in vivo, could be synthesised within five days using this method. This approach offers a much faster synthetic route compare to the conventional six-step process, which takes 35 days developed by Weisman and co-workers.[72]



Scheme 1.12 Alkylation of polyamines has a shorter reaction time under milling.

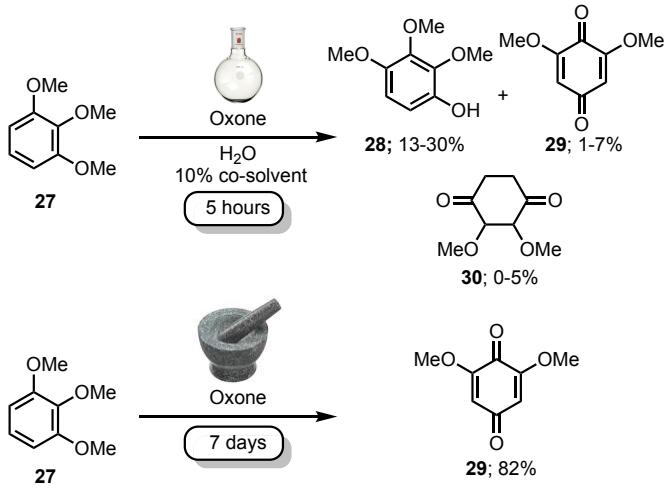
The examples described above demonstrate that mechanochemical conditions can, in several instances, lead to greatly reduced reaction times compared to the comparable reaction in solution. In some instances this is coupled with an increase in yield. This is an interesting general observation to note, and could be due to running reactions between neat reagents, increased energy input or a contribution from both. Regardless of the explanation, the experimental observation holds true that the use of mechanochemistry can reduce reaction times.

1.13 Altering selectivity

As well as reducing reaction times, mechanochemistry has been used to alter or control the selectivity of reaction outcomes. This section describes a few examples of reactions exhibiting a change in selectivity compared to reactions performed in solution.

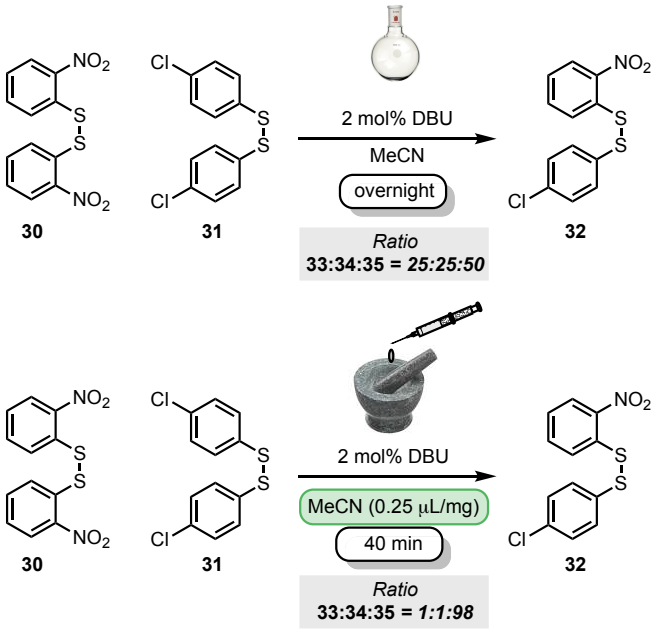
Plant biomass is a potential feedstock for the production of fuels and chemicals.[73] The degradation of lignin is one such method to convert the feedstock into commodity

chemicals. Mechanochemistry could have the potential to be used in industry for the degradation of lignin, cellulose and chitin.[74] In 2013, Anastas, Crabtree, Hazari and co-workers reported the mechanochemical oxidation of lignin-like methoxylated aromatic substrates **27** (Scheme 1.13) using Oxone (potassium peroxymonosulfate) as the oxidant.[75] When this reaction was carried out in aqueous solution, the major product was 2,3,4-trimethoxyphenol **28**, with several other side-products observed. In contrast, under mechanochemical conditions, quinone **29** was the only product formed. Making use of a rock tumbler/polisher, seven days were required for this transformation.



Scheme 1.13 Oxidation of trimethoxybenzene in solution and mechanochemically.

In 2010, Friščić and co-workers demonstrated that a thermodynamic equilibrium could be obtained under mechanochemical conditions. Using the base catalysed metathesis of aromatic disulfides as a model reaction (Scheme 1.14), it was shown that there was a significant difference in the position of equilibrium under mechanochemical and solution-based conditions. [76] In dilute acetonitrile solution, reactions afforded a ratio of 1:1:2 between homodimers (**30** and **31**) and heterodimer **32**. However, both LAG (with MeCN) or neat grinding led to almost complete conversion of homodimers, and afforded almost 98% heterodimer **32**. These different equilibrium compositions could be explained by crystal packing effects, which do not exist in solution, but are a factor for consideration under mechanochemical conditions.



Scheme 1.14 Disulfide metathesis in solution and mechanochemically.

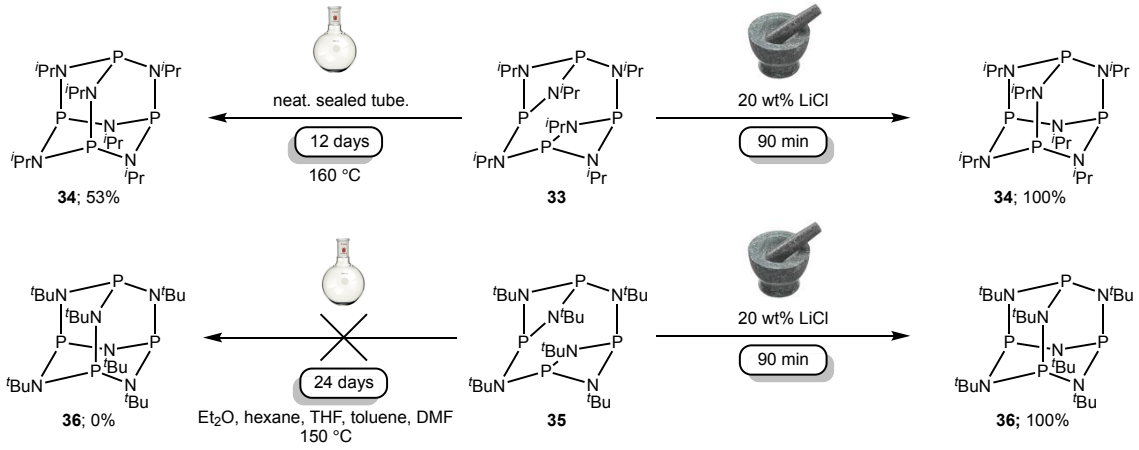
The examples shown above demonstrate that by switching from solution to mechanochemical conditions can alter the selectivity of reactions. The origins of the different selectivities observed experimentally are often not clear. However, altering or improving the selectivity of a transformation is frequently desirable for organic synthesis.

1.14 Alternative reactivity

Perhaps the most interesting observation arising from running reactions under mechanochemical conditions is that different products can be achieved. This suggests that the kinetics and thermodynamics of some reactions can be significantly altered by using a mill.

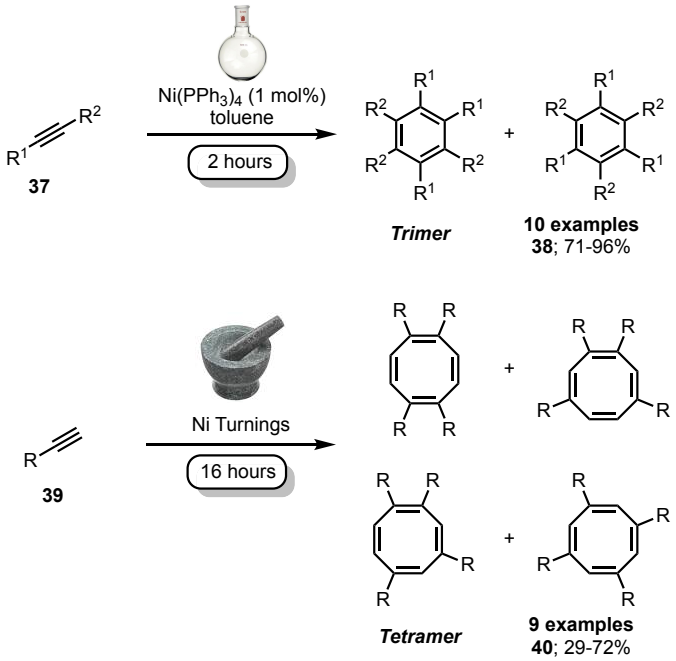
In 2016, García and co-workers developed the first example of using mechanochemistry for the synthesis of adamantoid substituted cyclophosphazenes (Scheme 1.15).[77] As strong non-carbon covalent backbones, phosphazanes (P-N) are interesting compounds, as they are used as multi-dentate ligands[78], catalysts[79] and antitumor drugs[80]. It was reported that subjecting the isopropyl-substituted macrocycle $[\{P(\mu\text{-}N^{i}Pr)_2\}_2(\mu\text{-}N^{i}Pr)]_2$ **33** to mechanochemical milling caused rearrangement to its adamantoid isomer $P_4(N^{i}Pr)_6$ **34** in 90 minutes.[77] However, the same rearrangement under high temperature (160 °C) conditions required 12 days (Scheme 1.15).[81] The

analogous *tert*-butyl-substituted macrocycle [{P(μ-N^{t}Bu)$_2$}$_2$(μ-N^{t}Bu)]$_2$ **35** could not be converted to its adamantoid isomer P$_4$(N^{t}Bu)$_6$ **36** using solution methods (reflux in DMF, THF, toluene etc.) or prolonged heating.[82] However, this compound was synthesised for the first time under mechanochemical conditions. Both adamantoid P$_4$(N^{i}Pr)$_6$ **34** and P$_4$(N^{t}Bu)$_6$ **36** could be synthesised in the mixer mill within 90 minutes in the presence of LiCl (20 wt%).



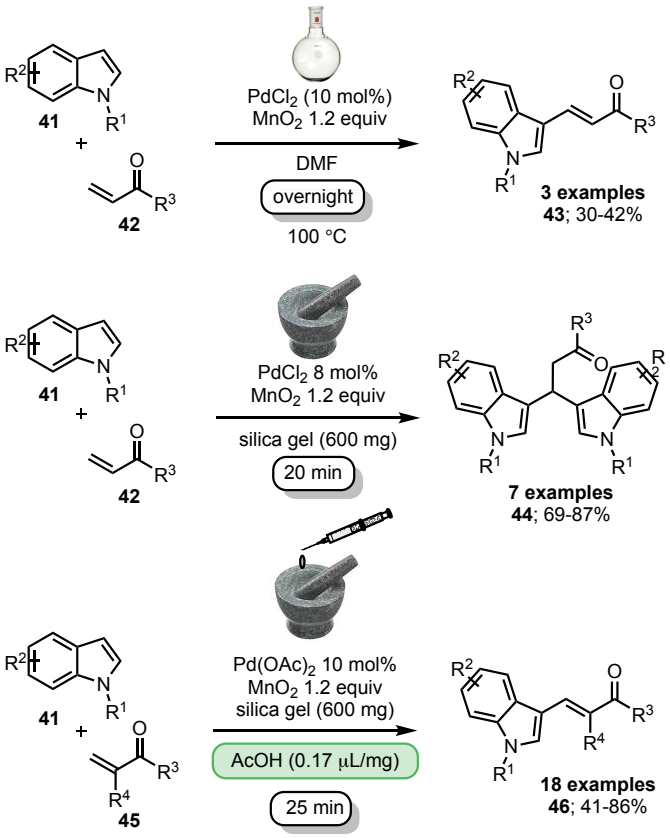
Scheme 1.15 Synthesis of adamantoid cyclophosphazanes.

It has been shown by Guan, Mack and co-workers that using a copper vial or balls instead of conventional ball mill materials, or adding silver foil enables elemental Cu (0) and Ag(0) to be used as active recyclable catalysts under ball milling conditions.[83] In 2016, they developed a method for the cyclotetramerisation of alkynes to afford cyclooctatetraenes (COT) **40** using recyclable Ni(0) pellets as the catalyst under ball milling conditions (Scheme 1.16).[84] Conversely, reactions performed in solution, catalyzed by Ni(0) complexes, yielded the major products as aromatic trimers **38**.[85] This proof-of-principle study demonstrates the potential of using Ni(0) pellets as active catalyst under mechanochemical conditions, which avoids the use of air-sensitive nickel complexes. It also demonstrates that mechanochemistry can achieve different reaction products compared to conventional solution methods.



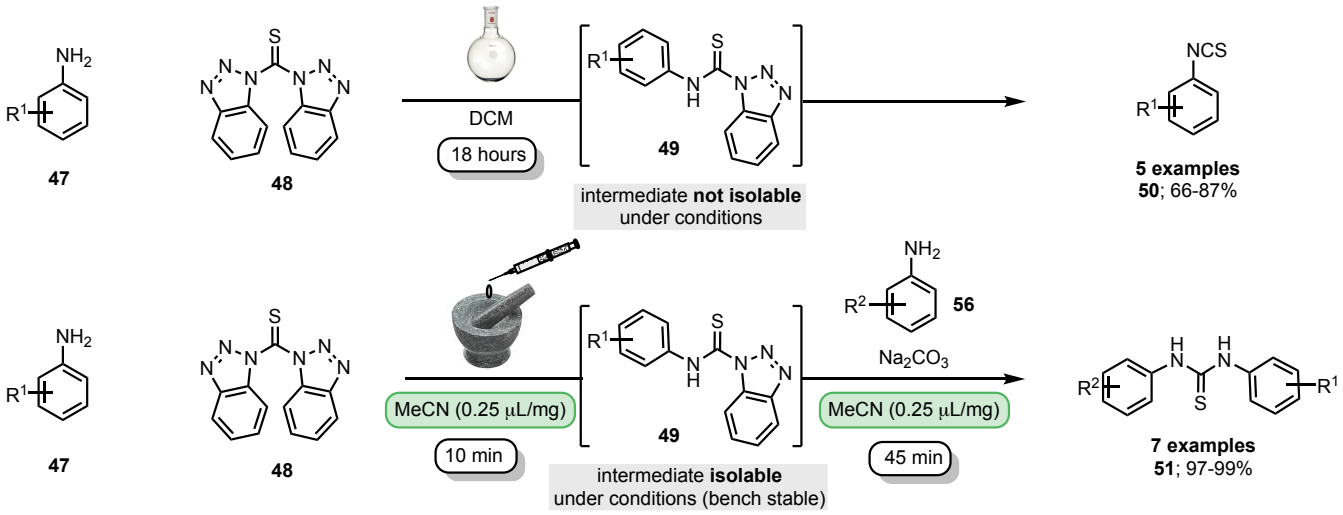
Scheme 1.16 Nickel catalysed cyclotri-/tetra-merisation of alkynes

Su and coworkers reported that 3-vinylindoles **43** and diindolyl propionates **44** could be synthesised by Pd(II) catalyzed oxidative coupling reactions between indoles and acrylates with MnO_2 as oxidant under ball milling conditions (Scheme 1.17).[86] It was found that the selectivity of the reaction is influenced by the Pd(II) source. When $Pd(OAc)_2$ was used with acetic acid as additive, high yields of 3-vinylindoles **43** were obtained. However, when using $PdCl_2$ as a catalyst without a liquid additive, diindolyl propionates were formed selectively. In contrast, solution conditions; DMF as solvent, 100 °C, overnight, only the 3-substituted-vinylindoles **43** were formed, with no trace of diindolyl propionates **44** being detected (Scheme 1.17).



Scheme 1.17 Palladium catalysed coupling of indoles with acrylates.

In solution, anilines react with bis(benzotriazolyl)methanethiones **48** and form their corresponding isothiocyanates **50** and benzotriazoles through intermediate *N*-(thiocarbamoyl)benzotriazoles **49** (Scheme 1.18).[87] Due to the high reactivity of *N*-(thiocarbamoyl)benzotriazoles **49** in solution, they were not isolable using conventional solution chemistry. In 2015, Friščić and co-workers reported the first isolation of *N*-(thiocarbamoyl)benzotriazoles **49** using mechanochemistry, which were characterized by solid state magic angle spinning ^{13}C NMR spectroscopy. [88] Excellent yields (> 97%) of *N*-(thiocarbamoyl)benzotriazoles could be obtained by milling anilines **47** with bis(benzotriazolyl)methanethiones **48** under LAG conditions within 10 minutes. *N*-(thiocarbamoyl)benzotriazoles were found to be bench stable in the solid state and could be used for further synthesis of both symmetrical and nonsymmetrical thioureas **51**. This novel example shows that mechanochemistry could be used to isolate reactive intermediates, which are not isolable in solution. It further demonstrates the ability to form different reaction products, isothiocyanates in solution and thioureas mechanochemically.



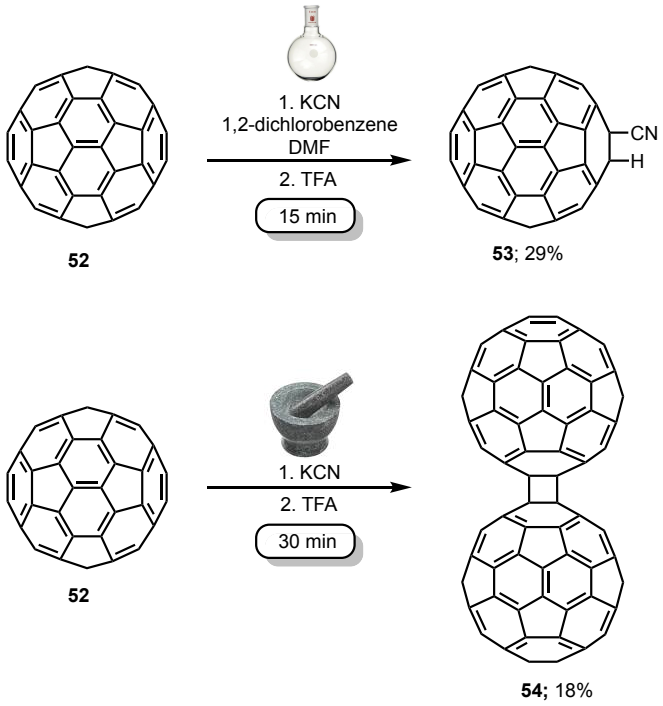
Scheme 1.18 Reaction of anilines with bis(benzotriazolyl)methanethiones and isolation of intermediate.

1.15 Reactivity not possible in solution

One of the most significant observations regarding mechanochemical reactions is that there are some examples where reactions can be performed mechanochemically but not in solution. It therefore could be the case that some chemical transformations can only be achieved using mechanochemistry.

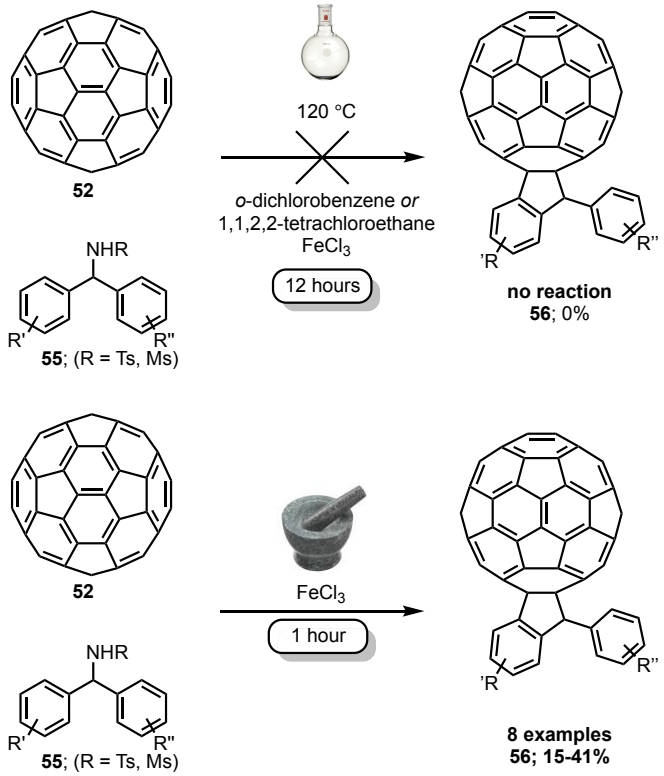
Due to the unique electronic and structural properties of fullerene and its functionalized derivatives, a number of methods for the functionalization of fullerene have been developed.[89] However, fullerene and fullerene-related materials, such as carbon nanotubes and graphite, often have low solubility in organic solvents and water, which can make their functionalization and application challenging. Mechanochemical techniques offer advantages to reactions of these carbon rich nanostructure materials and have been used to tackle these problems.[90] In 1997, Komatsu and co-workers developed the first method for the synthesis of a fullerene dimer, C_{120} **54** by the use of high speed vibration milling (Scheme 1.19).[91] Fullerene dimer C_{120} could be obtained in 30 minutes with 29% yield by milling fullerene C_{60} with KCN at 2800 cycles per minute followed by a trifluoroacetic acid wash. A similar yield could also be achieved by replacing KCN with other reagents such as K_2CO_3, KOAc, alkali metals (Li, Na, K) and 4-aminopyridine. A later study revealed that 4% fullerene trimer C_{180} could also be obtained when 4-aminopyridine was used as catalyst.[92] These compounds could not be obtained using liquid-phase protocols. Under solution based reaction conditions, Wudl

and co-workers only obtained cyano functionalised fullerene **53** by stirring fullerene with NaCN in a solvent mixture of 1,2-dichlorobenzene and DMF (Scheme 1.19).[93]



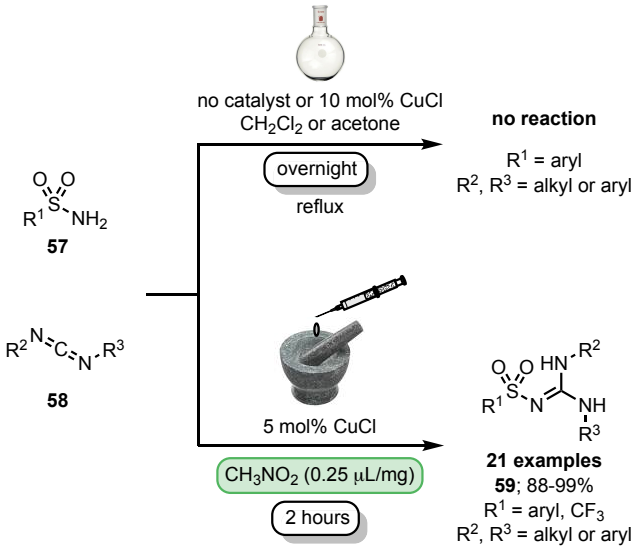
Scheme 1.19 Mechanochemical fullerene dimerization.

Another example of fullerene functionalisation was reported in 2013 by Wang and co-workers. C_{60}-fused indanes **56** could be synthesised by the reaction of fullerene **52** with N-benzhydryl sulphonamides **55** and $FeCl_3$ in a ball mill (Scheme 1.20).[94] C_{60}-fused indanes (yield: 15-41%) could be obtained within 1 hour under ball milling, whereas no product was formed using solution-based methods.



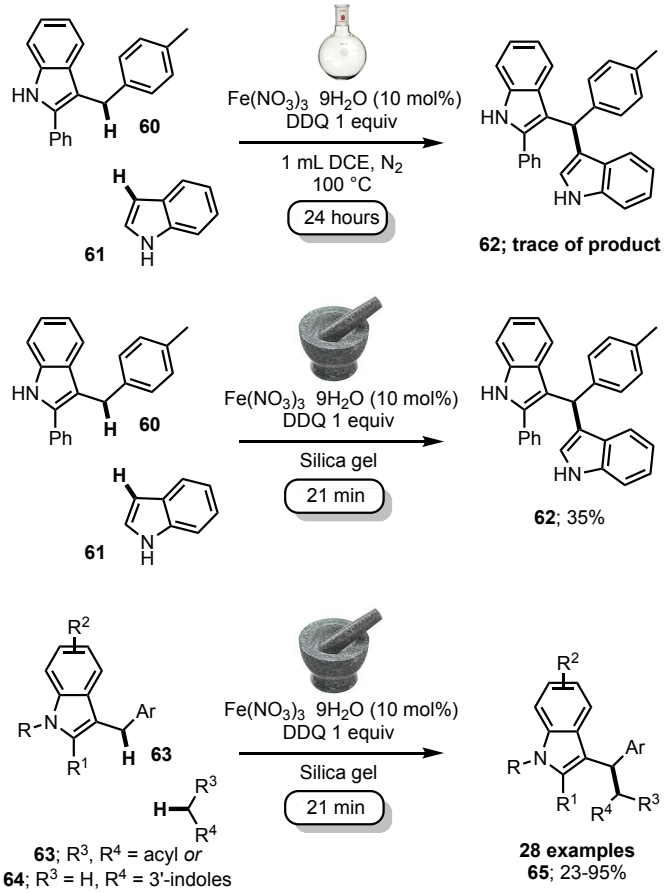
Scheme 1.20 Fullerene functionalisation.

In 2014, Friščić and co-workers demonstrated that sulfonyl-(thio)ureas could be synthesised from sulfonamides and isocyanates using catalytic CuCl under ball milling conditions.[95] They subsequently reported that N-sulfonylguanidines could be synthesised *via* the copper-catalyzed coupling of arylsulfonamides **57** and carbodiimides **58** under nitromethane LAG conditions (Scheme 1.21). [96] Further optimisation showed that acetone was the best LAG agent and good yields were obtained after milling for two hours. In contrast, refluxing arylsulfonamides and carbodiimides in solvents (DCM or acetone) overnight with or without CuCl led to no product formation.



Scheme 1.21 Coupling of sulfonamides and carbodiimides.

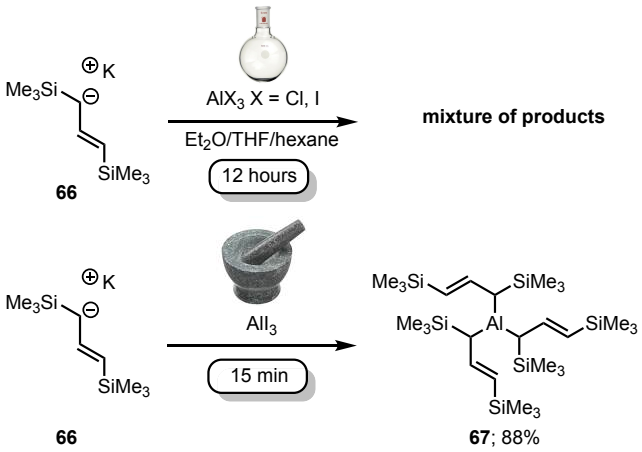
Su and co-workers developed an Fe(III)-catalyzed cross-dehydrogenative coupling of 3-benzylic indoles **60** with compounds bearing acidic methylene groups (**63** & **64**) under ball-milling conditions (Scheme 1.22).[97] This catalytic system was also successfully used for the synthesis of bisindoles **62** (yield: 24-77%). This was in contrast to the comparable solution-based reaction carried out at 100 °C under N_2 using DCE as solvent (Scheme 1.22), under which only trace amounts of product were observed.



Scheme 1.22 Cross dehydrogenative coupling of indoles.

Synthesising organometallics under mechanochemical conditions can extend the scope of suitable reactants without concern for solubility or potential interference from solvent, such as through coordination or quenching.

In 2014, an unsolvated tris(allyl)aluminium complex **67** was first isolated and reported by Hanusa and co-workers using mechanochemical conditions (Scheme 1.23).[98] Attempts to synthesise this complex by stirring K[1,3-$(SiMe_3)_2C_3H_3$] **73** with AlX_3 (X = Cl, I) in different solvents (Et_2O, THF, hexane) led to a mixture of unidentified products. The unsolvated tris(allyl)aluminium complex **67** (yield up to 88%) could be obtained within five minutes using a planetary ball mill. The reactivity of this newly synthesised complex **70** was tested by reaction with benzophenone in hexane at -78°C. Compared to the THF adduct $(C_3H_5)_3Al(THF)$, this unsolvated tris(allyl)aluminium complex **67** showed a faster reaction rate, despite its bulkier ligand.



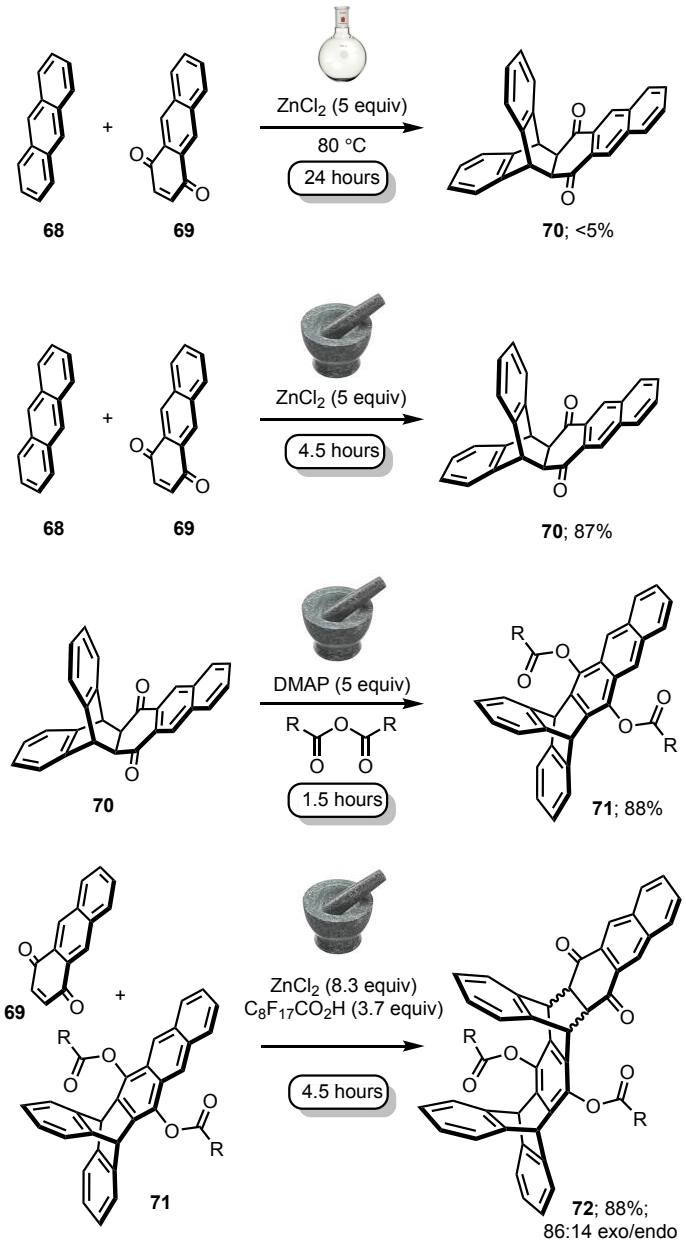
Scheme 1.23 Synthesis of an unsolvated tris(allyl)aluminium complex.

Overall, these examples show that mechanochemistry has been observed to enable alternative reactivity to reactions in solution and can be used to obtain alternative products from a reaction mixture. Furthermore, there exist examples of reactivity only observed to date under mechanochemical conditions, despite the reactions also being attempted in solution. This gives rise to the suggestion that it may only be possible to obtain certain compounds by using mechanochemical conditions.

1.16 Multistep reactions

Of particular interest for the applicability of a technique to organic synthesis is the ability to perform multistep syntheses. For example, continuous flow chemistry has become established as a method for efficient synthesis partly because of the ease in which different reaction steps can be directly telescoped together to perform a multistep process.[99] In particular, one-pot multistep processes are particularly desirable due to a reduction in the number of processing steps required when intermediates are not purified. This can therefore lead to efficient and more sustainable multistep synthesis.[100]

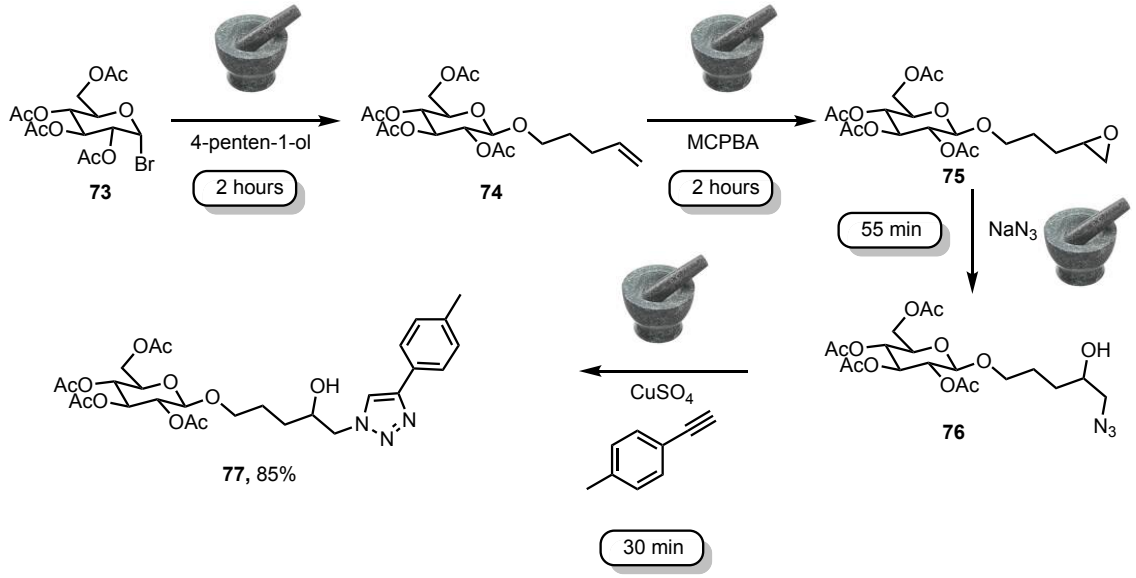
Applying mechanochemistry to multistep syntheses could lead to improvements, such as decreasing the reaction time as described above. If multistep mechanochemical processes are successfully developed, they will demonstrate the utility of mechanochemistry to organic synthesis. There are some reports of multistep and multicomponent mechanochemical processes to date, including the first mechanochemical synthesis of a pharmaceutical.[101, 102] Presented below are some examples of multistep mechanochemical processes reported to date.



Scheme 1.24 Iptycene synthesis.

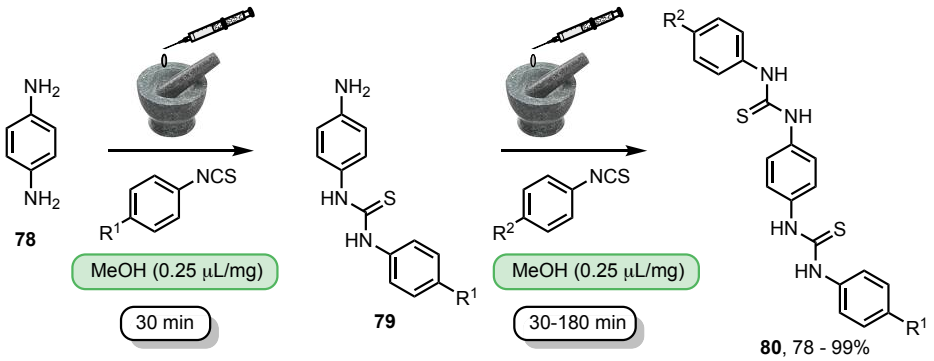
Iptycenes have three dimensional rigid molecular architectures, and potentially have multiple applications, such as molecular machines, novel liquid crystals and porous polymers.[103] In 2016, Swager and co-workers showed that highly functionalized iptycenes (molecular weight > 2000 g/mol) could be synthesised by iterative Diels-Alder/aromatisation reactions under solvent-free conditions (Scheme 1.24).[104] A good yield (87%) of adduct **70** could be achieved in a ball mill using $ZnCl_2$ as a Lewis acid. In contrast, only 5% of this material was obtained when the reaction was carried out in solution in the presence of $ZnCl_2$ at 80 °C after 24 h. To achieve extended iptycenes **72**, perfluorononanoic acid ($C_8F_{17}COOH$) was used as an additive to increase the

acidity and catalytic performance of the milled reaction. This multistep solvent free synthesis demonstrates the strengths of mechanochemical methods for the synthesis of large functionalized extended iptycenes over traditional methods.



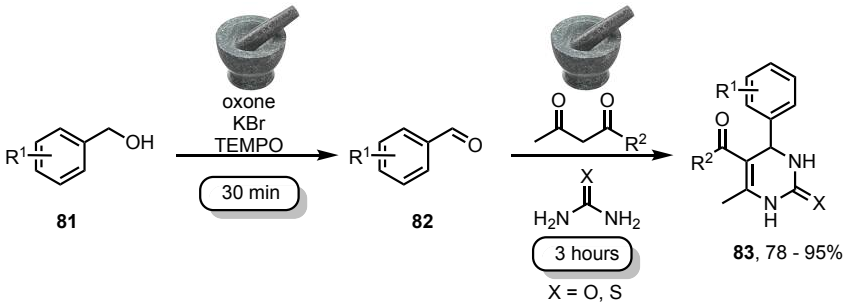
Scheme 1.25 Multistep mechanochemical synthesis of substituted glycosides.

The multistep mechanochemical preparation of a triazole substituted glycoside was reported in 2013 by Kartha and co-workers.[105] Initially, bromide **73** was treated with 4-penten-1-ol and underwent substitution to yield glycoside **74** (Scheme 1.25). This was treated with MCPBA to deliver epoxide **75**, which was ring opened with sodium azide to provide **76**. Subsequent click reaction afforded the desired triazole substituted glycoside **77** in 85% yield. These two examples highlight the most extensive multistep mechanochemical syntheses reported to date. However, there are several examples of two-step mechanochemical methods, mainly performed as one-pot procedures.



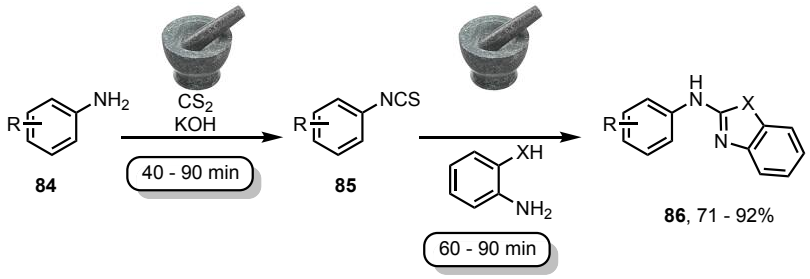
Scheme 1.26 Preparation of non-symmetrical thiourea derivatives.

In 2012, the one-pot preparation of thiourea derivatives from phenylenediamine was reported (Scheme 1.26).[106] Milling diamine **78** with a substituted isothiocyanate under LAG conditions formed the monosubstituted thiourea **79** without significant overreaction to the symmetrical thiourea derivative. Further milling with a different isothiocyanate led to the non-symmetrical thiourea derivative **80**.



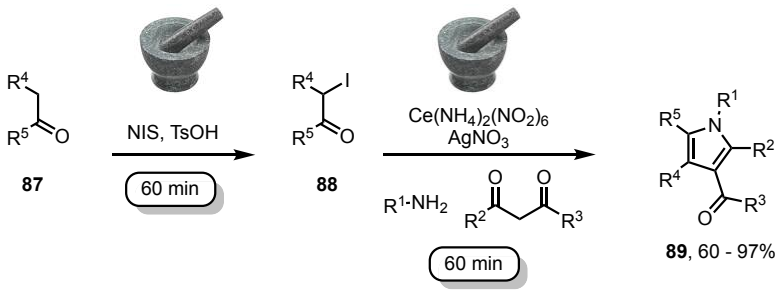
Scheme 1.27 Multistep Biginelli reaction to form dihydropyrimidones.

The one-pot synthesis of dihydropyrimidones via the three component Biginelli reaction was reported by Mal and co-workers in 2015 (Scheme 1.27).[107] Substituted benzyl alcohols **81** were oxidised to the aldehydes by milling with oxone, KBr and TEMPO. In a one-pot procedure, these were then milled for three hours with (thio)urea and a dicarbonyl to yield the dihydropyrimidones **83** in good yields. The choice of oxidising conditions in the first step was key in order for the resultant byproducts to be compatible with the second step.



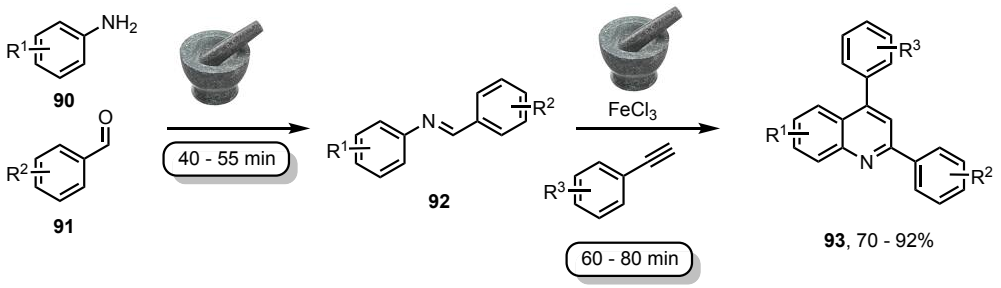
Scheme 1.28 One-pot mechanochemical synthesis of aniline-benzoxazoles and -benzothiazoles.

The one-pot, two-step mechanochemical synthesis of amino-benzoxazoles and benzothiazoles was reported in 2015 by Zhang *et al.* (Scheme 1.28).[108] Milling anilines **84** with carbon disulfide in the presence of KOH yielded the isothiocyanates **85**, which were then subjected to milling with 2-aminophenol or 2-aminothiophenol to yield the desired products **86** in good yields.



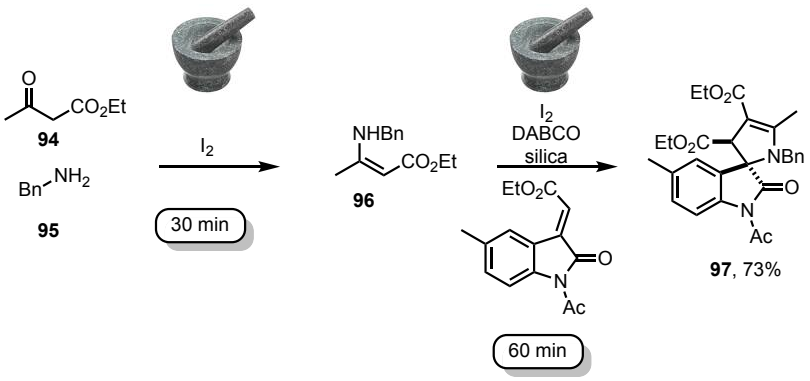
Scheme 1.29 Multistep mechanochemical Hantzsch-pyrrole synthesis.

The two-step, mechanochemical synthesis of pyrroles using the cerium ammonium nitrate promoted Hantzsch synthesis was reported in 2013 by Menéndez and co-workers (Scheme 1.29).[109] Initially, ketone **87** was iodinated by milling with N-iodosuccinamide. The iodinated ketone **88** was then milled with the desired primary amine and dicarbonyl in the presence of cerium ammonium nitrate and silver nitrate to afford the corresponding pyrroles **89** in good yields.



Scheme 1.30 Multistep mechanochemical synthesis of 2,4-diphenylquinolines.

In a further demonstration of multistep mechanochemical heterocycle synthesis, 2,4-diphenylquinolines were synthesised by Zhang and co-workers (Scheme 1.30).[110] Initially, the desired imine **92** was formed by condensation of the corresponding aldehyde and aniline under ball milling. This imine was then milled with a substituted alkyne in the presence of $FeCl_3$ to yield the desired quinolines in good yields.



Scheme 1.31 Synthesis of pyrrolinospirooxindoles.

Spirocyclic oxindoles are prevalent in natural products and bioactive molecules.[111] The first reported mechanochemical synthesis of spirocyclic oxindoles made use of a one-pot, two-step process (Scheme 1.31).[112] The iodine promoted reaction of benzylamine **95** with ethylacetoacetate **94** generated the desired intermediate **96**. On addition of the appropriate oxindole, I_2, DABCO and silica, the mixture was milled for a further 60 minutes to yield the desired pyrrolinospirooxindole **97**.

The examples presented in this section demonstrate that mechanochemical methods can be applied to multistep synthesis. In particular, there are several examples of one-pot multistep procedures for the synthesis of heterocycles. However, the conditions chosen are fairly specific to the exact transformations chosen. Given the importance of the texture of the reaction mixture described previously, it is of interest to develop an understanding of how to perform one-pot mechanochemical procedures that maintain compatibility between each step. For example, none of these examples report the use of a grinding auxiliary, however such additives can be important to achieve good mixing and energy transfer. In a one-pot process, this is more complex, as each step may require a different quantity of grinding auxiliary.

1.17 Conclusions and Outlook

Mechanochemistry can be successfully applied to many reactions that are important for organic synthesis. It offers the possibility of conducting reactions in the absence of a solvent, which can correspond to a more efficient, less wasteful and safer process than reactions in solution. However, perhaps of more interest for the investigation of novel chemical reactions is the observation that using mechanochemical methods can lead to faster reactivity, altered selectivity and alternative reactivity compared to the same

reactions in solution. In particular, this leads to the possibility that there may be some transformations that are only possible under mechanochemical conditions. Multistep mechanochemical syntheses have also been developed, including one-pot processes, which can drastically improve the efficiency of a process.
Despite the progress made, and the clear potential for mechanochemistry to enhance existing transformations and be used to discover new transformations, its effects on a reaction remain unpredictable. This is in part due to the many variables involved and also due to a lack of basic mechanistic understanding.

Further work establishing what is possible mechanochemically, especially when different reactivity is possible compared to solution is of interest. Once new reactivity is discovered, investigation of the mechanistic causes is important if mechanochemical transformations are to become more predictable and understood.

1.18 Thesis Aims and Objectives

The aim of this thesis is to investigate further the application of mechanochemistry to organic synthesis and probe what is made possible by switching from traditional solvent-based conditions to mechanochemical conditions. This will be achieved starting from a relatively simple model reaction, focusing on fluorination.

In particular, comparisons to the same reactions in solution are important in order to contextualise observed differences in reactivity. Probing of the underlying causes for observed differences will also be performed, where possible. If a basic understanding of the reasons behind changes in reactivity resulting from a switch to mechanochemical conditions can be achieved, then it may become possible to establish circumstances under which new reactions can be discovered using mechanochemistry.

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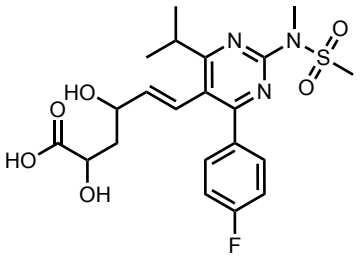
2 Mechanochemical Fluorination

2.1 Introduction

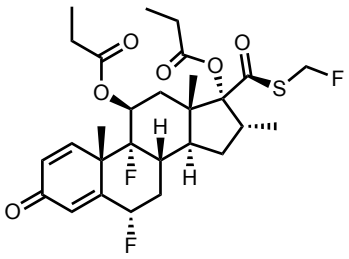
Initial investigations into using mechanochemistry to perform organic synthesis in the Browne lab were directed towards fluorination. Prior to this there was no report of the mechanochemical formation of a carbon-fluorine bond. This was chosen as a model first reaction to investigate partly because there remains significant interest in fluorination and because reactions can be easily investigated using ^{19}F NMR.

2.1.1 Fluorine in commodity chemicals

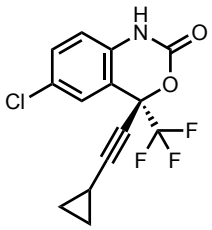
Molecules containing fluorine are frequently encountered in valuable chemical products, such as pharmaceuticals and agrochemicals. Indeed, it has been estimated that 15-20% of pharmaceuticals and 40% of agrochemicals contain a fluorine atom.[1] Furthermore, it has been suggested that incorporating fluorine into a lead compound can enhance the probability of finding a hit tenfold.[2] There are many factors that play a role in fluorine's utility, but they derive from both the fact that fluorine is the most electronegative atom and that it has a small atomic radius. The C-F bond (van der Waals radius 1.47 Å) is nearly isosteric to the C-O bond (van der Waals radius 1.52 Å), but is still close enough to that of the C-H bond (van der Waals radius 1.2 Å) that a fluorine atom can be introduced into a bioactive molecule in place of hydrogen without substantially changing the steric properties.[3] Fluorine can therefore sometimes be added without impairing binding with the target site. The electronegativity of fluorine means that adding fluorine to a molecule can significantly alter its properties, such as pKa, lipophilicity, conformation and solubility.[4] These properties can be tuned to improve the bioavailability and pharmacokinetic profiles of a bioactive compound. Fluorine, therefore, is highly useful as a substituent to enhance the properties of pharmaceuticals.[4-9] This is demonstrated in the number of fluorine containing blockbuster drugs developed[10,11] (three of the top selling drugs of 2013 are shown in Scheme 2.1).[12]



Crestor
Inhibits cholesterol biosynthesis
$5.2 billion



Fluticasone Propionate
Manages asthma
$5.0 billion

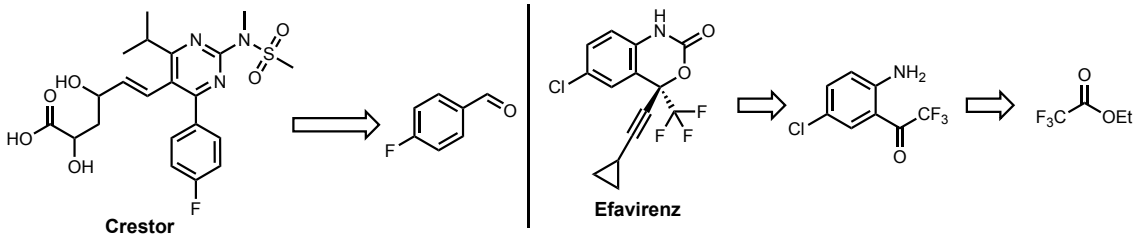


Efavirenz
HIV treatment
$2.8 billion

Scheme 2.1 Examples of top selling fluorine containing drugs in 2013.

2.1.2 Fluorinating reagents

The synthesis of fluorine-containing molecules can be performed either from fluorine containing synthons at the start of the synthesis or by late-stage fluorination.[13] The most common method is from fluorine-containing starting materials (Scheme 2.2). For example, Crestor is synthesised from commercially available 4-fluorobenzaldehyde, whereas the trifluoromethyl group in Efavirenz derives from readily available ethyltrifluoroacetate.[14]



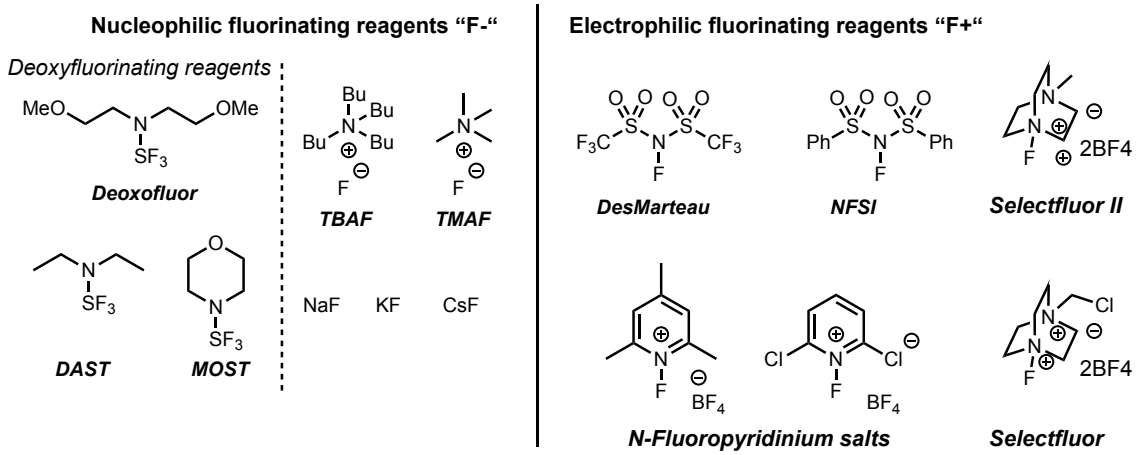
Crestor **Efavirenz**

Scheme 2.2 Examples of starting materials for the synthesis of Crestor and Efavirenz.

Late-stage fluorination can enable the synthesis of fluorinated molecules for which the required fluorine-containing starting materials are not readily available. As a synthetic strategy it can also allow fluorinated materials to be screened as part of a medicinal chemistry programme without having to redesign a synthesis to start from available fluorine-containing starting materials. Furthermore, it is necessary when introducing a ^{18}F atom for use in PET imaging, due to the short half life of ^{18}F.[15] However, in order to perform late-stage fluorination, the reaction conditions used to introduce the fluorine atom must have good functional group tolerance, as the fluorination would be performed on complex structures. The fluorination must also be selective, fluorinating only at the desired position.

In order to achieve fluorination, among the cheapest reagents are F_2 gas and HF. However, these reagents are toxic, difficult to handle and harsh reaction conditions are

typically used. They are often also not very selective, and can lead to fluorination at multiple sites. There has therefore been considerable development of alternative reagents to achieve selective fluorination (Scheme 2.3).[16-18]

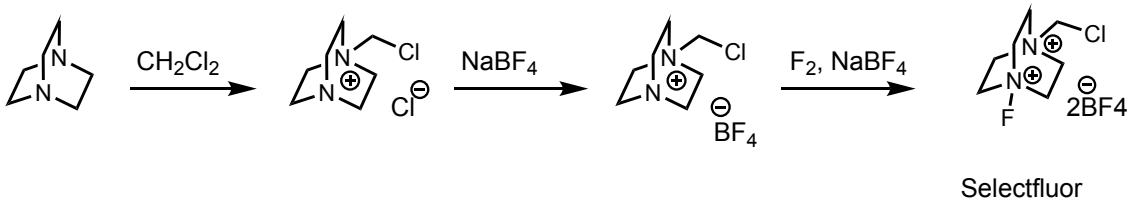


Scheme 2.3 Examples of fluorinating reagents.

In general, these reagents are safer and easier to handle than reagents such as HF, XeF_2 or F_2. They can, in general, be handled in any lab without special equipment, such as that required to handle F_2. They are also often more selective and have better functional group tolerance. For the electrophilic mechanochemical fluorination developed during this project, Selectfluor was chosen as the fluorinating reagent.

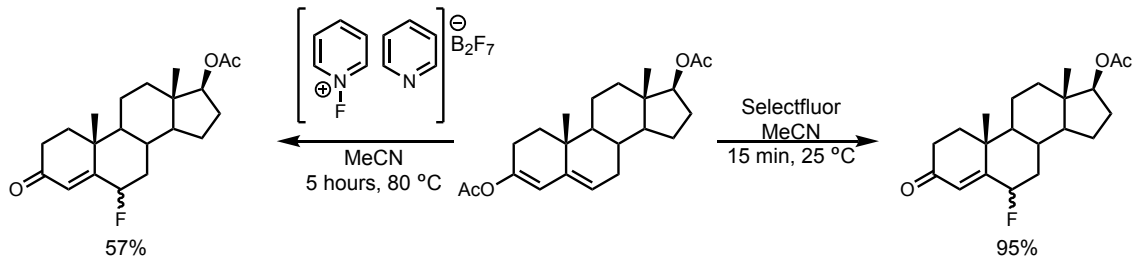
2.1.3 Selectfluor

Selectfluor is an air and moisture stable solid that is commercially available and an effective source of electrophilic fluorine. It is not hygroscopic and is safe to store and handle on large quantities in air. During thermal stability tests, pure Selectfluor was found to be stable up to 200 °C.[19] It is soluble and stable in water, with successful fluorination reactions having been performed in water.[20] These properties, especially its high stability, make it a sensible choice for use in a ball mill. It was developed by Banks and patented in 1992, being synthesised from DABCO and F_2 (Scheme 2.4).[21, 22]



Scheme 2.4 Synthesis of Selectfluor

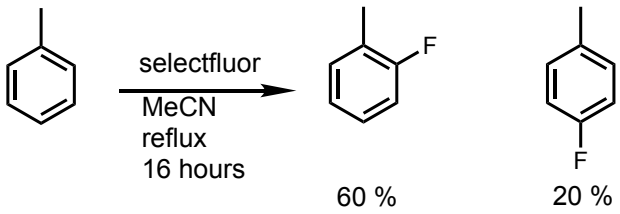
Selectfluor was found to be significantly more effective than the previously developed electrophilic fluorinating reagents based on the N-F bond, for example the N-fluoropyridinium salts. In 1992, Banks *et al.* demonstrated its efficiency by fluorinating a testosterone derivative (Scheme 2.5).[22]



Scheme 2.5 Comparison of reactivities of Selectfluor and N-fluoropyridinium salt.

It was found that in only 15 minutes at room temperature, 95% of the fluorinated product was obtained. However, using a previously developed N-fluoropyridinium salt as the source of electrophilic fluorine, only a 57% yield was obtained after heating to 80 °C for 5 hours.[23] This demonstrates the improved reactivity of Selectfluor, which is also supported by comparisons between electrochemical measurements of the reduction potentials for different fluorinating reagents.[24]

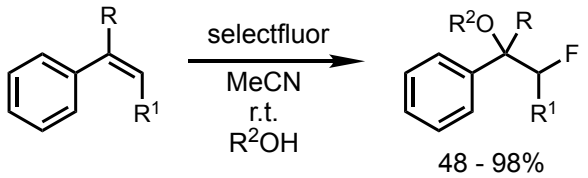
Many different nucleophilic species can be successfully fluorinated in operationally simple procedures using Selectfluor, including poorly nucleophilic molecules such as toluene (Scheme 2.6).[25] In 1993, Lal investigated the reactivity of Selectfluor, reporting the fluorination of toluene after refluxing a mixture of toluene and Selectfluor in acetonitrile for 16 hours. Both the ortho- and para-fluorinated toluene products were obtained in a good total yield. Xylenes could also be fluorinated using this method.



Scheme 2.6 Fluorination of toluene by Selectfluor.

It was also found that Selectfluor could directly fluorinate alkenes, and that in the presence of alcohols formed the oxy-fluorinated product (Scheme 2.7).[25] It was found that on treating styrene derivatives with Selectfluor in the presence of various alcohols by stirring at room temperature in acetonitrile led to oxy-fluorination. The

regioselectivity observed suggests the formation of an intermediate carbocation, being stabilised by the aromatic ring.



Scheme 2.7 Oxy-fluorination of alkenes by Selectfluor in the presence of alcohols.

Many other nucleophilic moieties can also be fluorinated by Selectfluor, including steroids[25], alkynes[26] and carbohydrates.[27] However, possibly the most investigated to date is the fluorination of a variety of 1,3-dicarbonyls.

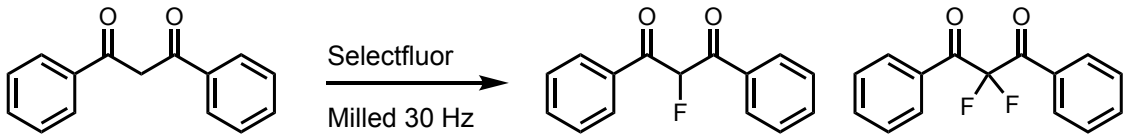
2.2 Fluorination of dicarbonyls by Selectfluor

In order to investigate the possibility of mechanochemical fluorination, a model reaction was required. Having decided that Selectfluor would be the fluorinating reagent, the electrophilic fluorination of 1,3-dicarbonyls was chosen as a model reaction to be investigated. The use of Selectfluor to fluorinate dicarbonyls was first reported in 1994 by Banks *et al*.[28] It was reported that 1,3-diketones, β-ketoesters and β-ketoamides could be monofluorinated at room temperature in good yields in 3 - 54 hours. In the presence of sodium hydride, the same substrates could be difluorinated with good yields. A similar transformation was also reported by Stavber and Zupan using Accufluor, a derivative of Selectfluor.[29] More recent work has focused on the enantioselective fluorination of dicarbonyls, using titanium catalysts and cinchona alkaloid derived catalysts.[30-32] As the importance of green chemistry has become a consideration in method development, the selective monofluorination of β-ketoamides in an environmentally benign solvent, PEG-300, was developed by Zhang and co-workers.[33] The emergence of new technologies for synthesis encouraged the investigation of fluorination under microwave conditions. Xiao and Shreeve were able to fluorinate 1,3-diketones, β-ketoesters and β-ketoamides in 10 minutes using a microwave reactor, obtaining good yields of monofluorinated and difluorinated analogues.[34] This reaction manifold is therefore a robust and well documented transformation, that is ideal to use as a model reaction to test the efficiency of C-F bond formation under mechanochemical conditions.

2.3 Optimisation for diketones

Initial results showed that the electrophilic fluorination of dibenzoylmethane **98** was possible under mechanochemical conditions. On milling dibenzoylmethane **98** with Selectfluor, the desired fluorinated products were obtained. For this one millimole scale reaction, 10 mL stainless steel jars were used with one ball of mass 4 g. These initial conditions were chosen so that no more than approximately one third of the volume of the jar was filled with reagents and ball. The crude reaction mixture was analysed by ^{19}F NMR spectroscopy and the yield determined by comparison of the integrals to trifluorotoluene as an internal standard. As expected, a mixture of both the monofluorinated product **99** and difluorinated product **100** was observed. A variety of conditions were then screened in order to optimise this reaction under milling conditions (Table 2.1).

Table 2.1 Mechanochemical fluorination of dibenzoylmethane



98 **99** **100**

Entry	Equiv selectfluor	Time / h	Additive	Yield **99**[a]	Yield **100**[a]
1	1	1	-	53%	4%
2	2	1	-	87%	11%
3	2	1	MeCN (0.25 mL)	79%	0%
4	2	2	-	74 %	26%
5	2	2	MeCN (0.25 mL)	91%	7%
6	2	2	H_2O (0.25 mL)	0%	0%
7	2	2	^{i}PrOH (0.25 mL)	9%	3%
8	2	2	Toluene (0.25 mL)	30%	2%
9	2	2	CH_2Cl_2 (0.25 mL)	20%	0%
10	2	2	MeCN (0.125 mL)	100%	0%
11	2	2	Na_2CO_3 (1 equiv)	6%	94%
12	2	2	K_2CO_3 (1 equiv)	2%	87%
13	2	2	Cs_2CO_3 (1 equiv)	2%	68%
14	2	2	$CaCO_3$ (1 equiv)	53%	19%

[a] Determined by ^{19}F NMR compared to trifluorotoluene as a standard.

Initially, it was found that upon subjecting diketone **98** to milling at 30 Hz with one equivalent of Selectfluor for one hour furnished a 53% yield of monofluorinated diketone **99** (Table 2.1, Entry 1). However, the reaction mixture also contained some difluorinated product **100**, demonstrating that over reaction occurs even with a stoichiometric quanitity of fluorinating reagent. Doubling the quantity of Selectfluor then achieved almost quantitative total yield (Table 2.1, Entry 2). The addition of a small quantity of liquid (LAG) was then investigated. Intriguingly, it was observed that upon addition of acetonitrile, there was a decrease in the total yield, but a dramatic enhancement in the selectivity of monofluorination (Table 2.1, Entry 3). However, on increasing the reaction time, the total yield was improved (Table 2.1, Entry 5). In comparison to milling without a liquid additive, the selectivity enhancement can be clearly seen (Table 2.1, Entry 4). On investigating a range of other solvents possessing different properties, all were found to have a detrimental effect on the yield of the reaction (Table 2.1, Entries 6 - 9). Decreasing the quantity of acetonitrile was found to form exclusively monofluorinated product **99** in quantitative yield (Table 2.1, Entry 10). This exciting and unexpected result will be discussed later in more detail. Having established optimal conditions for the selective monofluorination of dibenzoylmethane **98** under mechanochemical conditions, the possibility of selective difluorination was investigated.

In order to enhance the rate of difluorination, a base was used to form the reactive enolate of **99** (Table 2.1, Entries 11 - 14). After testing a range of carbonate bases, it was found that addition of 1 equivalent of sodium carbonate furnished the difluorinated product **100** in 94% yield after milling for 2 hours (Table 2.1, Entry 11). The ability to use a carbonate base is interesting, as previous reports in solution required very strong bases or long reaction times to achieve difluorination, with the comparable product in solution reported to require 192 hours for complete reaction.[28]

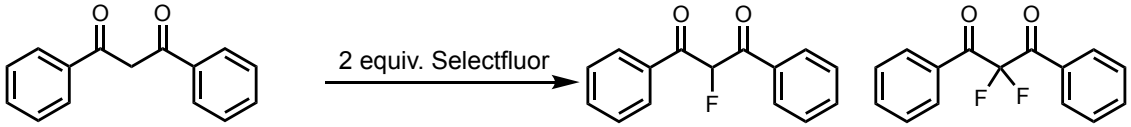
2.4 Comparison to solution reactions

In order to test if there were any advantages in running these reactions mechanochemically compared to in solution, direct comparisons of these reaction conditions were attempted.

It was found that upon stirring **98** with 2 equivalents of Selectfluor in acetonitrile at room temperature, 3.5 hours was required to consume all the starting material. After extraction, **99** was isolated in 88% yield, with a greater than 50:1 ratio of **99**:**100** (Table 2.2, Entry 1). In the case of monofluorination, the mechanochemical reaction occurs

slightly faster than the solution reaction, forming **99** in a higher yield after a shorter time (Table 2.2, Entry 2).

Table 2.2 Comparison of monofluorination under milling and in solution

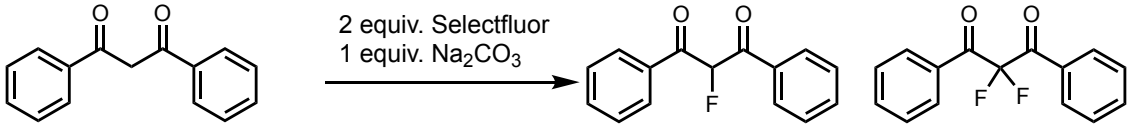


98 **99** **100**

Entry	Conditions	Time / hours	Total isolated yield	Ratio (**99**:**100**)
1	20 mL MeCN, stir r.t.	3.5	88 %	>50 : 1
2	0.125 mL MeCN, Milled 30 Hz	2	95 %	>50 : 1

On investigation of the difluorination of **98** in acetonitrile with Selectfluor and sodium carbonate, it was found that 24 hours were required to convert all of the starting material. The desired product **100** was then isolated with a 93% yield and a 7:1 ratio to the monofluorinated product **99** (Table 2.3, Entry 1). This compares to a similar yield but significantly shorter reaction time for the mechanochemical reaction (Table 2.3, Entry 2).

Table 2.3 Comparison of difluorination under milling and in solution



98 **99** **100**

Entry	Conditions	Time / hours	Total isolated yield	Ratio (**99**:**100**)
1	MeCN, stir r.t.	24	93 %	1 : 7
2	Milled 30 Hz	2	90 %	1 : 9

Overall, it was found that monofluorination under milling and in solution gave similar reaction outcomes. However, in the case of difluorination, there is a significant time saving observed under milling conditions.

2.5 Selectivity enhancement by Liquid Assisted Grinding

A highly interesting observation about the mechanochemical monofluorination of dibenzoylmethane is the significant selectivity enhancement observed under LAG with acetonitrile, when compared to the mechanochemical reaction in the absence of acetonitrile. The origin of this selectivity was investigated further by investigating the behaviour of the reactions at different times.

2.5.1 Reaction profile with time

The behaviour of the fluorination of dibenzoylmethane with 2 equivalents of Selectfluor in the mill at 30 Hz was investigated both in the presence and absence of acetonitrile for different reaction times (Figure 2.1). In the absence of acetonitrile, full conversion of starting material was observed after 1 hour in the mill (Table 2.4). However, there was already some over-fluorination to the difluorinated product observed. Milling for longer times leads to further conversion to the difluorinated product **100**.

Table 2.4 Yields at different times for neat grinding

Time / min	Yield Mono **99** / %	Yield Di **100** / %
5	7	0
30	53	4
45	78	9
60	87	11
90	76	24
120	61	38
180	57	43

This is in stark contrast to what is observed under liquid assisted grinding conditions. In this case, 2 hours are required for the reaction to reach full conversion (Table 2.5). However, after 2 hours, there is still no difluorination observed. Upon milling for an additional hour, a small quantity of difluorinated product **100** is observed.

Table 2.5 Yields at different times for LAG with acetonitrile

Time / min	Yield Mono **99** / %	Yield Di **100** / %
5	12	0
45	47	0
90	75	0
120	100	0
180	95	3

These observations show that the addition of acetonitrile to the reaction mixture has two effects, which alter the selectivity. Under liquid assisted grinding, the overall fluorination is slowed down, requiring two hours for full conversion of starting material, instead of one hour in the neat grinding case. However, LAG seems to also inhibit further fluorination of **99** to **100**. At full conversion (120 minutes), there is still no difluorinated product observed (Table 2.5), whereas under neat grinding conditions at full conversion (60 minutes), 11% of **100** is observed. This inhibition of over-fluorination is the origin of the selectivity enhancement observed. However, it is still not clear what the physical cause of this inhibition is.

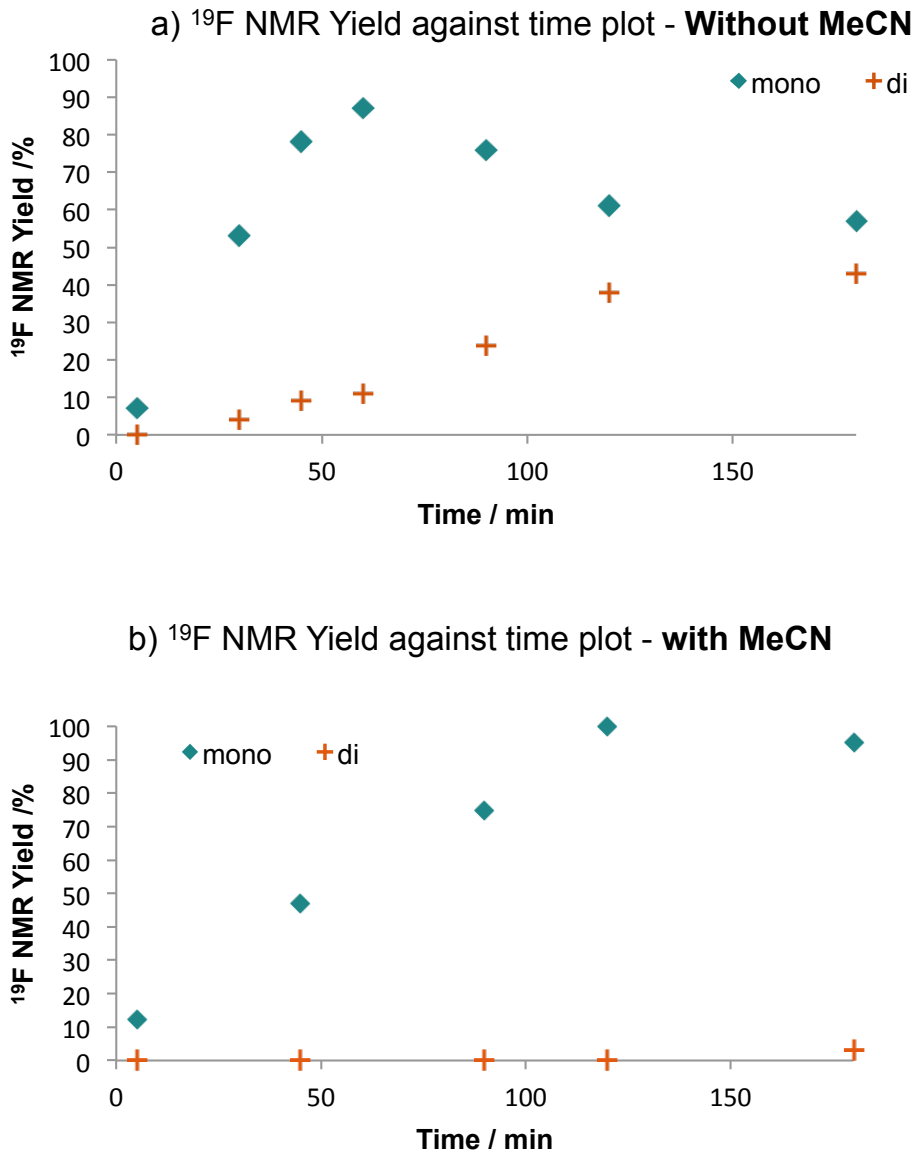
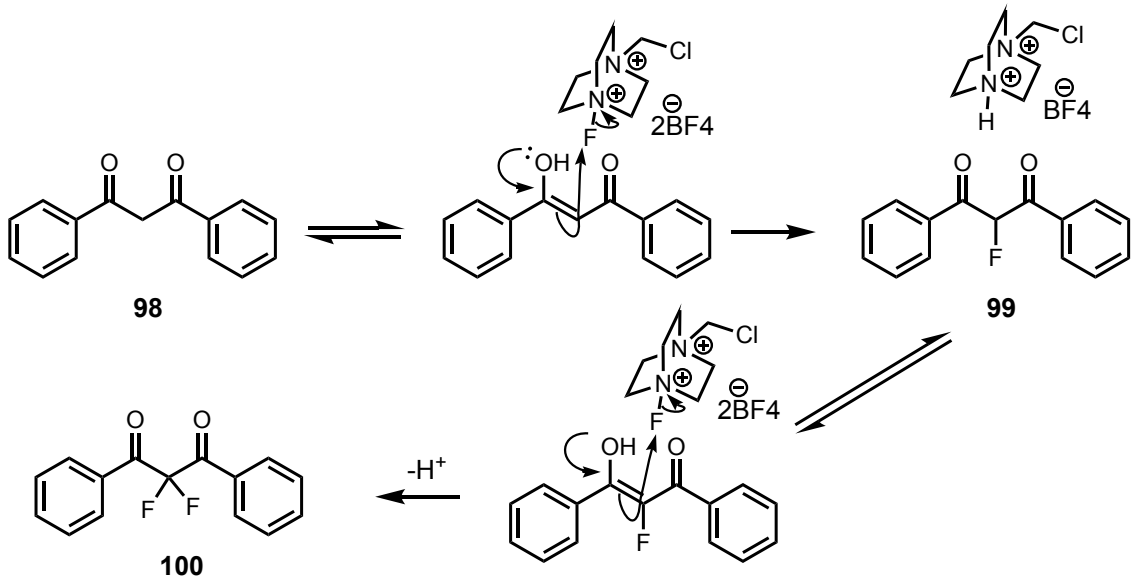


Figure 2.1 Yields of mono- and difluorinated products at different times a) without and b) with acetonitrile.

In order to propose and ultimately test hypotheses on the cause of this intriguing effect of LAG, the mechanism of this reaction manifold must be considered. A proposed mechanism is shown in Scheme 2.7. Initially, the diketone tautomerises to the reactive enol form. This can than attack Selectfluor and after proton transfer, possibly mediated by the DABCO derived fragment of defluorinated Selectfluor, the monofluorinated product **99** is formed. In order to react further, forming difluorinated product **100**, the keto form must tautomerise to the reactive enol form. Under basic conditions, this may proceed via the enolate, which would be significantly more reactive than the enol.



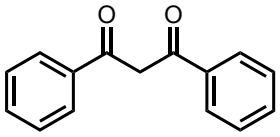
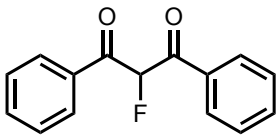
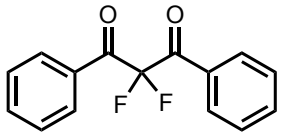
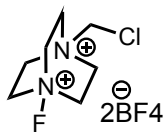
Scheme 2.7 Proposed mechanism for the fluorination of **98**

Having considered the mechanism, it is clear that in order to form the difluorinated product **100**, the enol or enolate of **99** must be formed in the presence of a sufficient concentration of Selectfluor. This leads to three potential hypotheses to explain the physical origin of this selectivity observed.

It is known that in solution, the solvent used can affect the keto:enol ratio of ketones. It is therefore possible that in the presence of acetonitrile, the monofluorinated product **99** is trapped in its unreactive keto form, whereas in the solid state without any solvent, a higher quantity of the reactive enol form could be present. On subjecting a pure sample of **99** to ^{1}H NMR spectroscopy in MeCN-d3, only the keto form was observed, which seems to support this hypothesis. Likewise, in $CDCl_3$, the only form observed was also the keto form, suggesting that this is usually the preferred form in solution.

An alternative hypothesis that could explain the selectivity enhancement observed under LAG conditions relies on the possibility of different solubilities of each component of the reaction in acetonitrile. If the starting diketone **98** is more soluble than **99**, a quantity of **98** will dissolve and become more mobile and able to "find" a molecule of Selectfluor to react with. On forming less soluble **99**, this would then precipitate out of solution, making it less mobile and less likely to "find" a molecule of Selectfluor with which to react further. In order to test this, the approximate solubilities of the different components in acetonitrile were measured as follows. A known quantity of the sample to be measured was placed in a vial and acetonitrile was added in 10 μL portions and subjected to ultrasound. This was continued until no more solid was visible and the approximate solubilities of each species in acetonitrile were calculated (Table 2.6). While this method does not accurately determine the solublility, as it is possible that the system had not reached equilibrium, it does provide a fast and simple method to determine approximate solubilities. Indeed, this method has been used previously to quickly determine approximate solubilities.[35]

Table 2.6 Approximate solubilities of compounds in acetonitrile.

Compound	Approximate solubility in acetonitrile / $mgmL^{-1}$	Approximate solubility in acetonitrile / $moldm^{-3}$
 **98**	113	0.504
 **99**	360	1.49
 **100**	290	1.12
 **Selectfluor**	69	0.195

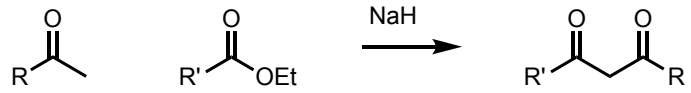
It can be seen that dibenzoylmethane **98** is significantly less soluble in acetonitrile than either monofluorinated **99** and difluorinated **100** (Table 2.6). This suggests that this hypothesis is not true. This could be explained if the fluorination is fastest in the solid phase. The least soluble components (**98** and Selectfluor) would then react faster than the more soluble components, forming **99**, which would then preferentially be in solution.

A third hypothesis relies on the observation that using LAG can lead to the formation of different polymorphs, or crystal structures, of pure materials.[36] It has also been previously shown that different polymorphs of the same material can react differently.[37-39] It is therefore possible that the monofluorinated product **99** is formed in different polymorphs in the presence and absence of acetonitrile. It is therefore possible that the polymorph formed under LAG conditions reacts slower with Selectfluor than the polymorph formed under neat grinding.

Currently, it remains unclear what the exact reason behind the observed effect of LAG on this reaction. Further studies are required to fully understand the physical processes involved. For example, in situ solid state magic angle spinning NMR of the solid reaction mixture could allow the exact composition of the reaction mixture at different time points to be obtained without having to dissolve the mixture. Combined with powder X-ray diffraction, this type of technique could add more information regarding any effects caused by different polymorphs. However, such experiments would require significant collaboration and expertise. At this point, it was decided to test the applicability of this observation to other 1,3-diketones.

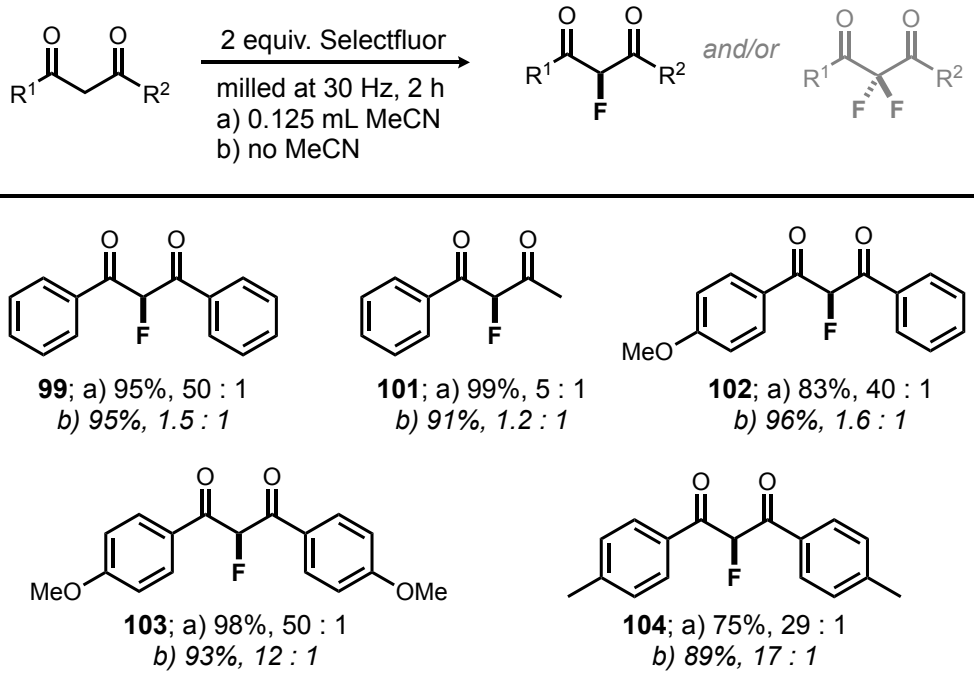
2.6 Substrate scope for monofluorination

In order to probe the applicability of mechanochemical fluorination to other diketones, a range of 1,3-diketones had to be obtained. The chosen procedure for the synthesis of non-commercially available diketones was the deprotonation of substituted acetophenones with sodium hydride and subsequent addition to the corresponding esters (Scheme 2.8).[40]



Scheme 2.8 Synthesis of 1,3-diketones

With a variety of diketones in hand, the mechanochemical fluorination was investigated (Scheme 2.9).

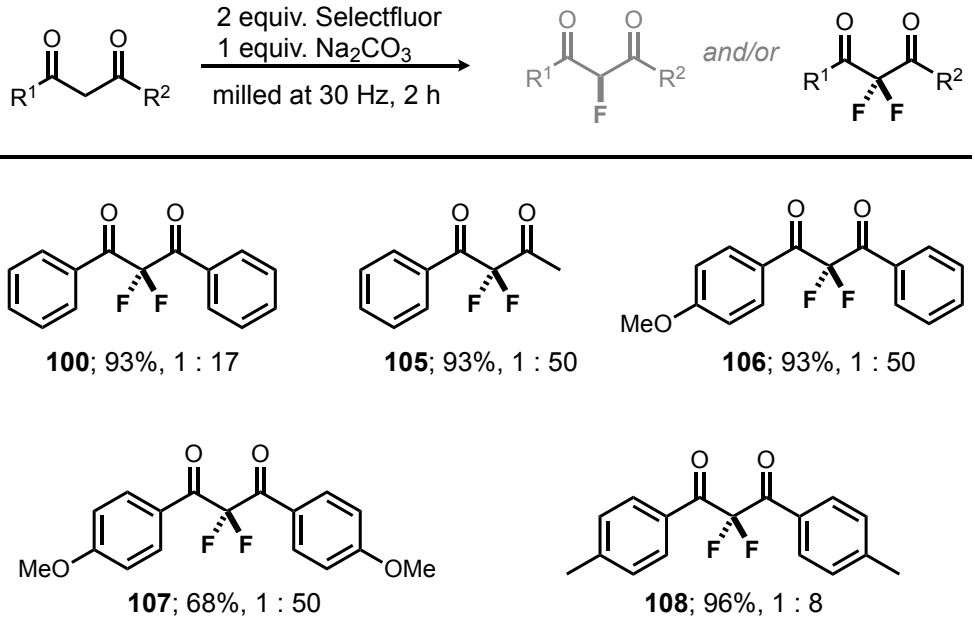


Scheme 2.9 Scope of monofluorination: a) under LAG conditions & b) under neat grinding. Yields based on total mass of material isolated, ratios, mono:di, determined by ^{19}F NMR spectroscopy.

For these aromatic 1,3-diketones, monofluorination could be achieved mechanochemically with good yields obtained for all cases. It was also observed that the selectivity enhancement observed for dibenzoylmethane under LAG conditions also seems to apply to other diketones.

2.7 Substrate scope for difluorination

Applying the optimised conditions for difluorination to the same range of diketones was also tested (Scheme 2.10). Pleasingly, all the tested 1,3-diketones were successfully difluorinated upon milling for two hours in the presence of Selectfluor and sodium carbonate, with good yields obtained.



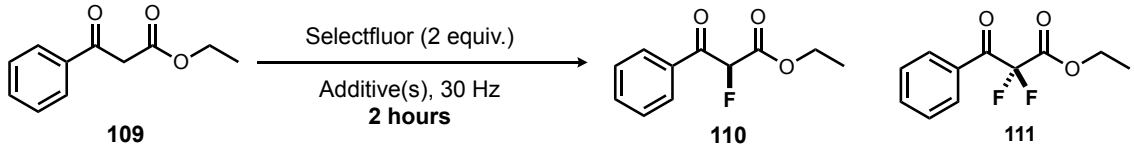
Scheme 2.10 Scope of difluorination. Yields based on total mass of material isolated, ratios, mono:di, determined by ^{19}F NMR spectroscopy.

Having successfully demonstrated the first mechanochemical fluorination of a range of diketones, the reactivity of other 1,3-dicarbonyls was investigated.

2.8 Optimisation for β-ketoesters

In order to probe the scope of mechanochemical fluorination, it was decided to investigate the feasibility of fluorinating β-ketoesters mechanochemically. However, the conditions had to be altered in order to achieve this. Perhaps the most important difference was that the β-ketoester used to test this reaction is a liquid. Liquids can behave differently under mechanochemical conditions, leading to the formation of a gum or paste in the mill, which may not mix efficiently. To overcome this problem, grinding auxiliaries can be added to the reaction mixture to improve the texture. It has also been previously reported that β-ketoesters are significantly less reactive than diketones towards fluorination.[28] This is due to the extended conjugation provided by the lone pair on the oxygen atom of the ester, further delocalising the partial negative charge at the α position, thus making it less nucleophilic.

Table 2.7 Optimisation of the monofluorination of a β-ketoester.



Entry	Additives	Yield[a]	Ratio 110:111
1	-	70%	2.7:1
2	NaCl[b]	32%	15:1
3	MeCN (0.125 mL)	69%	7.6:1
4	NaCl[b], MeCN (0.125 mL)	83%	11:1
5	NaCl[b], MeCN (0.25 mL)	96%	13:1
6	NaCl[b], Na_2CO_3 (1 equiv)	98%	1:7

[a] Total yield of 110 and 111 determined by ^{19}F NMR spectroscopy compare to trifluorotoluene as a standard. [b] Twice the total mass of reagents.

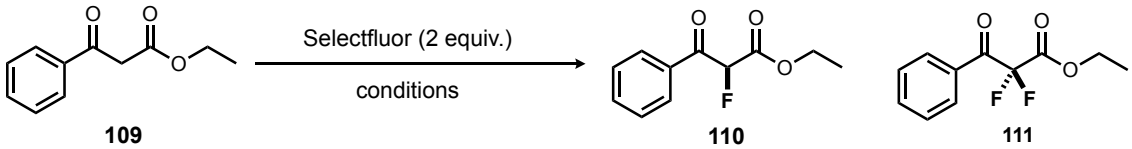
Initial milling of liquid ethylbenzoylacetate **109** with two equivalents of Selectfluor for two hours led to significant fluorination, with a good total yield but relatively poor selectivity (Table 2.7, Entry 1). Addition of acetonitrile improved the selectivity, as was also the case for the fluorination of diketones (Table 2.7, Entry 3). Addition of sodium chloride as a grinding agent improved the yield and selectivity (Table 2.7, Entry 4), whereas without acetonitrile the yield was much lower (Table 2.7, Entry 2). Increasing the quantity of acetonitrile led to the highest yield and good selectivity (Table 2.7, Entry 5). These conditions were chosen as optimal for monofluorination. Pleasingly, simply replacing acetonitrile with one equivalent of sodium carbonate enabled difluorination in a high yield and good selectivity.

2.9 Comparison to solution reactions

Having established optimal conditions for the selective mono and difluorination of ethyl benzoylacetate **109** in the mill, this reactivity was also investigated in solution. This would help to determine whether there are any advantages to performing this reaction under mechanochemical conditions.

On stirring **109** with two equivalents of Selectfluor at room temperature in acetonitrile, it was found that five days were required for the monofluorination to occur (Table 2.8, Entry 1). This is in stark contrast to mechanochemical conditions, under which only two hours are required to obtain a higher yield (Table 2.8, Entry 2).

Table 2.8 Comparison of mechanochemical and solution based monofluorination

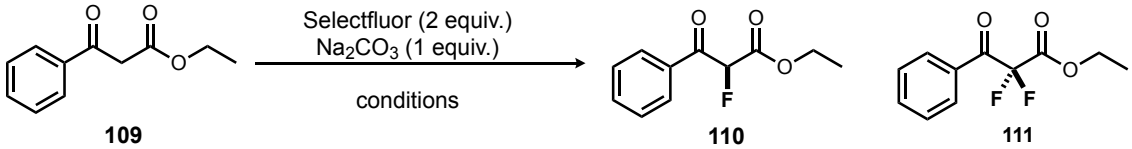


109 **110** **111**

Entry	Conditions	Time / hours	Total yield	Ratio (**110**:**111**)
1	20 mL MeCN, stir r.t.	120	88 %	20 : 1
2	0.25 mL MeCN, NaCl, Milled 30 Hz	2	96 %	13 : 1

Difluorination of ethylbenzoylacetate **109** also required significantly longer to difluorinate in solution. After stirring the reaction mixture at room temperature in acetonitrile for five days, a yield of 89% and ratio of 3:1 was obtained (Table 2.9, Entry 1). Using the ball mill, only two hours were required for the reaction to reach completion (Table 2.9, Entry 2).

Table 2.9 Comparison of mechanochemical and solution based difluorination



109 **110** **111**

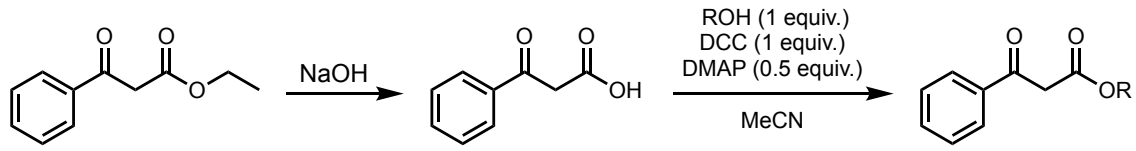
Entry	Conditions	Time / hours	Total yield	Ratio (**110**:**111**)
1	20 mL MeCN, stir r.t.	120	89 %	1 : 3
2	0.25 mL MeCN, NaCl, Milled 30 Hz	2	98 %	1 : 7

Having established that selective mono and difluorination of ethylbenzoylacetate can be performed under mechanochemical conditions with a significant time saving over the same reactions in solution, it was decided to test if this transformation could be applied to a substrate scope of different β-ketoesters.

2.10 Substrate scope for monofluorination of β-ketoesters

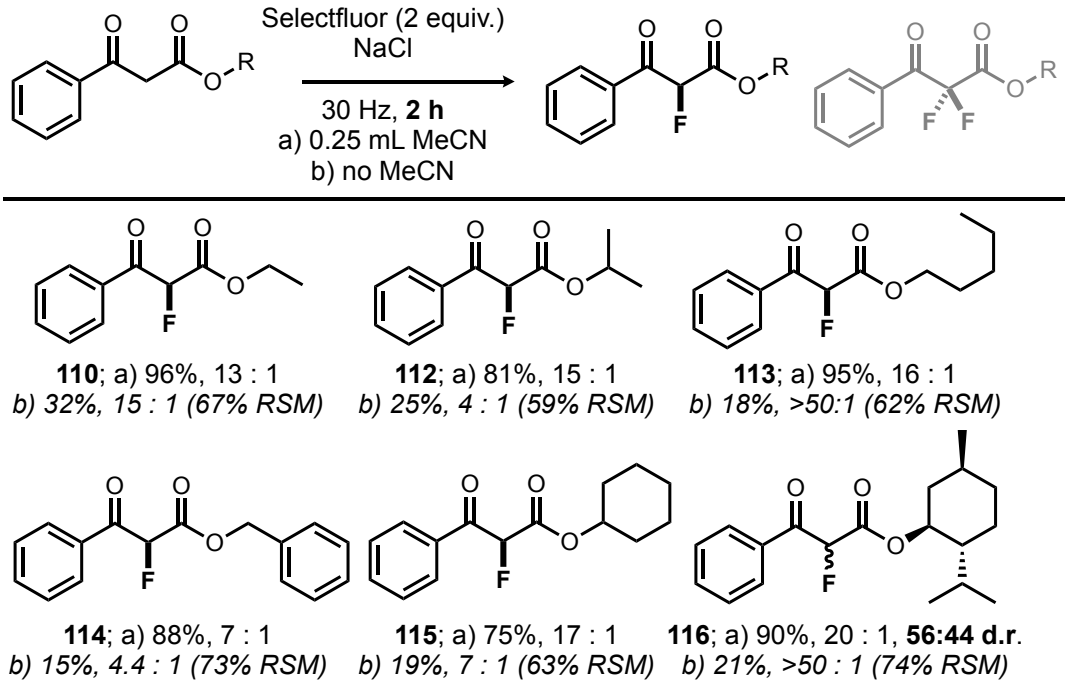
In order to test the scope of this reaction, a range of different β-ketoesters were required. These were synthesised from commercially available ethylbenzoylacetate. Initial attempts, focusing on transesterification, were unsuccessful. Ultimately, the most

reliable procedure for the synthesis of β-ketoesters was found to be the Steglich esterification from the corresponding carboxylic acid.



Scheme 2.11 Procedure used to synthesise a range of β-ketoesters

However, the required β-ketoacid was found to be prone to decarboxylation to the acetophenone on storing over about five days. Fresh batches were therefore prepared only when needed by hydrolysis of ethylbenzoylacetate with sodium hydroxide and used immediately. Esterification of this β-ketoacid with dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) yielded the desired β-ketoesters (Scheme 2.11). With a range of β-ketoesters in hand, the scope of monofluorination with and without LAG was investigated (Scheme 2.12).



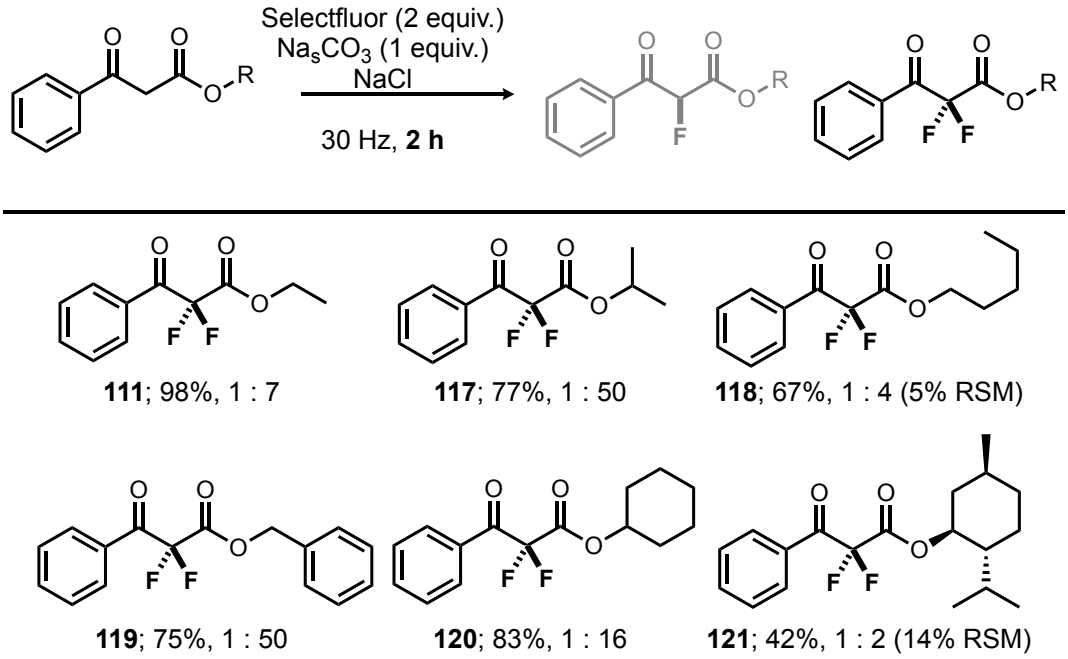
Scheme 2.12 Substrate scope of monofluorination a) under LAG conditions, b) under neat grinding. Yields based on mass of material isolated, ratios mono:di determined by ^{19}F NMR spectroscopy. RSM = remaining starting material.

It was found that the optimal conditions for the monofluorination of ethylbenzoylacetate **109** were applicable to a range of β-ketoesters. All monofluorinated products were obtained in good yields and selectivities, although on comparing the results with and without acetonitrile it can be seen that the trend is not the same as it was for

1,3-diketones. It seems that the addition of acetonitrile is speeding up the reaction, as without acetonitrile the yields are generally poor, with significant amounts of starting material remaining.

2.11 Substrate scope for difluorination of β-ketoesters

The same β-ketoesters were also subjected to the optimised conditions for mechanochemical difluorination. Good yields of the difluorinated products were obtained apart from the menthol derived β-ketoester **121** (Scheme 2.13).



Scheme 2.13 Substrate scope of difluorination. Yields based on mass of material isolated, ratios mono:di determined by ^{19}F NMR. RSM = remaining starting material.

The difluorination of β-ketoesters under mechanochemical conditions is therefore also applicable to a variety of substrates.

2.12 Conclusions and Outlook

The first mechanochemical C-F bond formation has been achieved. Specifically, the electrophilic fluorination of 1,3-dicarbonyls was performed in a mixer mill using Selectfluor as the fluorine source. It was found that 1,3-diketones could be selectively mono or difluorinated depending on the conditions applied. Under LAG conditions with acetonitrile, the monofluorinated products were formed selectively, without over reaction to the difluorinated products. The selectivity was greater than under neat grinding conditions. This is of particular importance, as using LAG to achieve better

selectivity had not been previously reported. It was found that the addition of acetonitrile both slowed down the overall reaction and inhibited difluorination. By swapping acetonitrile for sodium carbonate, difluorination of 1,3-diketones could also be achieved by milling at 30 Hz for two hours.

These conditions were adapted to the fluorination of β-ketoesters. However, as these substrates were liquids, sodium chloride was added to the reaction mixture as a grinding auxiliary. Both mono- and di-fluorination were successful, again using LAG conditions to monofluorinate. However, in this case, LAG was found to enhance the reactivity.

Despite the interesting selectivity differences observed using LAG, it was perhaps surprising that in general this reaction manifold behaved reasonably predictably. Adapting a well-known reaction from solution to the ball mill seemed to behave approximately as expected. As this was also the first attempt at a mechanochemical process in the Browne group, it was especially notable and encouraging that during the initial investigations, the reaction proceeded fairly well. This demonstrates that it can be relatively straightforward to translate known processes to milling.

Further work in this area focused on further functionalization to more useful molecular scaffolds, by the mechanochemical synthesis of fluorinated heterocycles (See Chapter 3). In the future, it would be interesting to further investigate the physical cause of the enhanced selectivity observed under LAG conditions. If the origin of this can be established, then it may become possible to predict other scenarios where LAG could help improve a synthetic process. Further work to build a complete understanding would require collaborations across different fields of chemistry as expertise from physical, theoretical and solid state chemists would need to be combined to establish a sound underlying theory.

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3 Mechanochemical one-pot two step synthesis of fluorinated pyrazolones

3.1 Introduction

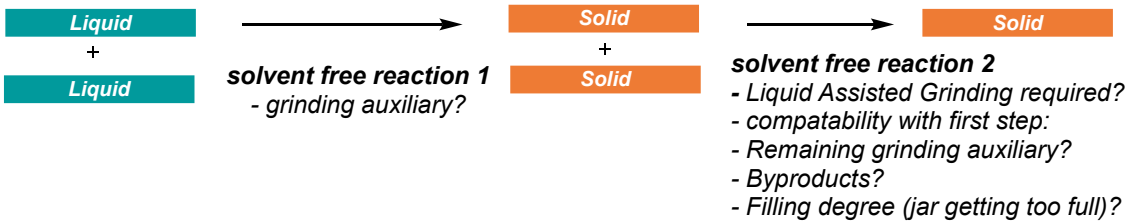
In order to further probe the applicability of mechanochemical methods to synthesis, a one-pot multistep process was envisaged. Having developed a process for the mechanochemical formation of C-F bonds, it was decided that one step would be a fluorination. Due to their prevalence in pharmaceutically active compounds, the overall aim would be to synthesise fluorinated heterocycles.

3.1.1 One-pot procedures and considerations

One-pot, multistep procedures are particularly efficient, with the same reaction vessel being used for all the transformations without intermediate purification or removal of side products from the reaction mixture. After one step is complete, the reagents required for the next step are simply added to the reaction mixture. The workup and purification is therefore only performed once, after the entire process has been completed.[1] This can significantly improve the process, requiring fewer processing steps. Intermediate purification steps can be time and resource consuming, generating significant quantities of waste, usually harmful solvents. When the side products of one reaction are not detrimental to the next desired reaction, then there is the possibility of performing the entire transformation as a one-pot process. The extension of one-pot procedures to mechanochemistry could offer further improved efficiencies and timesavings. Indeed, there are several examples of mechanochemical reactions having been performed either as one-pot multistep processes or as multicomponent reactions, in which all the reagents for every step are added at the start of the procedure (See chapter 1).[2]

When developing one-pot procedures, it is important to consider all of the components that will be present at each point and their compatibilities with subsequent steps. This therefore usually includes any unreacted starting materials, catalysts, side products and solvents. These can interfere with subsequent reactions, leading to unfavourable results such as unfavourable pH, catalyst poisoning or undesired reactivity. One of the main difficulties encountered during the development of one-pot multistep procedures is solvent compatibility between steps. In solution, it is usually necessary to maintain all of the components of a reaction dissolved in order for efficient mass transfer. When performing multiple reactions in a one-pot process, it would be unlikely for the optimum solvent for every step to be the same, so compromises are often required. However, in

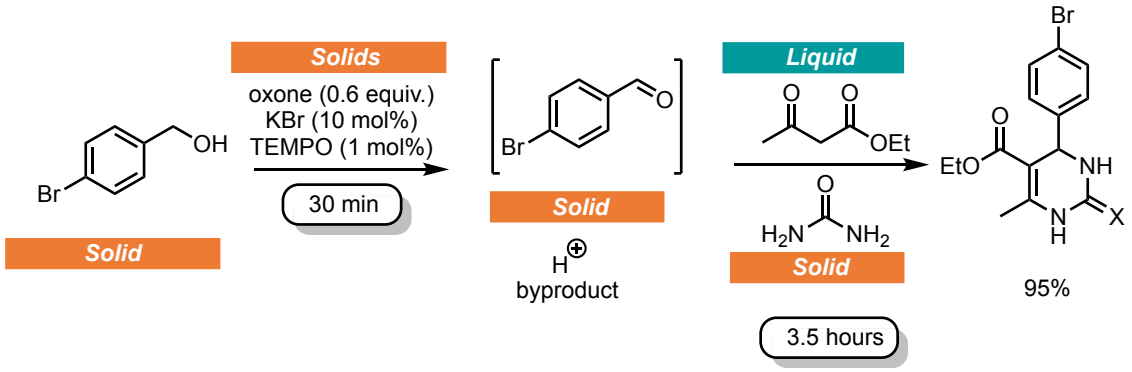
a mechanochemical process this solvent compatibility is not an issue, as reactions are performed under solvent free conditions.



Scheme 3.1 Some of the considerations relevant to one-pot mechanochemical procedures.

There are other considerations under mechanochemical conditions that are not usually important or even considered for reactions in solution (Scheme 3.1). The physical state of compounds can be important for good mixing and energy transfer in a ball mill. Liquids, for example, do not absorb kinetic energy as well as solids. A grinding auxiliary is often required in order for mechanochemical reactions between liquids to perform well. However, reactions frequently require the addition of several different reagents, each of which often will have a different physical form. When performing a series of transformations in a one-pot process, the possibility of the texture of the reaction mixture changing at each step is likely. This is known to significantly alter the kinetics of mechanochemical reactions.[3] Maintaining an optimal texture throughout is therefore important, such as by adding a grinding auxiliary. This could be very challenging in a one-pot procedure, since different quantities of grinding agent may be required for each step but there is no opportunity to remove material once it is inside the reaction vessel. Another consideration is the use of liquid assisted grinding (LAG), which can favourably alter the reactivity of one step, but may cause problems for another subsequent step. Like in solution one-pot procedures, the side products of each step remain in the reaction vessel for subsequent steps. These can have chemical influences, as previously discussed, but the extra consideration in a mechanochemical process is that these can act as grinding auxiliaries or LAG agents, whether desired or not, in subsequent steps.

A final potential limitation to one-pot, multistep mechanochemical processes lies with the filling degree. As discussed in chapter 1, how full the milling vessel is can significantly alter the performance of a reaction. By its very nature, during a one-pot procedure, material is added at each step but none is removed. Even if all the other considerations can be successfully addressed, ultimately there will be a limit to how many steps can be achieved as the milling vessels will become too full, and the energy input from the ball(s) will become insufficient for effective reactivity.



Scheme 3.2 Development of the one-pot, two step mechanochemical synthesis of dihydropyrimidones.

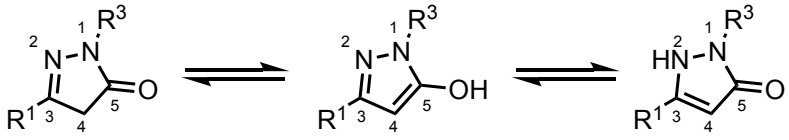
A one-pot, two step mechanochemical reaction for the formation of dihydropyrimidones was developed by Mal and co-workers, as briefly described in chapter 1.[4] In this process, all of the reagents were solids, except for the ethylacetoacetate required for the second step (Scheme 3.2). No grinding auxiliary was therefore required in this process. The first step was the oxidation of the benzyl alcohol to the aldehyde. The reaction chosen made use of oxidation by catalytic KBr, which under these conditions can be oxidised to Br+ or Br radicals.[5] This process can result in over oxidation to the benzoic acid in solution, but under mechanochemical conditions it was found to be highly selective to the benzaldehyde. Choice of the exact mixture of reagents for this oxidation always resulted in a high performance of the first step, but the success of the second step was highly dependent on the exact conditions of the first step. Changing from TBAB as the bromide source to KBr was found to be important, as was decreasing the quantity of TEMPO to 1 mol%. This demonstrates the importance of controlling the side products of the first reaction in order for subsequent reactions to be successful. Ultimately, the authors were able to use a side product to their advantage, as acid is generated during the oxidation step. The second step is acid catalysed, so no additional acid had to be added for the second step.

In this chapter, the one-pot two step mechanochemical synthesis of fluorinated pyrazolones is reported. Optimisation of this procedure was challenging, mainly due to the different conditions required for each step and different physical state of the reagents.

3.1.2 Pyrazolones

Pyrazolones are the class of pyrazoles that are substituted with an oxygen atom. Like pyrazoles, they consist of two adjacent nitrogen atoms in a five membered unsaturated

heterocycle. One of these nitrogen atoms has a lone pair in conjugation with the π-system in the ring, analogous to in pyrrole. The other nitrogen atom has its lone pair oriented outside the ring in an sp_2 orbital, analogous to in pyridine. When the oxygen is in the 5 position, these pyrazolin-5-ones can exist in three tautomeric forms (Scheme 3.3).[6] These consist of an aromatic enol form **123**, a keto form **122** and a keto form that maintains both C=O and C=C double bonds (**124**). Although the enol form is aromatic, the keto form is observed to be the favoured tautomer in most cases. This is due to the formation of the strong C=O bond.

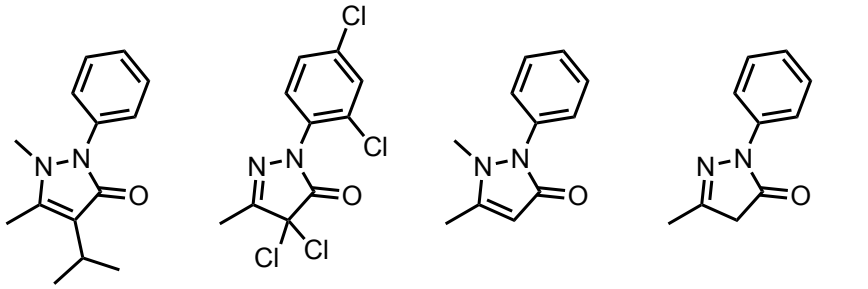


122 **123** **124**

Scheme 3.3 The three tautomers of pyrazolin-5-ones.

The general reactivity of pyrazolones can be explained by these tautomeric forms. Like pyrazoles, they are nucleophilic at C-4. If R^3 is a proton, they can also be nucleophilic at N-1, as well as at the oxygen. They are electrophilic at C-3 and C-5.

Pyrazolones are amongst the oldest class of synthetic pharmaceuticals, with the first synthesis of phenazone, an analgesic, reported in 1883.[7] Since then, a range of pyrazolone derived drugs have been developed (Scheme 3.4).[8, 9]



Propyphenazone *analgesic & antipyretic*

Telin *anticancer*

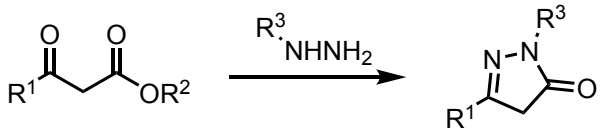
Phenazone *analgesic & antipyretic*

Edaravone *amyotrophic lateral sclerosis treatment*

Scheme 3.4 Examples of approved pyrazolone based drugs

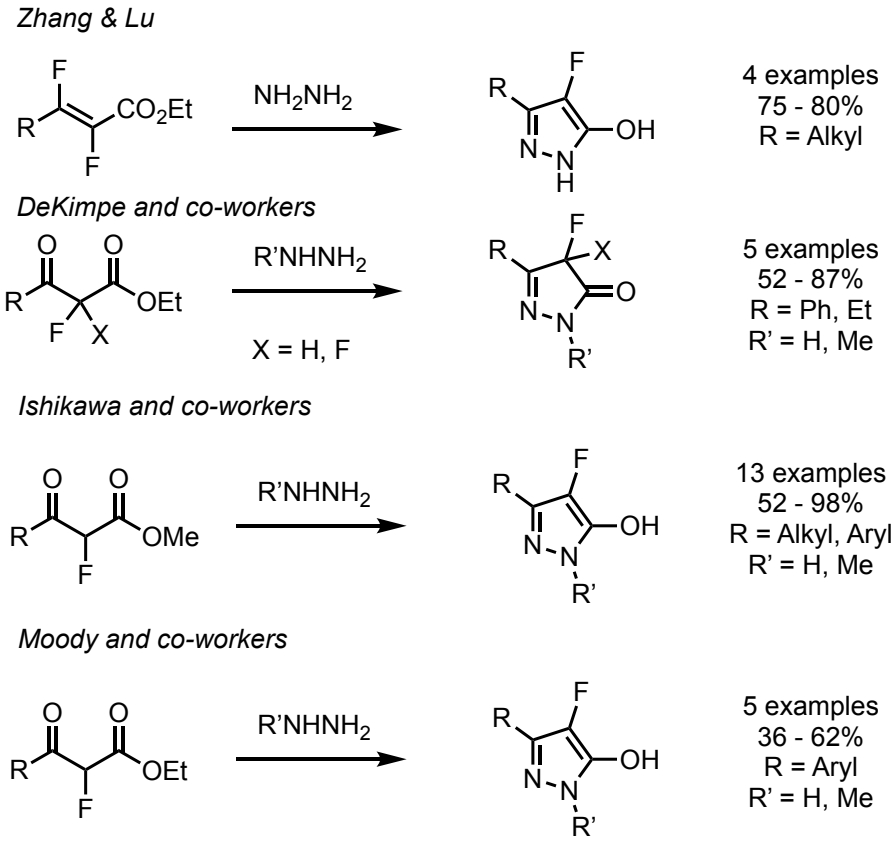
Pyrazolones are typically synthesised from the condensation of hydrazines with β-ketoesters (Scheme 3.5). This reaction is usually performed with an acid catalyst for long times at high temperatures, such as refluxing in acetic acid for three hours.[10-13]

Pyrazolone synthesis using a microwave reactor has also been reported to decrease the reaction time required to five minutes.[14]



Scheme 3.5 Synthesis of pyrazolones

Having previously discussed the potential advantages that can be achieved by the incorporation of fluorine into bioactive compounds, it was decided to attempt the one-pot two step synthesis of fluorinated pyrazolones. There are relatively few reports of fluorinated pyrazolones (Scheme 3.6). In 2000, Zhang and Lu reported the synthesis of monofluorinated pyrazolones by condensation of hydrazine with an unsaturated, fluorine-containing ester.[15]



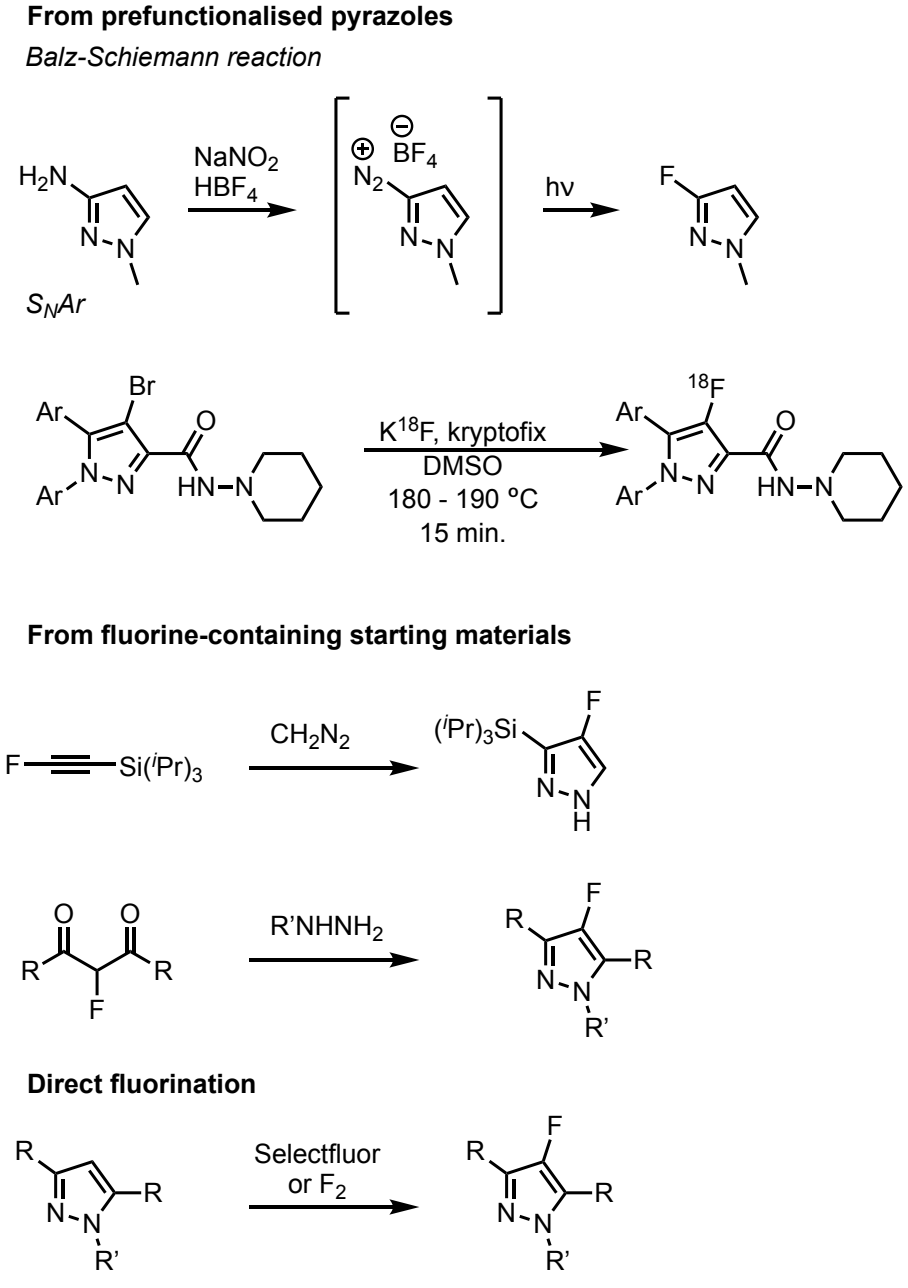
Scheme 3.6 Previous work on the synthesis of fluorinated pyrazolones.

Monofluorinated pyrazoles have also been reported by the Moody and Ishikawa groups, starting from the monofluorinated β-ketoester.[16, 17] In addition to their work on

synthesising monofluorinated pyrazolones, the DeKimpe group also reported the synthesis of difluorinated pyrazolones.[18]

All of these approaches require fluorine-containing starting materials, which can be problematic to obtain. How challenging it is depends on the commercial availability of the desired starting materials. This approach also does not allow an easy screening of fluorinated pyrazolones, as each target would require a new total synthesis from different fluorinated starting materials. Prior to the work in this chapter, there was no report on the direct fluorination of pyrazolones.

In order to develop an approach to the synthesis of fluorinated pyrazolones by direct fluorination, it is interesting to note the methods developed to date for the synthesis of fluorinated pyrazoles (Scheme 3.7). Fluorination at a later stage of the synthesis has been reported from prefunctionalised pyrazoles. The Balz-Schiemann reaction was reported in 1978 from an amine prefunctionalised pyrazole.[19] In this process, diazotisation is performed using sodium nitrite in the presence of fluoroboric acid. The intermediate diazonium salt then decomposes under photochemical conditions to release nitrogen gas, leaving an aryl cation, which is fluorinated by a tetrafluoroborate anion. Another example requiring the use of prefuncitonalised pyrazoles was the synthesis of an ^{18}F - labelled radiotracer.[20] This method made use of a brominated pyrazole which was fluorinated by an S_NAr process with $K^{18}F$. However, this S_NAr reaction also required an electron withdrawing substituent on the pyrazole, high temperatures and the synthesis of the required brominated pyrazole starting material.



Scheme 3.7 Examples of approaches for the synthesis of fluorinated pyrazoles.

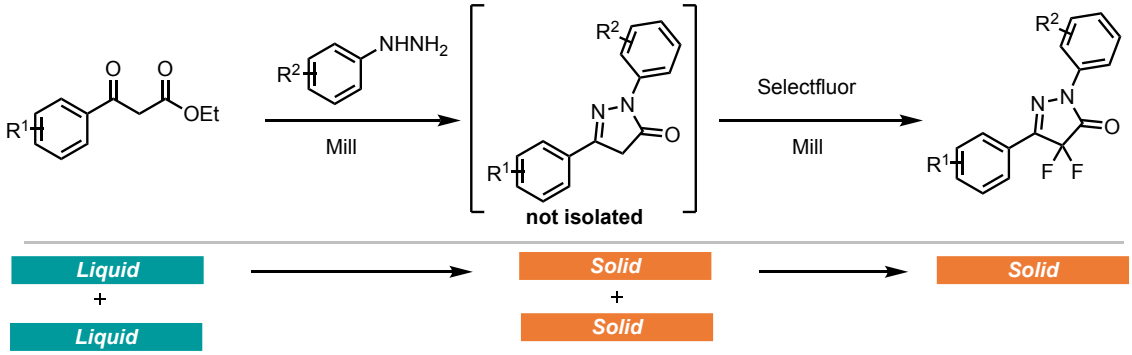
The other most common methods, as is the case for fluorinated pyrazolones, make use of fluorinated starting materials. The most straightforward starts from fluorinated 1,3-diketones.[21] Other methods have been developed, including cycloadditions of fluorine containing alkenes or alkynes with diazo compounds.[22-26] However, possibly the most straightforward synthesis of fluorinated pyrazoles is the direct fluorination. This approach takes advantage of the inherent nucleophilicity of pyrazoles, and can be performed with electrophilic fluorinating reagents, such as Selectfluor, or fluorine gas.[27-29] Given that pyrazolones are also nucleophilic at C-4, the direct fluorination of

pyrazolones could also be possible using Selectfluor or other electrophilic fluorinating reagents.

Given the previous fluorination in the ball mill using Selectfluor, it was decided to investigate the possibility of the direct fluorination of pyrazolones. This avoids the necessity to use fluorine-containing starting materials, or to synthesis prefunctionalised pyrazolones. A one-pot, two step process was proposed, synthesising the pyrazolone and then directly fluorinating without intermediate purification.

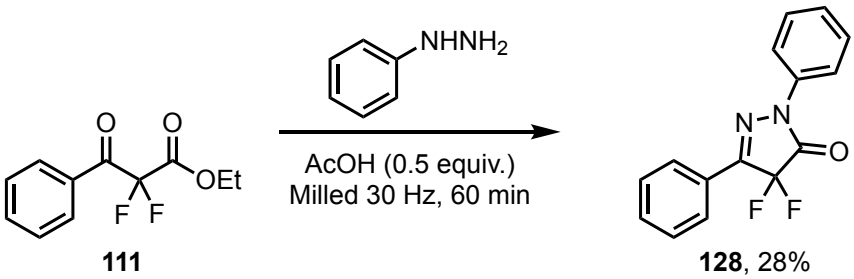
3.1.3 Development of one-pot process

In the envisaged process, there are several considerations that need to be addressed in order to ensure compatibility between both reaction steps (Scheme 3.8). Early investigations revealed that pyrazolone formation from fluorinated β-ketoesters was prohibitively slow.



Scheme 3.8 Envisaged one-pot, two step procedure.

Milling difluorinated β-ketoester **111** with phenylhydrazine and a catalytic amount of acetic acid for one hour formed the difluorinated pyrazolone **128** in 28% yield (Scheme 3.9). It was therefore decided to first synthesise the pyrazolone and then perform fluorination as the second step.



111 **128**, 28%

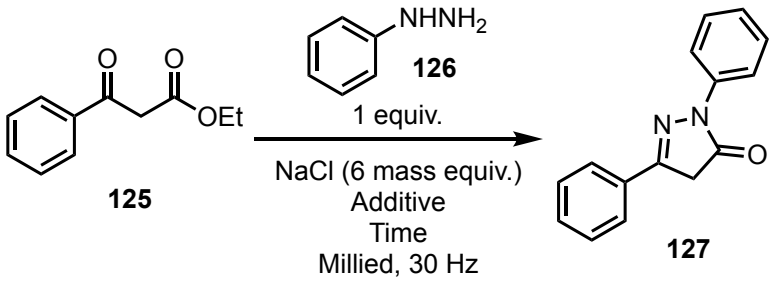
Scheme 3.9 Initial results on forming pyrazolone from fluorinated β-ketoester **111**.

It was proposed that the pyrazolone could be formed initially from the condensation of a β-ketoester with the desired hydrazine. These starting materials are both liquids, so a grinding auxiliary may be necessary for effective energy transfer. However, the pyrazolone product is a solid, so the texture of the reaction mixture will change as the reaction progresses. This could either be beneficial or detrimental, depending on the quantity of grinding auxiliary. Pyrazolone formation is usually performed under acidic conditions, so an acid may need to be added. The side product of this reaction is ethanol, which could lead to LAG effects, possibly interfering with the fluorination step. For the fluorination step, the starting materials are now both solid, so the presence of a grinding auxiliary from the first step may be detrimental to mixing. The compatibility of this second step with any other required additives remaining from the first step, such as acid, may also present challenges.

3.2 Optimisation of mechanochemical pyrazolone synthesis

Initial results established that under mechanochemical conditions, the condensation of phenylhydrazine hydrochloride with ethylbenzoylacetate was unsuccessful. However, on switching to the free hydrazine from the hydrochloride salt, reactivity was observed. The reagents required are therefore both liquids, which can have a significant effect on the performance of a mechanochemical reaction.

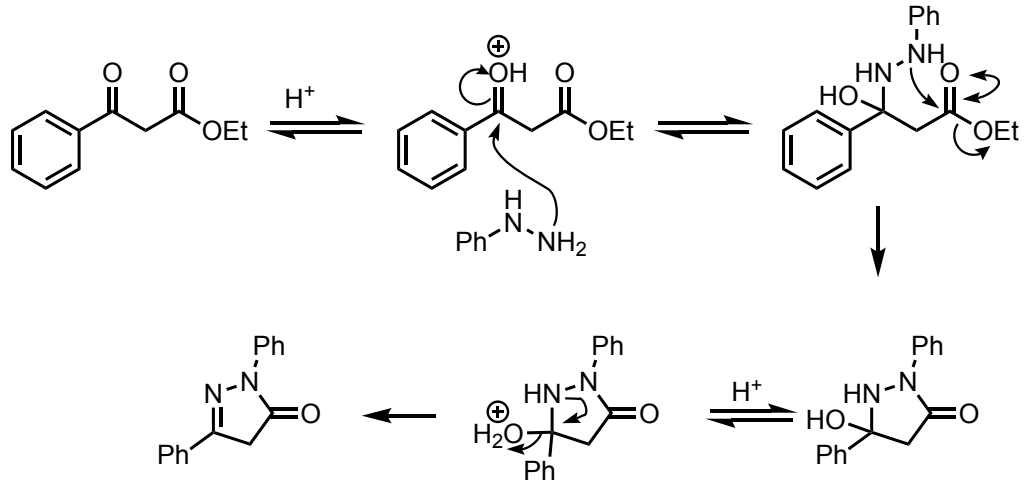
Table 3.1 Optimisation of acid additive. Thanks to William Nicholson for these results.



Entry	Additive (equiv.)	pKa	Time / min	Yield[a]
1[b]	-	-	10	20%
2	-	-	10	66%
3	-	-	40	53%
4	-	-	60	53%
5[c]	-	-	1440	58%
6	HCl (0.5)	-7	10	43%
7	Tosic acid (0.5)	-2.8	10	37%
8	Oxalic acid (0.5)	1.2	10	22%
9	Citric acid (0.5)	3.1	10	38%
10	Benzoic acid (0.5)	4.2	10	88%
11	Acetic acid (0.5)	4.7	10	88%

[a] Determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard.
[b] Mechanochemical reaction with no NaCl. [c] solvent based reaction: heating under reflux in toluene, no NaCl.

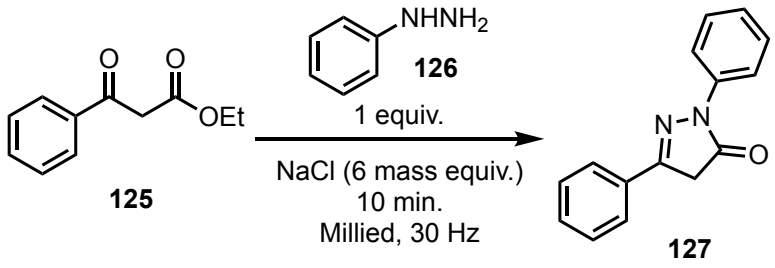
Milling **125** and **126** for ten minutes resulted in a poor yield (Table 3.1 Entry 1), so the addition of a grinding auxiliary was investigated. It was found that on addition of sodium chloride, the yield was improved to 66% (Table 3.1, Entry 2). This is likely due to the improved energy transfer between the ball and solids compared to between the ball and liquids. Increasing the reaction time led to a slight decrease in yield, suggesting degradation of the product (Table 3.1, Entries 3 & 4). The same reagents (**125** and **126**) were also subjected to reaction in toluene under reflux, and after 24 hours, the yield of the desired pyrazolone **127** was close to that achieved under mechanochemical conditions after only 10 minutes (Table 3.1, Entry 5). This demonstrates the enhanced reactivity of this reaction manifold under mechanochemical conditions.



Scheme 3.10 Proposed mechanism of acid catalysed pyrazolone formation.

As pyrazolone formation is normally conducted under acidic conditions, a range of acids were then screened (Table 3.1, Entries 6 - 11). Acidic conditions will promote the initial attack of the hydrazine to the β-ketoesters by protonating the carbonyl, making it more electrophilic (Scheme 3.10). A variety of both solid and liquid acids were tested, as a solid acid could act as a grinding auxiliary for this reaction between liquids. It was observed that there was a general trend of improved yields for weaker acids, possibly due to acid promoted degradation of the starting material or products. Interestingly, both solid benzoic acid and liquid acetic acid gave the same yield. The envisioned second step of the process (fluorination) is thought to be enhanced by base so the weakest acid tested (acetic acid) was used for subsequent optimisation.

Table 3.2 Optimisation of quantity of acid added on pyrazolone formation. Thanks to William Nicholson for these results.



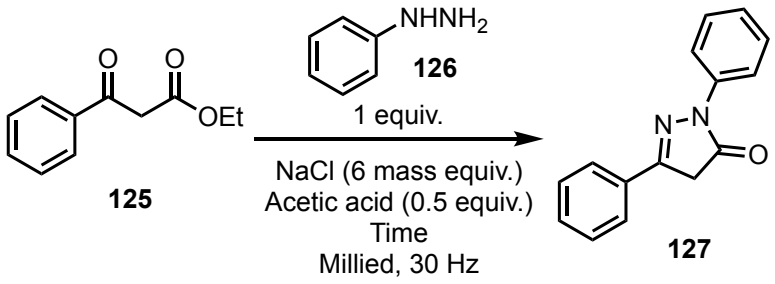
Entry	Equiv. Acetic acid	Yield[a]
1	0.08, 5 µL	75%
2	0.5, 30 µL	88%
3	1.7, 100 µL	97%
4	4.2, 250 µL	73%

Having established that acidic conditions with acetic acid were optimal, the effect of the quantity of acid used was investigated (Table 3.2).

It can be seen that there is an increase in yield up to the addition of 100 µL of acetic acid (Table 3.2, Entry 3), when the reaction is complete, with 97% yield of the desired pyrazolone **127** obtained. However, increasing the quantity of acid further, to 250 µL, caused a decrease in the yield. When deciding which conditions to proceed with, in the optimisation of a normal reaction, entry 3 would be chosen as it has the highest yield. In this case, where a one-pot process was being developed, it is important to consider compatibility with the other step in the process. As previously mentioned, the fluorination is likely to be inhibited by acid, so the smallest quantity of acid with a high yield was chosen as a compromise (Table 3.2, Entry 2).

In order to improve the yield but keep conditions compatible with the second step, further optimisation was performed, investigating the effect of reaction time (Table 3.3).

Table 3.3 Effect of reaction time on mechanochemical pyrazolone formation. Thanks to William Nicholson for these results.



Entry	Time / min	Yield[a]
1	10	88%
2	20	86%
3	40	97% (92%[c])
4	60	97%
5	120	97%
6[b]	1440	80%

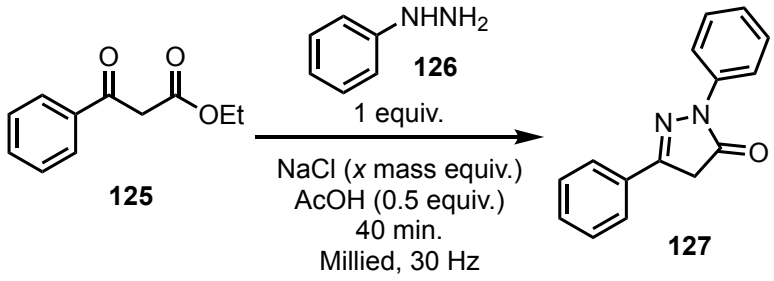
[a] Determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard.
[b] Solvent based reaction: heating under reflux in toluene, no NaCl.
[c] Isolated yield

Maintaining a constant quantity of acid and varying the reaction time showed that the reaction was complete after 40 minutes in the ball mill (Table 3.3, Entry 3). Longer

reaction times did not improve the yield of pyrazolone **127**. Therefore, optimal conditions for the first step had been established; milling β-ketoester **125** with hydrazine **126** and 0.5 equivalents of acetic acid for 40 minutes using sodium chloride as a grinding auxiliary. A final comparison to these conditions in solution was performed (Table 3.3, Entry 6). On heating β-ketoester **125** with hydrazine **126** and acetic acid in refluxing toluene, it was found that after 24 hours, 80% of the pyrazolone product was obtained. These reaction conditions are inferior to the conditions required in the ball mill, resulting in a poorer yield after significantly longer reaction time.

With the conditions established for a high yield of the desired pyrazolone, the compatibility of these conditions with the fluorination step was considered. One such compatibility issue could be the presence of a grinding auxiliary after the first step. It was therefore investigated whether the quantity of grinding auxiliary could be decreased without significantly affecting the yield of pyrazolone formation (Table 3.4).

Table 3.4 Investigation into quantity of grinding auxiliary. Thanks to William Nicholson for these results.



Entry	NaCl *x* mass equiv.	NaCl / g	Yield[a]
1	6	1.8	97%
2	5	1.5	91%
3	4	1.2	91%
4	3	0.9	82%
5	2	0.6	67%
6	1	0.3	92%

[a] Determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard.

It was found that on decreasing the quantity of sodium chloride, in general the yield of the reaction was poorer (Table 3.4, Entries 1-5). Interestingly, when decreasing the quantity further from 0.6 g to 0.3 g, the yield dramatically increased. This suggests a significant change in the texture of the reaction mixture, leading to a faster reaction.

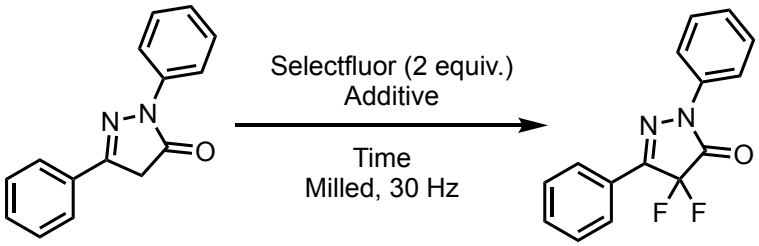
However, the highest yield was still obtained for 6 mass equivalents of grinding auxiliary. This was the quantity therefore chosen for further experiments.

With optimised conditions for mechanochemical pyrazolone formation in hand, attention was turned to optimisation of the fluorination step. It was important to bear in mind the compatibility of conditions between the steps, as this is crucial for the successful development of a one-pot process.

3.3 Optimisation of mechanochemical pyrazolone fluorination

After isolating pure pyrazolone **127**, the conditions required for the fluorination step were probed. Notably, the difluorinated pyrazolone **128** was observed under all reaction conditions attempted, with no monofluorinated pyrazolone detected. The fluorination of the monofluorinated intermediate must therefore be faster than the initial monofluorination.

Table 3.5 Optimisation of pyrazolone fluorination. Thanks to William Nicholson for these results.

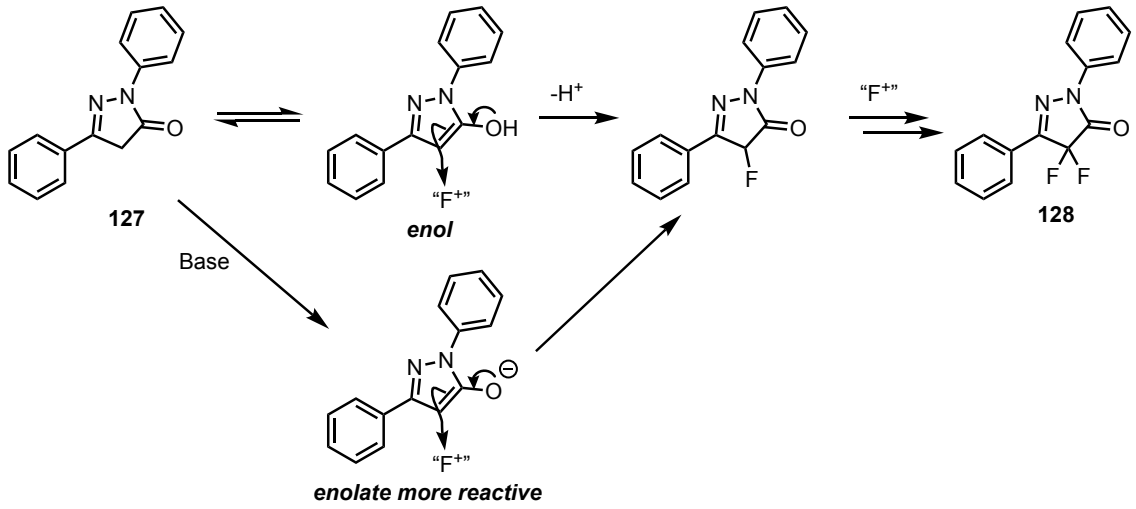


127 **128**

Entry	Additive (equiv.)	Time / min	Yield[a]
1	-	10	11%
2	-	30	41%
3	-	60	83%
4	-	120	95%
5	-	180	94%
6	Na_2CO_3 (1.0)	10	20%
7	Na_2CO_3 (1.0)	30	85%
8	Na_2CO_3 (1.0)	60	100%
9	NaCl (6.0)[b]	120	68%
10	Acetic acid (0.5)	120	75%
11	Acetic acid (0.5), NaCl (6.0)[b]	120	52%
12	NaCl (6.0)[b], Na_2CO_3 (1.0)	60	100%

[a] Determined by ^{19}F NMR spectroscopy. [b] Mass equivalents NaCl.

Initially, pyrazolone **127** was subjected to a range of milling times in the presence of two equivalents of Selectfluor (Table 3.5, Entries 1 - 5). It was found that the reaction was finished after milling at 30 Hz for two hours, yielding the difluorinated product **128** in 95% yield (Table 3.5, Entry 4). It was hypothesised that the rate of this process would be enhanced by the addition of a base. The proposed mechanism requires tautomerisation to the reactive enol form, which can then nucleophilically attack Selectfluor, leading to the monofluorinated intermediate (Scheme 3.11). However, in the presence of a base, the enolate can be obtained, which will be a more reactive nucleophile than the enol.

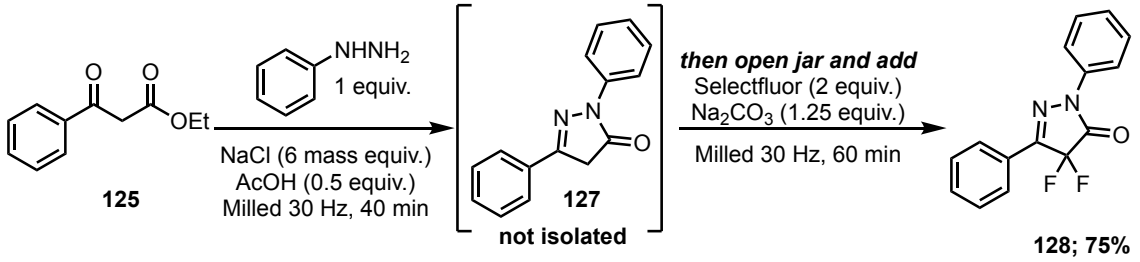


Scheme 3.11 Proposed mechanism for the fluorination of pyrazolone **127** by Selectfluor.

Therefore, investigation into the addition of a base revealed that the rate of difluorination was enhanced, affording complete reaction after one hour with one equivalent of sodium carbonate (Table 3.5, Entries 6 - 8). As a one-pot process was envisaged, the other additives present in the optimised conditions for the first step (pyrazolone formation) were tested for compatibility with the fluorination step (Table 3.5, Entries 9 - 11). Given that pyrazolone **127** is a solid at room temperature, whereas the starting materials for the first step are liquids, the grinding auxiliary may inhibit the second step (fluorination). It was found that the addition of acetic acid, sodium chloride or both had a deleterious effect on the yield. However, it was found that on adding sodium carbonate and sodium chloride to the reaction, the yield could be recovered so that the fluorination was complete in one hour (Table 3.5, Entry 12). With the optimal conditions now established for each step in isolation, the two steps could now be combined to a one-pot, two step procedure.

3.4 Development of a one pot two step process

Having established that the optimised conditions for the first step required acid, and that the second step required base, is was clear that a compromise was required in order to obtain an optimal one-pot two step process. Under a one-pot procedure, it was therefore decided to investigate the addition of 1.25 equivalents of base with the other reagents for the second step. This is in order to neutralise the 0.5 equivalents of acid present from the first step and leave one equivalent remaining for the second step. The side product of the neutralisation, carbon dioxide, should not interfere with the fluorination reaction. However, the release of gas could be problematic on larger scales. Pleasingly, this process was successful, and so the optimised conditions for the one-pot two step process are shown in Scheme 3.12.

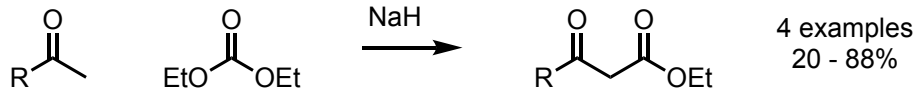


Scheme 3.12 Optimised conditions for the one-pot two step process

After milling β-ketoester **125** for 40 minutes with phenylhydrazine in the presence of sodium chloride and acetic acid the jars were opened. Selectfluor and sodium carbonate were then added directly, and the reaction mixture was milled for a further 60 minutes to yield the difluorinated pyrazolone **128** in 75% isolated yield. Having developed this operationally simple, one-pot two step mechanochemical synthesis of difluorinated pyrazolone **128**, the scope of this process was investigated.

3.5 Substrate scope

A range of β-ketoesters were synthesised from the corresponding acetophenones by treating with sodium hydride and diethyl carbonate (Scheme 3.13).

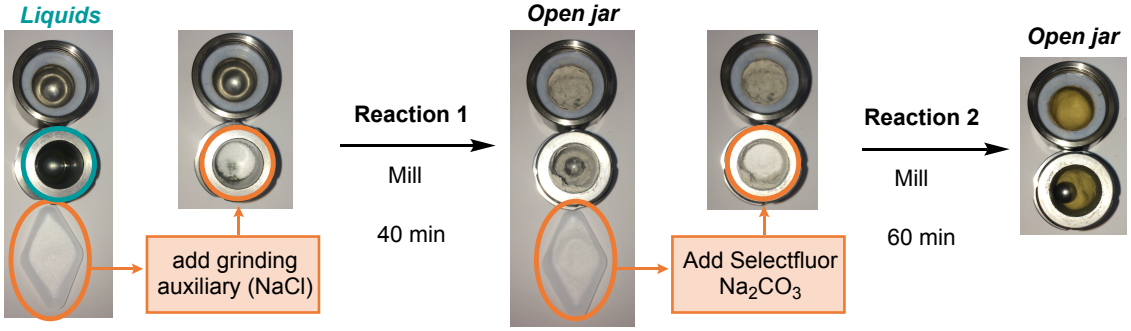


Scheme 3.13 Synthesis of β-ketoesters from acetophenones.

With a range of β-ketoesters in hand, they were subjected to the optimised one-pot two step conditions. Good yields of the novel fluorinated pyrazolones were achieved, with

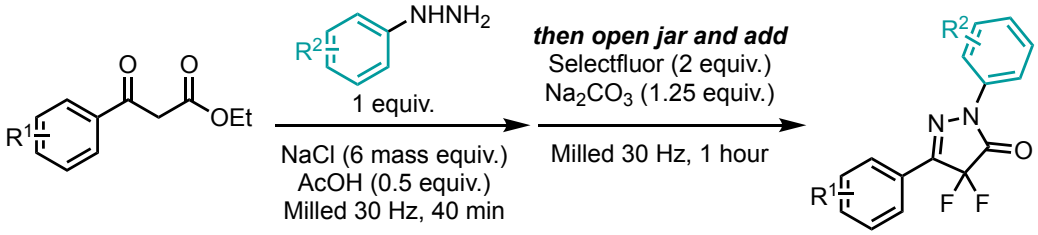
both electron-donating and withdrawing groups tolerated (Scheme 3.15). However, a poorer yield was obtained for the electron poor trifluoromethyl substituent **132**. This may be due to the electron withdrawing effect on the nucleophilic carbon centre, decreasing the reactivity towards Selectfluor. A range of substituted hydrazines were also tested, with good yields obtained for several substrates. Again, trifluoromethyl substituted hydrazine performed poorly (**135**). In this case, a ^{19}F NMR of the crude reaction mixture was taken after the pyrazolone formation step, with a conversion of only 41% measured. This suggests that the cause of the lower yield in this example is the pyrazolone formation step.

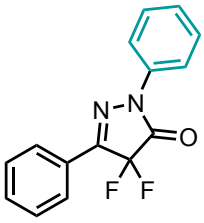
Finally, the difluorinated derivative of edavarone **139** was synthesised using this procedure, albeit in a low yield of 30%. This is the only example without an aromatic group as the substituent and it features another enolisable position, perhaps leading to unwanted side reactions. It was also possible to synthesise the monofluorinated pyrazolone **140** using one equivalent of Selectfluor by blocking the α position on the starting β-ketoester with a methyl group.



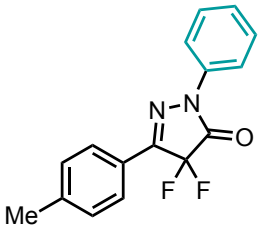
Scheme 3.14 Photographs of practical procedure.

Overall, this procedure is operationally simple (Scheme 3.14). Sodium chloride is added to the liquid starting materials, and the pyrazolone formation (step 1) is complete after milling for 40 minutes. Then, the jars are simply opened, Selectfluor and sodium carbonate added, the jars closed and milled again.

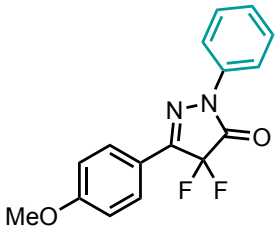




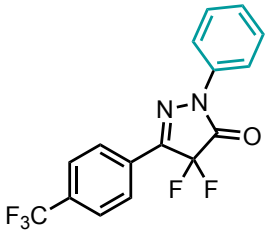
129; 75%



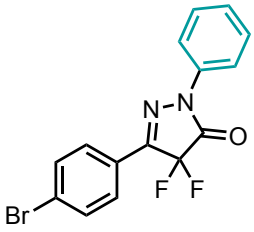
130; 83%



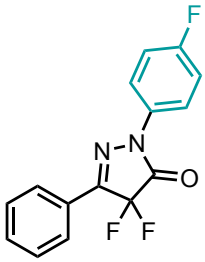
131; 74%



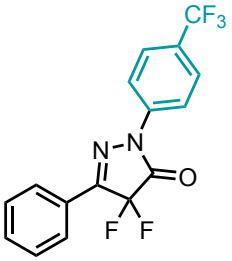
132; 40%



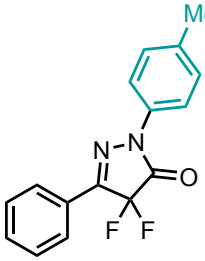
133; 53%



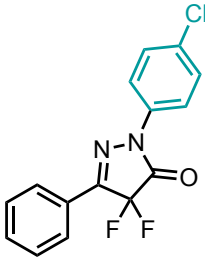
134; 67%



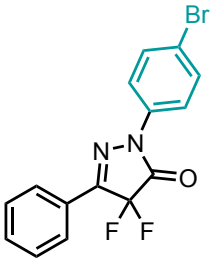
135; 37%



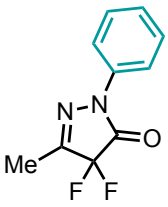
136; 59%



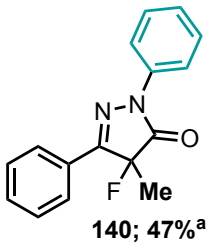
137; 67%



138; 70%



Edaravone derivative
139; 30%



140; 47%[a]

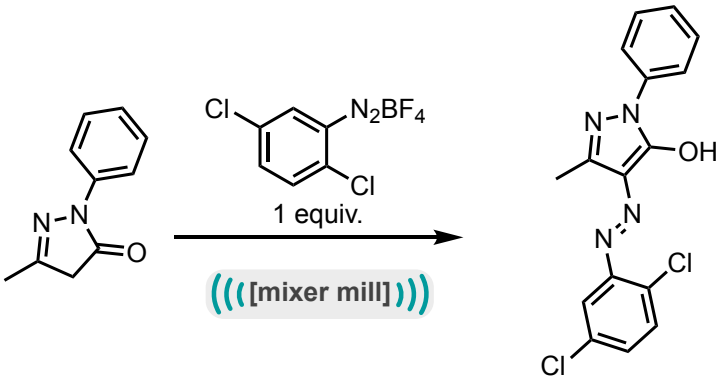
[a] 1 equiv. Selectfluor used

Scheme 3.15 Substrate scope for one-pot synthesis of fluorinated pyrazolones.

3.6 Conclusions and Outlook

A one-pot, two step mechanochemical synthesis of fluorinated pyrazolones has been developed. The first step was the formation of the pyrazolone, and the second step was the fluorination using Selectfluor. Determining optimal reaction conditions to be compatible with both steps was challenging, with the first step requiring acid and the second step requiring base. Also relevant to the compatibility was the physical state of the materials for each step, with the overall starting materials being liquids, but making a solid pyrazolone. These challenges were successfully overcome by using an excess of base in the second step, to neutralise the acid remaining from the first step, and by using sodium chloride as a grinding auxiliary.

The successful development of this procedure and its application to a small range of substrates further demonstrates the possibility of applying mechanochemical methods to synthetic challenges. In particular, this shows that efficient one-pot processes are also possible under ball milling. Further developments to this procedure could include mechanochemical electrophilic pyrazolone functionalisation with a variety of electrophiles. For example, the synthesis of dyes is one possible application, which could benefit from mechanochemical synthesis. The industrial dye, pigment yellow 10, could be synthesised under the method developed here, using a diazonium salt as the electrophile in place of Selectfluor (Scheme 3.16).



Pigment Yellow 10

Scheme 3.16 Possible mechanochemical synthesis of a dye.

This procedure could also be further adapted in order to synthesise other heterocycles and use other electrophiles. For example, pyrazoles could be synthesised simple by using 1,3-diketones as substrates instead of β-ketoesters or 1,4-diketones to synthesise pyrroles by reaction with amines.

This systematic development of this one-pot mechanochemical process also systematically demonstrates the considerations that need to be taken in any such process. It is therefore likely that other one-pot, multistep procedures performed in ball mills will continue to be investigated.

3.7 References

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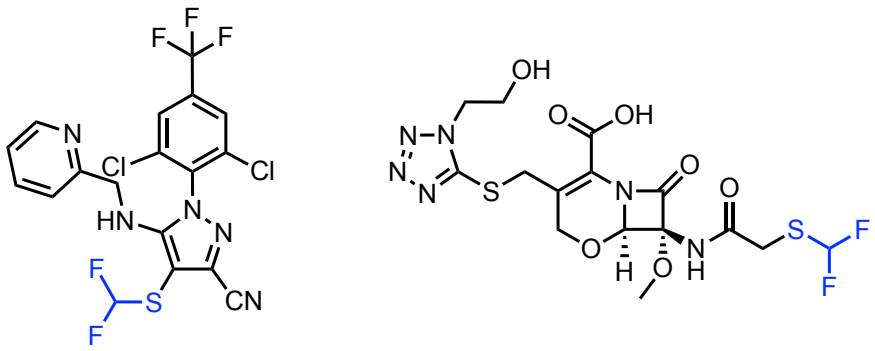
4 Using mechanochemistry to alter reaction pathway

4.1 Introduction

Having established that fluorination can be successfully achieved in the ball mill, and further that one-pot multistep processes are also possible, attention was turned to the synthesis of potentially bioactive difluoromethyl thioethers. Methyl thioethers are rarely found in biologically active materials, due to their poor metabolic stability. *In vivo*, they are readily oxidised to the corresponding sulfones and sulfoxides, which are then easily removed before reaching their biological target. In order to improve this, the trifluoromethyl analogue has been used and features in several bioactive compounds, with many synthetic methodologies reported to synthesise trifluoromethylthioethers.[1] Following on from this, the difluoromethylthioether (-SCF_2H) group has been studied recently as it possesses interesting properties from a drug design perspective. It has a better metabolic stability than methylthioethers, and is lipophilic. However, it also features a relatively acidic proton, which is able to undergo hydrogen bonding.[2] The difluoromethylthioether motif features in a number of commercially available bioactive compounds (Scheme 4.1).

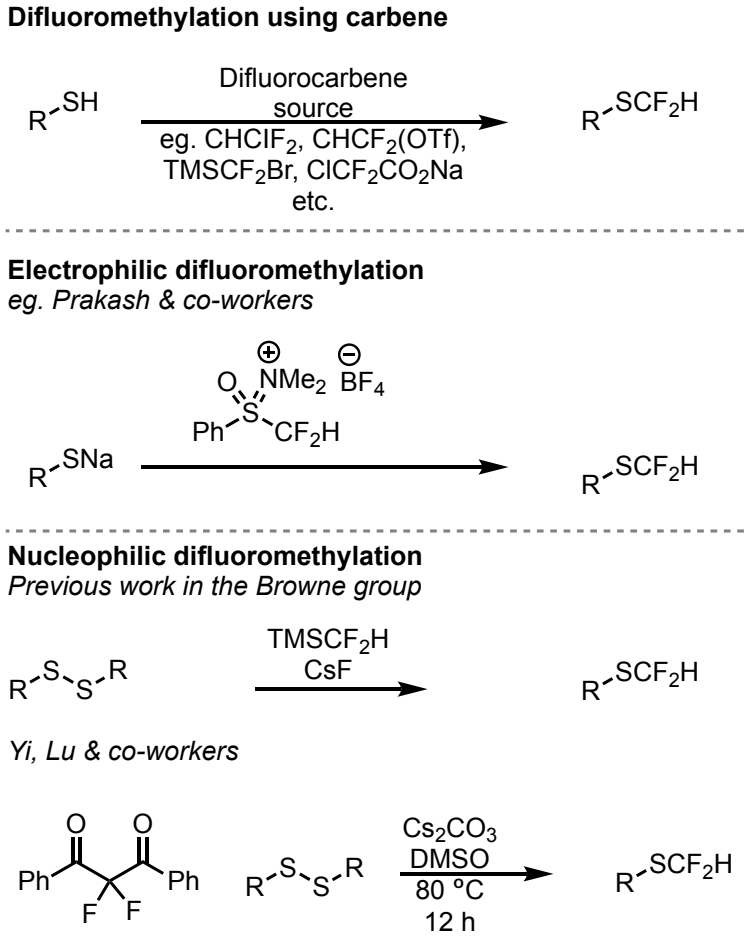


pyriprole
insecticide

flomoxef
antibiotic

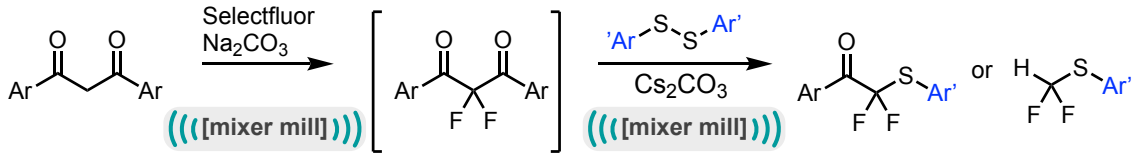
Scheme 4.1 Examples of bioactive compounds containing the -SCF_2H group.

Consequently, there has been significant interest in developing methods for the synthesis of the -SCF_2H moiety, including previous work in the Browne group.[3, 4] These methods generally involve difluoromethylation of a sulfur-containing substrate (Scheme 4.2). The most common methods make use of the reaction of thiols with difluorocarbene. However, many of the difluorocarbene precursors are ozone-depleting species, so alternative methods have been developed.



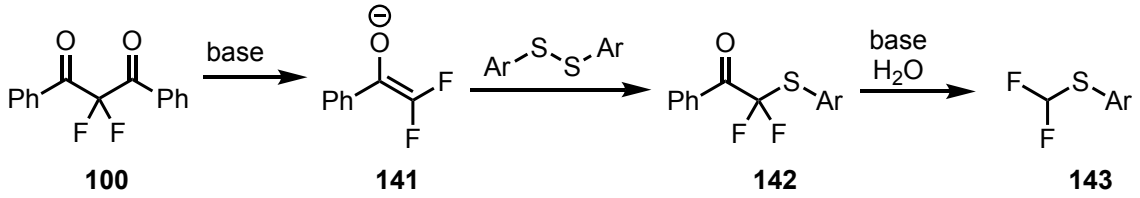
Scheme 4.2 Examples of methods for the synthesis of difluoromethylthioethers.

Another important method makes use of electrophilic sources of the difluoromethyl group, such as reagents developed by the Prakash or Hu groups.[5,6] A further alternative approach uses the nucleophilic difluoromethylation of disulfides. For example, previous work in the Browne group, as well as by Goossen and co-workers uses $TMSCF_2H$.[4, 7] There are also further examples where the entire -SCF_2H group is transferred, making use of reagents such as organometallic [M]-SCF_2H species.[3] An interesting nucleophilic source of the difluoromethyl group was reported by Yi, Lu and co-workers in 2016.[8] It was found that on treating a difluorinated 1,3-diketone with cesium carbonate in the presence of disulfides at 80 °C for 12 hours, the corresponding difluoromethylthioether could be obtained. Given the previously described optimised method for the mechanochemical synthesis of such fluorinated dicarbonyls (Chapter 2), and encouraged by the successful development of a one-pot, two-step mechanochemical process (Chapter 3), it was envisaged that such a multistep mechanochemical synthesis of biologically useful difluoromethylthioethers could be developed (Scheme 4.3).



Scheme 4.3 Proposed one-pot, two-step mechanochemical synthesis of difluorinated thioethers.

The mechanism for this transformation as proposed by Yi, Lu and co-workers begins with the base mediated fragmentation of difluorinated diketone **100** (Scheme 4.4).

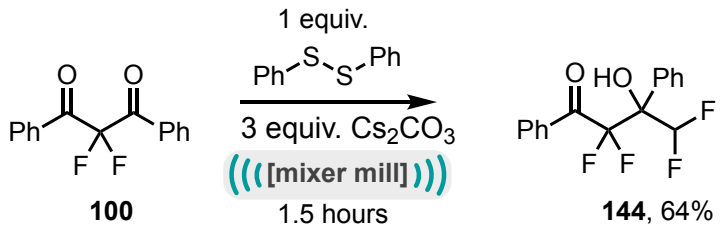


Scheme 4.4 Mechanism as proposed by Yi, Lu and co-workers.

The proposed product of this fragmentation is the difluorinated enolate **141**, which can then attack the electrophilic disulfide, forming **142**. It is then suggested that at high temperature or longer reaction times, a further fragmentation occurs, mediated by base and water, to yield the difluoromethylthioether **143**.

4.2 Initial results

Preliminary results demonstrated that on milling 0.25 millimoles of difluorinated diketone **100** with cesium carbonate and phenyl disulfide in the mixer mill at 30 Hz for 90 minutes, the starting material **100** was consumed (determined by ^{19}F NMR spectroscopy). However, the major product was determined to be **144** (Scheme 4.5).



Scheme 4.5 Preliminary results on the mechanochemical reaction of **100**.

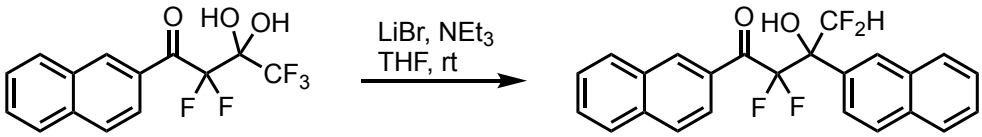
This is in stark contrast to the reactivity reported in DMSO solution by Li, Yu and co-workers and suggests that the use of mechanochemistry is significantly altering the reactivity.

Given the different, potentially reactive intermediates involved, it is reasonable that a change in reaction environment could give rise to different reactivity. It has previously been demonstrated that by switching from solution to mechanochemical conditions can lead to a change in the thermodynamics. Belenguer *et al.* reported that for reversible disulfide metathesis, the position of equilibrium was altered significantly in the ball mill.[9] This means that the thermodynamic product of a reaction can be altered using mechanochemistry. It was suggested that this difference was due to the contribution of crystal lattice enthalpy to the overall thermodynamics of the system. As mechanochemical reactions do not typically contain solvent, crystals of the different species can form. These crystallisation events will contribute to an extra stabilisation of certain species that will not occur in solution, where crystals would not form. However, the exact values of this extra stabilisation by crystallisation are not easy to predict.

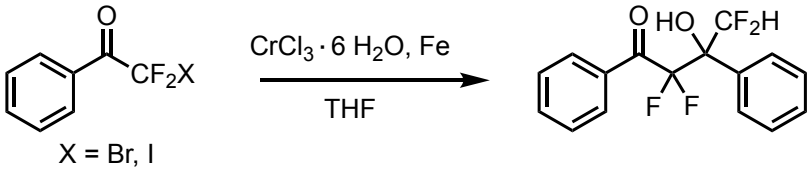
It has also been reported that changing from solution to mechanochemical conditions can lead to a significant change in the kinetic profile of a reaction.[10] James and co-workers reported differences in the kinetics of a Knoevenagel condensation between the reaction in solution and under mechanochemical conditions. The differences observed were attributed to a change in the texture of the reaction mixture.

The fragmentation and self-aldol reactivity observed in this attempted difluoromethyation under mechanochemical conditions has been previously observed in solution, though from different starting materials (Scheme 4.6).

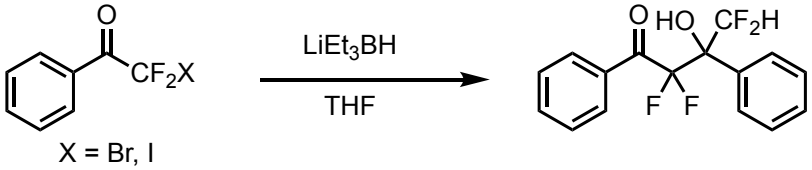
Colby and co-workers



Chai



Wu and co-workers



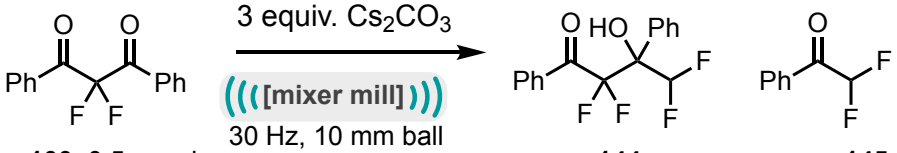
Scheme 4.6 Previously reported syntheses of hydroxyketone motifs.

Colby and co-workers reported generation of the difluorinated enolate by fragmentation and the loss of a trifluoroacetate group. This enolate was then trapped by aldol reaction with aldehydes. However, the self-aldol reaction was observed as a side reaction during development of this method when the naphthyl derivative was used.[11] In 1999, it was reported by Chai that the same difluoroenolate could be prepared by loss of a halide, promoted by a bimetallic Cr(III)/Fe system. It was suggested that radical processes were involved in the mechanism.[12] The same transformation was reported in 2017 by Wu and co-workers, who made use of lithium triethylborohydride to generate the difluoroenolate and also observed the self-aldol reaction product.[13] However, there currently exists no report of the formation of **144** from the difluorinated diketone **145**.

4.2.1 Reaction time

Having observed this different behaviour under ball milling, it was decided to optimise the reaction. Initially, the reaction time was investigated in the absence of disulfide (Table 4.1).

Table 4.1 Optimisation of reaction time.



100, 0.5 mmol **144** **145**

Entry	Time / min.	Yield 144[a]	Yield 145[a]
1	30	40%	32%
2	60	55%	23%
3	120	19%	44%
4	180	33%	34%

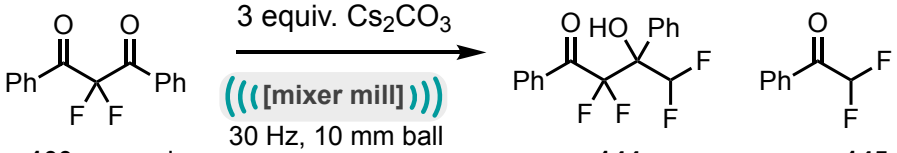
[a] Determined by ^{19}F NMR using trifluorotoluene as internal standard.

In all cases, both aldol product **144** and difluorinated ketone **145** were obtained. The highest yield of **144** was obtained after milling for one hour (Table 4.1, Entry 2). Milling for longer times did not improve the overall yield of the reaction, however the ratio of **144** : **145** changed, favouring ketone **145** after longer times. For further investigation of reaction conditions, 60 minutes was chosen as the milling time.

4.2.2 Reaction scale

The next variable to be investigated was the scale of the reaction, which can have a significant effect on the outcome of the reaction. Filling the jars to different degrees can significantly alter the trajectory of the ball bearings and the texture of the reaction mixture, leading to different mixing and energy transfer.

Table 4.2 Optimisation of reaction scale. Thanks to Michael Brand for these results.



100, *x* mmol **144** **145**

Entry	*X* / mmol.	Total mass of reagents / g	Yield 144[a]	Yield 145[a]
1	0.25	0.309	76%	14%
2	0.50	0.618	55%	23%
3	0.75	0.927	43%	28%
4	1.00	1.236	30%	36%

[a] Determined by ^{19}F NMR using trifluorotoluene as internal standard.

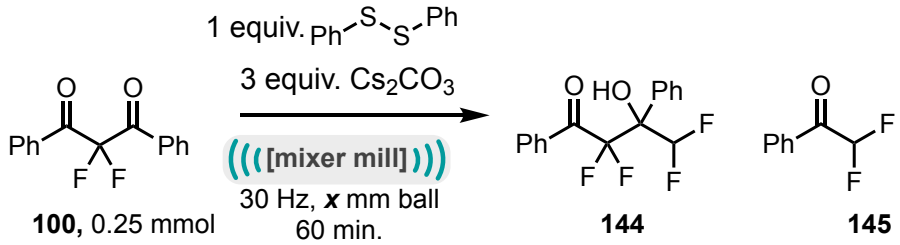
It can be seen that the scale of the reaction does indeed have a significant effect on the outcome. The highest yield of **144** was obtained for the smallest scale (Table 4.2, Entry 1), with a clear trend of decreasing yield on increasing the scale of the reaction. This could be due to the energy imparted by the collisions of the balls with the reagents. As

the jar is filled with more material, the ball is blocked from moving freely and may be impeded and slowed, leading to less energy being transferred. A scale of 0.25 mmol was chosen for subsequent reactions.

4.2.3 Ball size and quantity

The nature of the ball was the next parameter to be investigated. Phenyl disulfide was included at this point in order to test that the selectivity difference originally observed between milling and the reaction in solution (Scheme 4.5) was still holding true.

Table 4.3 Effect of size and quantity of milling balls on reaction. Thanks to Michael Brand for these results.



Entry	Ball size, *x* mm (g)	Quantity	Yield 144[a]	Yield 145[a]
1	7 (1.4)	1	35%	14%
2	7 (1.4)	2	40%	32%
3	10 (4.2)	1	88% (72%[b])	10%
4	10 (4.2)	2	45%	3%
5	14 (11.8)	1	70%	9%

[a] Determined by ^{19}F NMR spectroscopy using trifluorotoluene as internal standard. [b] Isolated.

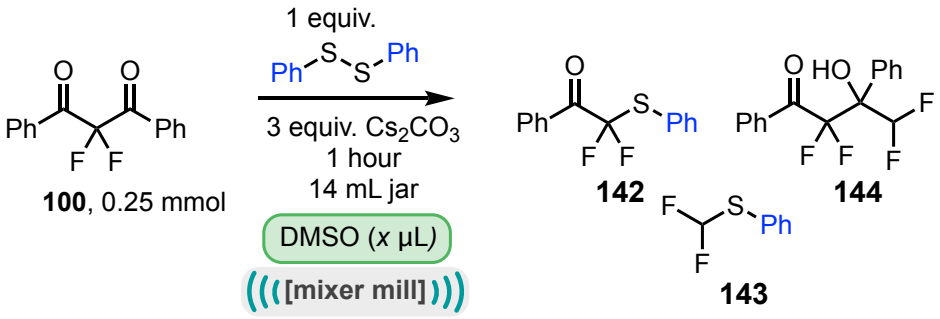
Interestingly, after adding disulfide to the reaction mixture, the yield of **144** was improved further from 76% (Table 4.2, Entry 1) to 88% (Table 4.3, Entry 3), isolating 72% after purification by flash column chromatography. As the disulfide was also obtained unchanged after the reaction, this suggests that phenyl disulfide may be acting as a grinding auxiliary, possible leading to a better yield by improving mixing and energy transfer. In general, on changing the size of the ball in the reaction, the yield increases with ball size, to a maximum using one 10 mm ball (Table 4.3, Entry 3). Increasing the ball size further led to a decrease in yield (Table 4.3, Entry 5), possibly due to degradation of the product. The higher the mass of the ball, the more kinetic energy it will possess prior to colliding with the reagents, so the more energy will be input into the reaction mixture, leading to a faster reaction. However, the larger diameter of a ball with a higher mass, the less space available in the jar for effective mixing. When increasing the number of balls the yield decreased significantly (Table 4.3, Entries 2 & 4). The balls are not able to pass each other, so will disrupt each other's motion, so each ball will have less kinetic energy. Having now established

optimum conditions for the mechanochemical synthesis of **144**, attention was turned to the mechanochemical synthesis of **142**.

4.3 Screen of Liquid Assisted Grinding conditions

As the formation of **142** and **143** from this reaction mixture are reported in a DMSO solution, the possibility of using liquid assisted grinding (LAG) to alter the reaction products was investigated. Using DMSO as the added liquid, the effect of the quantity on the selectivity of the reaction was investigated (Table 4.4).

Table 4.4 Effect of LAG with different quantities of DMSO.



Entry	*x* /µL	Yield 142[a]	Yield 143[a]	Yield 144[a]
1	0	0%	0%	88% (72%[b])
2	25	16%	10%	32%
3	50	62% (56%[b])	12%	0%
4	100	32%	19%	0%
5	150	21%	22%	0%

[a] Yield determined by ^{19}F NMR spectroscopycompared to trifluorotoluene as an internal standard.
[b] Isolated yield.

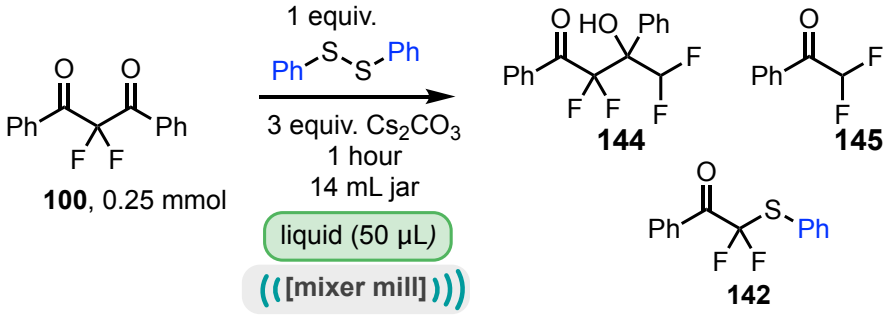
It was found that on addition of DMSO, reaction with phenyl disulfide was observed, with a switch in reactivity observed depending on the quantity of DMSO added. On addition of 25 µL, some conversion to ketone **142** was observed (16%, Table 4.4, Entry 2). On adding more than 50 µL of DMSO, the reactivity was completely switched, with no hydroxyketone **144** observed and only the products of reaction with phenyl disulfide obtained. With 50 µL of DMSO, ketone **142** was obtained in good yield (Table 4.4, Entry 3). With larger quantities of DMSO, **142** was further converted to difluoromethylthioether **143** (Table 4.4, Entries 4 & 5).

This LAG induced switching of reactivity is intriguing. Similar to the results presented in Chapter 2, using LAG is leading to a change in selectivity. However, it is now not just a

different outcome from the same reaction pathway, such as mono- or di- addition. Here, a completely different reaction is occurring; under neat grinding, the disulfide is untouched, however under LAG conditions with DMSO, the disulfide is consumed. This is therefore an example where the chemoselectivity of a reaction is being altered by using mechanochemistry. In order to probe this further, a range of solvents were investigated for their use in LAG.

It has been previously reported that the polymorphic outcome of a cocrystallisation can depend on the solvent used in LAG.[14-16] It is therefore possible that different solvents used in LAG would alter the selectivity of the reaction. Solvents spanning a range of properties were therefore screened, sorting by their dielectric constant, and the yields of the different possible products were measured using ^{19}F NMR.

Table 4.5 Effect of different solvents on reaction selectivity. Thanks to Michael Brand for these results.



Liquid	Dielectric constant	Yield 142[a]	Yield 144[a]	Yield 145[a]
-	-	0%	88%	10%
hexane	1.88	1%	86%	4%
toluene	2.38	1%	66%	6%
EtOAc	6.02	1%	76%	5%
THF	7.58	1%	60%	7%
DCM	8.93	3%	60%	4%
^{i}PrOH	17.9	1%	74%	3%
EtOH	24.5	1%	26%	8%
NMP	32.2	**25%**	15%	5%
DMF	36.7	**27%**	23%	4%
MeCN	37.5	4%	55%	4%
DMA	37.8	**25%**	31%	0%
DMSO	46.7	**62%**	0%	5%
H_2O	80.1	0%	28%	35%

[a] Yield determined by ^{19}F NMR spectroscopy compared to trifluorotoluene as an internal standard.

Similar to the previous observations on the effect of quantity of DMSO on the reaction selectivity, a general trend can be observed of a switching of product ratios as the

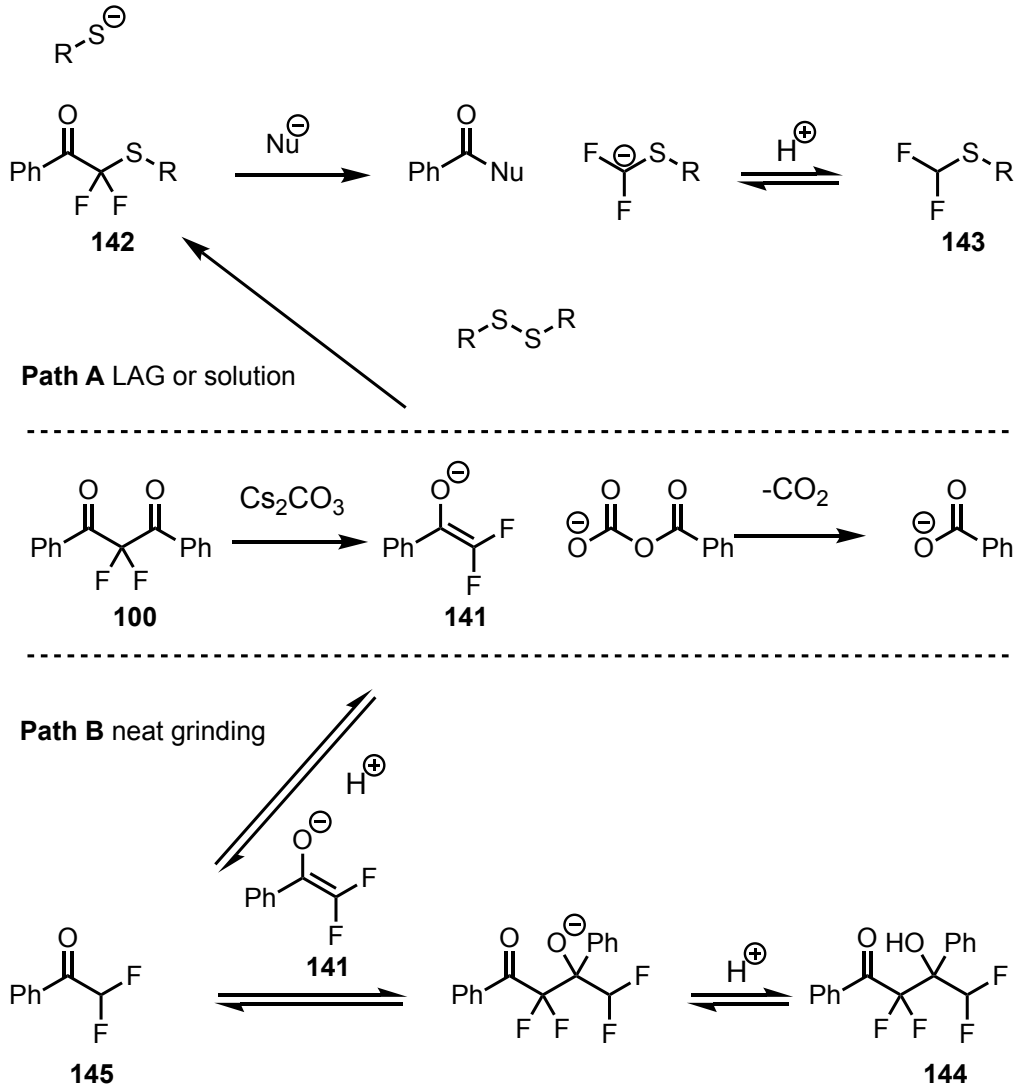
dielectric constant of the added liquid increases (Table 4.5). In general, for non-polar additives, **144** is obtained as the major product. However, for the most polar additives, a switch in reactivity is observed, and the major product is **142** when the dielectric constant is greater than 30. However, this is with the exception of water and acetonitrile. Interestingly when water was used as the additive, the selectivity of the reaction changed again, with difluorinated ketone **145** being the main product observed.

Having established the factors that effect the selectivity of the reaction, it was important to investigate the underlying causes of the altering of chemoselectivity. The first step in approaching this problem was to understand the mechanism of the reaction.

4.4 Proposed mechanism

Initially, the difluorinated diketone fragments to yield difluoroenolate **141**, as proposed previously.[8] This fragmentation may be enhanced by the motif of three adjacent partially positively charged carbon atoms. Cesium carbonate is necessary for the transformation, suggesting that it plays a role in this initial fragmentation (Scheme 4.8). The carbonate anion may behave as a nucleophile, attacking a ketone to initialise the fragmentation. Once this enolate (**141**) has been formed, the possible reaction pathways diverge (Scheme 4.7). Under LAG conditions with polar additives, the enolate reacts with the electrophilic disulfide with the loss of phenyl thiolate to yield the major observed product **142** (Path A). Under certain conditions, such as high temperature or extended reaction times in solution, **142** can fragment further to form difluoromethylthioether **143**.

Under neat milling or LAG with non-polar additives, different reactivity is observed (Scheme 4.7, Path B). In these circumstances, the difluorinated enolate **141** does not react with the disulfide. Instead, some amount of **141** must be protonated to the ketone **145**, which then undergoes an aldol reaction with enolate **141**. After subsequent protonation, the major product observed under neat milling (**144**) is obtained. It is possible that the overall formation of **144** from enolate **141** is reversible.



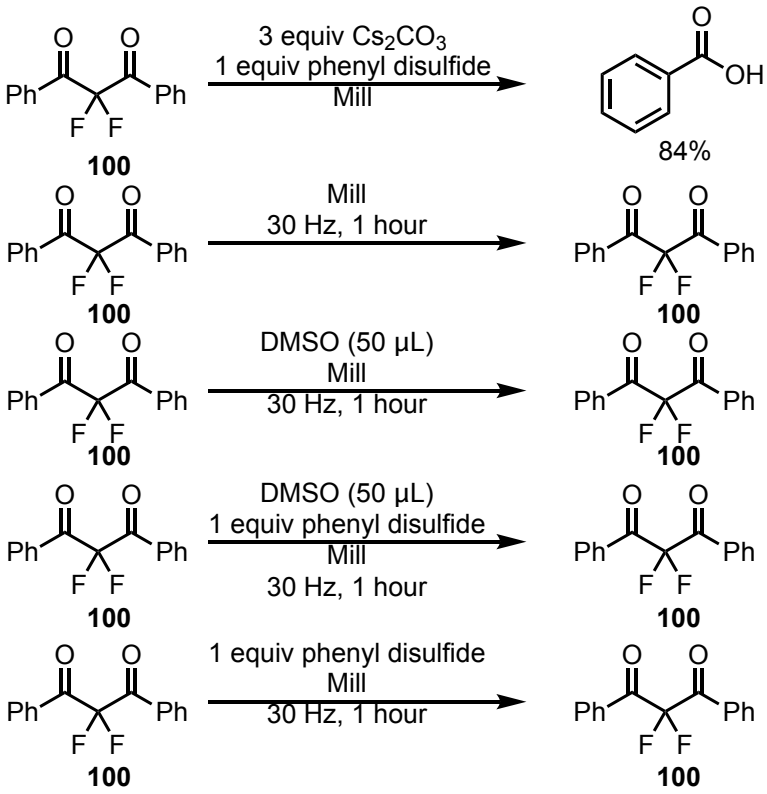
Scheme 4.7 Proposed mechanism.

Next, it was decided to probe the validity of this proposed mechanism by testing the reversibility of different steps and by verifying the participation of the proposed intermediates in the reaction.

4.5 Mechanistic experiments

Initially, the fragmentation of **100** was investigated. Under the optimal reaction conditions for the formation of **144**, treating **100** with cesium carbonate and phenyl disulfide under neat milling, benzoic acid could also be isolated in 84% yield by an acid/base extraction. This is the expected side product of the fragmentation of **100** induced by a nucleophile and would be the side product from direct addition of water to **100**. However, it is also a possible side product of the initial nucleophilic attack of the

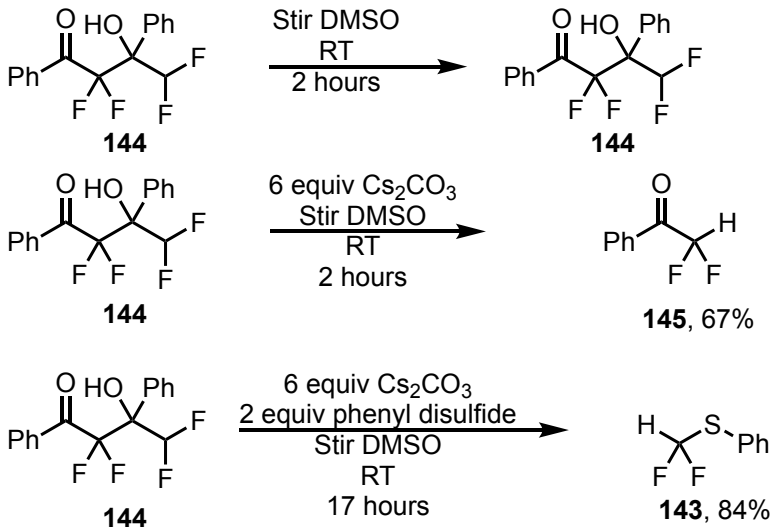
carbonate anion, as shown in Scheme 4.7. The potentially unstable carbonate formed could then quickly decarboxylate, with the loss of carbon dioxide, to form benzoic acid.



Scheme 4.8 Investigating the initial fragmentation

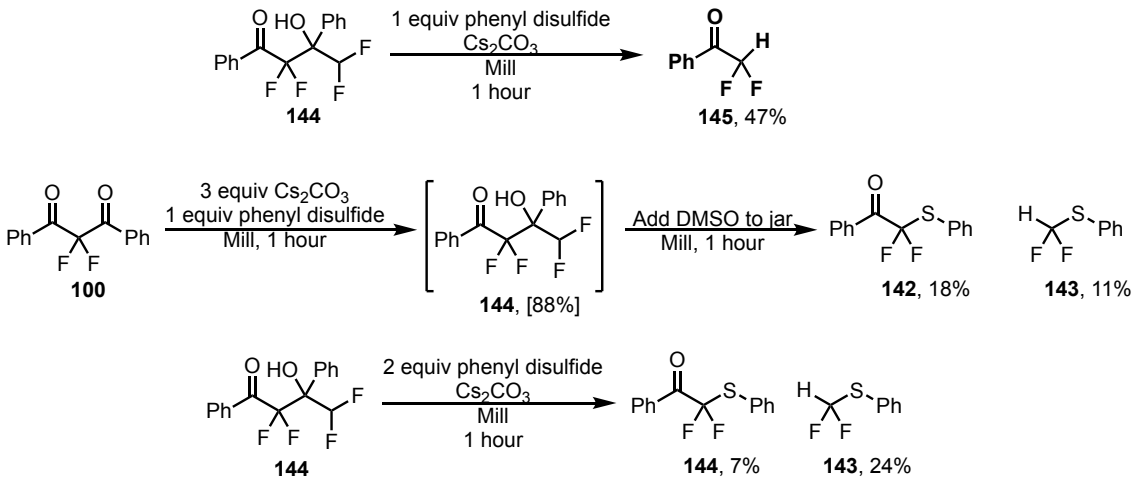
Subsequent control experiments confirmed that the fragmentation does not occur spontaneously under ball milling of **100** (Scheme 4.8). Upon milling **100** in the absence of cesium carbonate, only the starting material was observed, with any combination of added DMSO and phenyl disulfide (Scheme 4.8). This demonstrates that DMSO and phenyl disulfide do not cause the initial fragmentation, and that cesium carbonate is required for the initial step of the reaction mechanism. Furthermore, this suggests that the identity of the nucleophile inducing the fragmentation is the carbonate anion of cesium carbonate. The only other possibility is that the fragmentation is induced by water present in cesium carbonate. However, that would suggest that **100** would be moisture sensitive, but it is stable for extended periods in air. The reaction was also performed and found to proceed successfully from dried starting materials, drying cesium carbonate in a drying pistol.

Subsequent mechanistic experiments were directed at establishing whether the reversibility proposed for the formation of **144** from **141** is correct. A sufficient quantity of **144** was isolated by performing ten reactions in parallel and isolation by column chromatography. It was then investigated whether **144** was a reactive starting material in solution (Scheme 4.9).



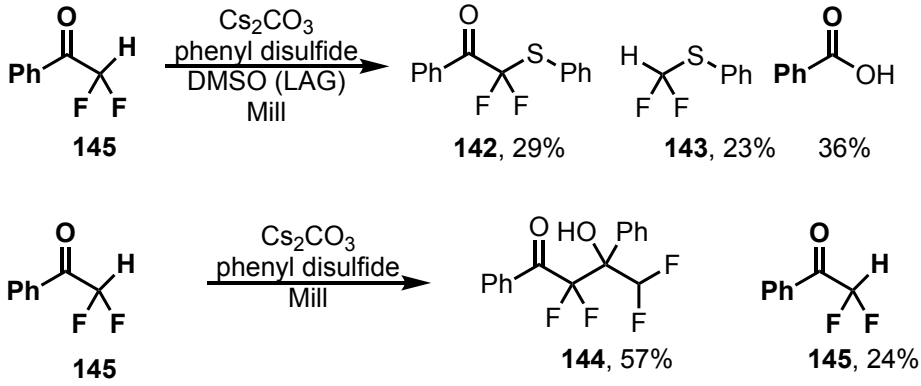
Scheme 4.9 Experiments testing the reversibility of **144** formation in solution.

Initially, on stirring **144** in DMSO solution for two hours, only **144** was observed. However, on addition of cesium carbonate, diketone **145** was obtained in 67% yield. This demonstrates that the formation of **144** from **145** is reversible in the presence of cesium carbonate. It also suggests that difluorinated ketone **145** is an intermediate in the overall reaction mechanism. On stirring **144** in a DMSO solution with cesium carbonate and phenyl disulfide for extended reaction times, difluoromethylthioether **143** was formed in 84% yield. This confirms that **144** formation is reversible under the reaction conditions in solution and that it is a competent starting material for reaction with disulfide.



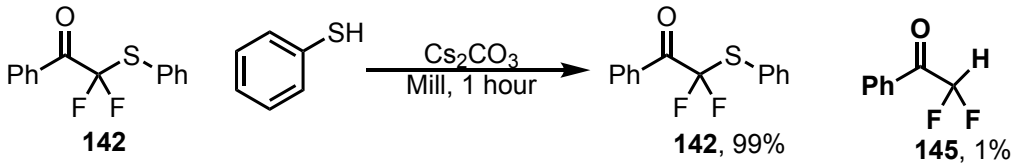
Scheme 4.10 Testing reversibility in mixer mill.

The reversibility of **144** formation was also investigated under mechanochemical conditions. On subjecting **144** to neat grinding with phenyl disulfide and cesium carbonate for one hour, ketone **145** was obtained in 47% yield. This confirms that the formation of **144** is reversible under milling. The use of **144** for formation of thioethers **142** and **143** in the mill was also tested in a one-pot procedure. The optimum conditions for the formation of **144** were used (Table 4.3, Entry 3), then the jar was opened, DMSO added and then milled for a further hour. Thioethers **142** and **143** were observed, demonstrating that the reaction pathway can be switched by adding DMSO to the crude reaction mixture, and that **144** is a competent starting material for this transformation. To further test this, purified **144** was milled for one hour in the presence of DMSO, cesium carbonate and phenyl disulfide, and only thioethers **142** and **143** were observed as products by ^{19}F NMR spectroscopy, though in low yields.



Scheme 4.11 Confirmation of common intermediate.

Next, the proposed intermediate ketone **145** was tested both under neat milling and LAG with DMSO (Scheme 4.11). It was found that **145** was a competent starting material for both reactions. This supports the proposed mechanism of **145** as an intermediate that is common to both reaction pathways.



Scheme 4.12 Reversibility of C-S bond formation on milling.

The final test of the proposed mechanism was probing the reversibility of the C-S bond formation step (Scheme 4.12). This step is proposed to explain the formation of **142** from **141** (Scheme 4.7, Path A). In the proposed mechanism, enolate **141** attacks phenyl disulfide, liberating phenylthiolate. It can be envisaged that this step could be reversible, requiring the thiolate to attack **142** at sulfur, reforming phenyldisulfide and enolate **141**. This could be promoted by the electron poor nature of the carbon α to the carbonyl, caused by the electron withdrawing fluorine atoms. To test the feasibility of this back-reaction, thioether **142** was milled for one hour with thiophenol and cesium carbonate (Scheme 4.12). While 99% of **142** remained after one hour, 1% of the difluorinated ketone **145** was observed. This shows that under milling, the C-S bond formation is reversible. However, it is either very slow or the position of equilibrium strongly favours the thioether **142**, given the low observed yield of ketone **145**.

In summary, these experiments all support the proposed mechanism (Scheme 4.7). The initial fragmentation requires cesium carbonate, and benzoic acid has been isolated as a side product, suggesting that CO_3^{2-} is acting as a nucleophile and causing the initial fragmentation. It was then confirmed that ketone **145** (and by inference its enol form **141**) is a common intermediate to both reaction pathways. The formation of **144** was determined to be reversible under the reaction conditions. However, despite now having a reasonable mechanistic understanding of the overall process, the origin of which reaction pathway is observed is still not clear. In solution or LAG with polar additives for one hour, path A is observed. However, under neat milling or LAG with non-polar additives, path B is observed.

4.6 Origin of altering reaction pathway

In any reaction, the observed selectivity is due to a combination of kinetic and thermodynamic factors. Therefore in order to change the selectivity, the thermodynamics, kinetics or both must be altered by a change in reaction conditions. Therefore, the switch from solution (or LAG with polar additives) to neat grinding (or LAG with non-polar additives) must be either altering the thermodynamic product of the reaction, or changing the rate of a key step in the mechanism, or a combination of these effects. Indeed, it has been observed previously that performing reactions under mechanochemical conditions can lead to differences in kinetics and thermodynamics compared to the same reactions in solution.[9, 10]

In order to gain some insight into the possible underlying cause of the different reaction outcomes observed, the reaction profile with time under different conditions was investigated.

Investigations into the early part of the reaction under LAG conditions with DMSO show an interesting reaction profile with time (Figure 4.1). Early on in the reaction, the main product observed was **144**, in significant contrast to the product ratio observed after milling for one hour. However, **144** and **145** then decrease over time, and the yield of the thioether **142** increases over time until there is no **144** remaining after one hour. This suggests that under liquid assisted grinding with DMSO, the fragmentation of **100** occurs rapidly to form enolate **141,** which can then reversibly form **144**. However, after one hour, this has all reacted with the disulfide to form thioether **142**.

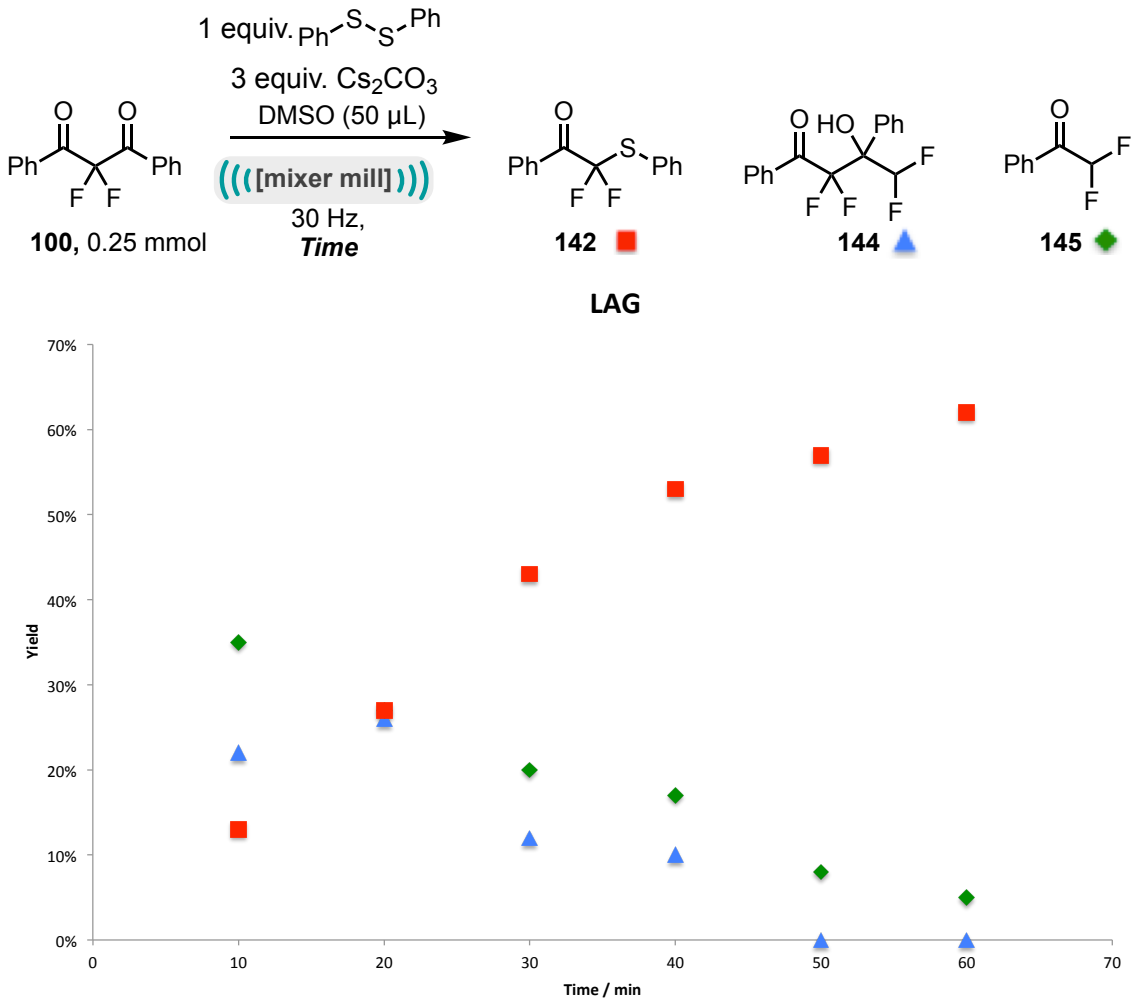


Figure 4.1 Reaction profile with time for liquid assisted grinding with DMSO.

Having observed **144** at short reaction times under LAG conditions with DMSO, that suggests that the reaction of enolate **141** with phenyl disulfide to form **142** is much faster than under neat milling. It was therefore suggested that at long reaction times under neat milling, some conversion to **142** may be observed. To test this, the reaction profile for long reaction times under neat milling was investigated (Figure 4.2).

It was found that on milling for longer times than one hour, the amount of **144** significantly decreased, and conversion to ketone **145** was then observed. As it has already been shown that the formation of **144** from **145** is reversible, then they must be in equilibrium. After extended milling times this mixture slowly reacts with the disulfide, forming thioether **142**.

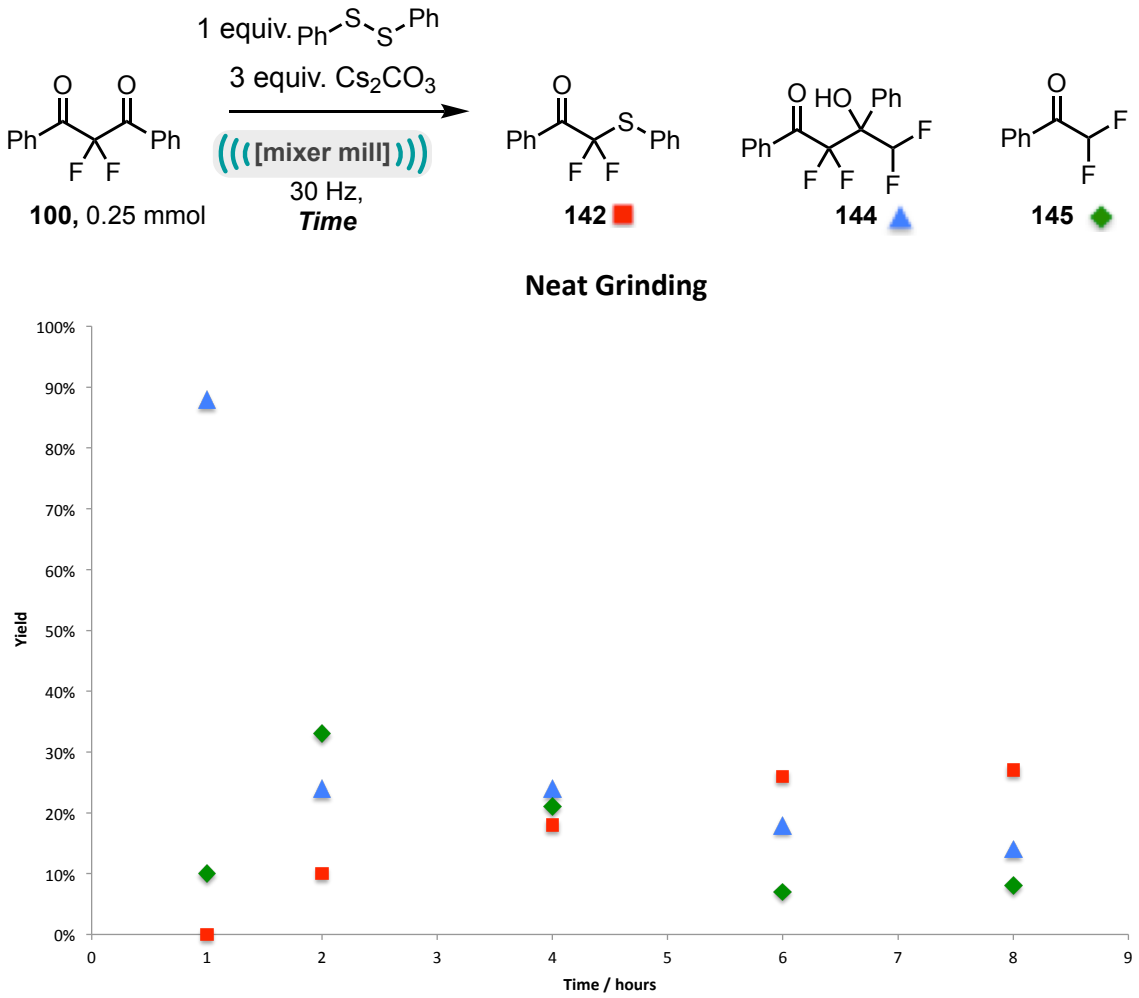
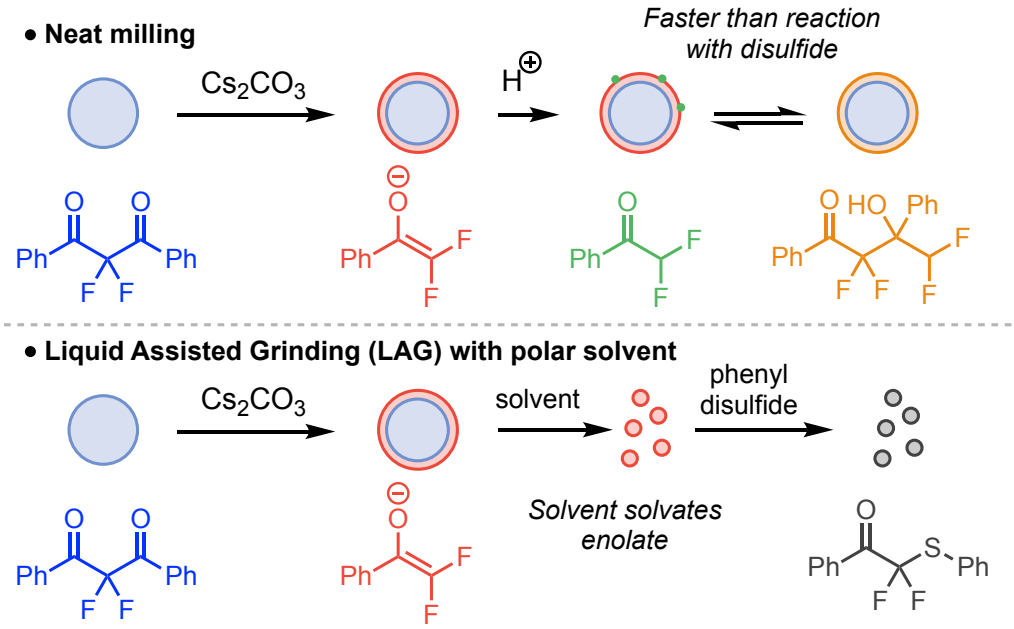


Figure 4.2 Reaction profile for long reaction times under neat milling.

This confirms that the key difference in reactivity observed between neat milling (or LAG with non-polar additive) and LAG with polar additive (or solution) is due to differences in the rate of formation of **142** from **141** (Scheme 4.7, Path A). In both cases, at long reaction times, them main product is thioether **142**, suggesting that this is the thermodynamic product of this reaction manifold. However, in both cases at shorter reaction times, **144** is observed. This suggests that **144** is the kinetic product, which under neat milling, can be obtained in good yield after one hour. The origin of the different reaction selectivity has therefore been determined. It is a kinetic effect, where the use of LAG with a polar additive or solution leads to a faster reaction of **141** with the disulfide. Under neat milling (or LAG with a non-polar additive), this step is significantly slower, so the main product after one hour is **144**.

With the cause of the reaction pathway switching now established as a kinetic effect, this still does not confirm the underlying physical cause. It has been previously demonstrated that using mechanochemical conditions can alter the kinetic profile of a

reaction.[10] In that study it was proposed that the cause of the different kinetics was due to a change in the texture of the reaction. However, that example simply demonstrated different kinetics for one reaction that exhibited no selectivity differences. Here, the difference in rate of one step can be exploited to give different reaction products. Taking this proposal of different textures as inspiration, a hypothesis to the physical cause of the observed rate differences was postulated (Scheme 4.13). The fundamental cause seems to be the non-homogeneous nature of mechanochemical reaction mixtures.



Scheme 4.13 Proposed physical cause of kinetic differences observed.

Initially in the ball mill, the reaction mixture will be mixed and the particle size of reagents decreased. The first chemical transformation under both sets of reaction conditions is the cesium carbonate mediated fragmentation of difluorinated diketone **100** to the difluoroenolate **141**. This will initially be formed at the interface of a particle of **100** and Cs_2CO_3, on the surface of a bulk particle of **100** (Scheme 4.13). The rate of the next reaction depends on the local concentrations of each starting material. Under neat milling, if some of enolate **141** is protonated to form ketone **145**, it will be formed surrounded by a locally very high concentration of enolate **141**. Therefore, the aldol reaction to form **144** will be much faster than the reaction with phenyl disulfide, as observed under neat miling or LAG with non-polar additives. Under LAG with a polar solvent, the coating of enolate **141** on unreacted **100** could be broken up by a polar solvent, significantly increasing its mobility. The enolate could then react much faster with phenyl disulfide.

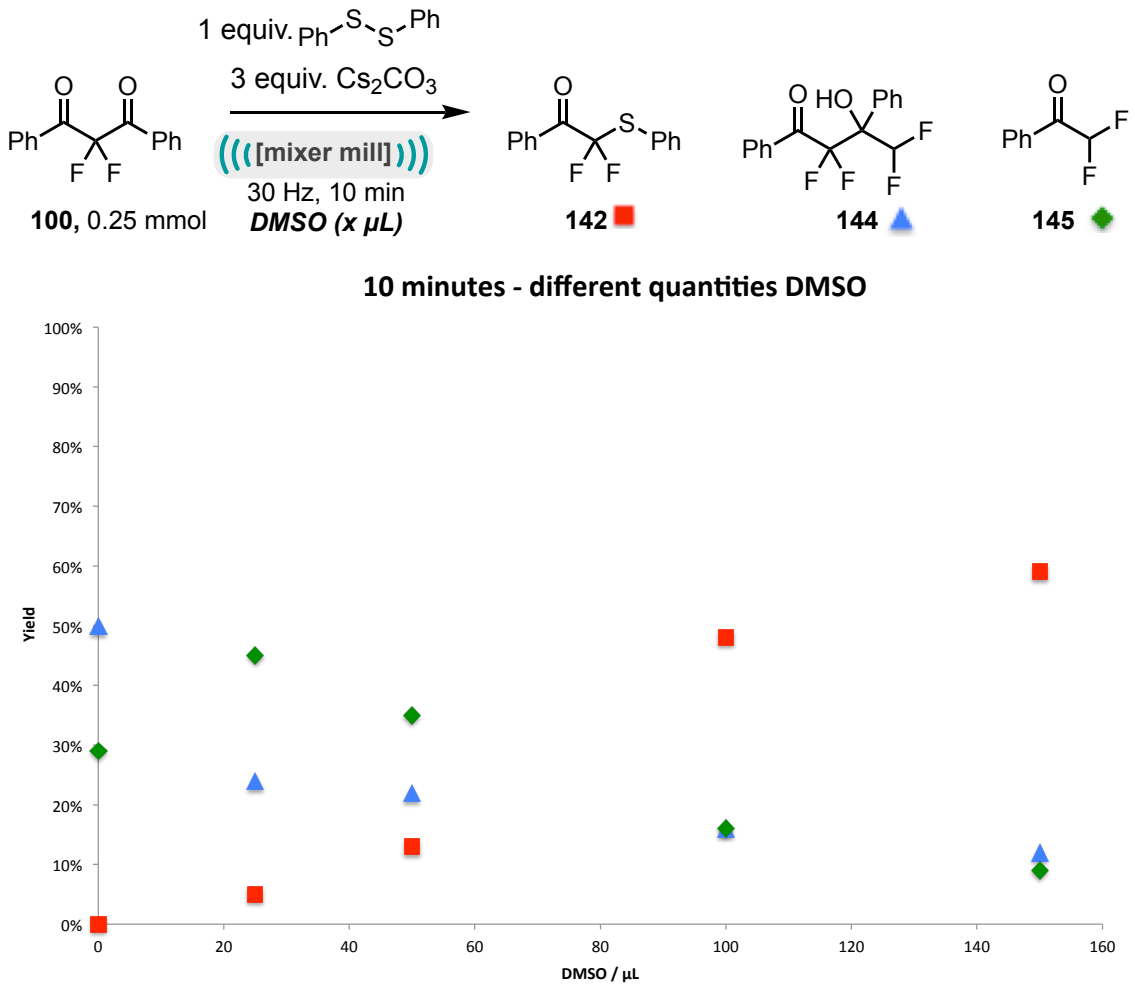


Figure 4.3 Yields of different products after milling with different quantities of DMSO.

In order to test this hypothesis, the effect of milling with different quantities of DMSO at an early time point in the reaction was investigated (Figure 4.3). It was found that on milling the reaction mixture for 10 minutes in the absence of DMSO, only **144** and **145** were observed. However, on subjecting this mixture to ball milling for 10 minutes with different quantities of DMSO, an interesting trend emerged. On increasing the quantity of DMSO, more of **142** was obtained, suggesting that with more DMSO in the reaction mixture the reaction of enolate **141** with disulfide is faster. This is what would be expected if the hypothesis depicted in Scheme 4.13 is a fair representation of the physical cause of the different reaction rates observed. With more DMSO in the mixture, more of enolate **141** can be solvated, leading to increased mixing and faster reaction with the disulfide to form **142** than with **145** to form **144**.

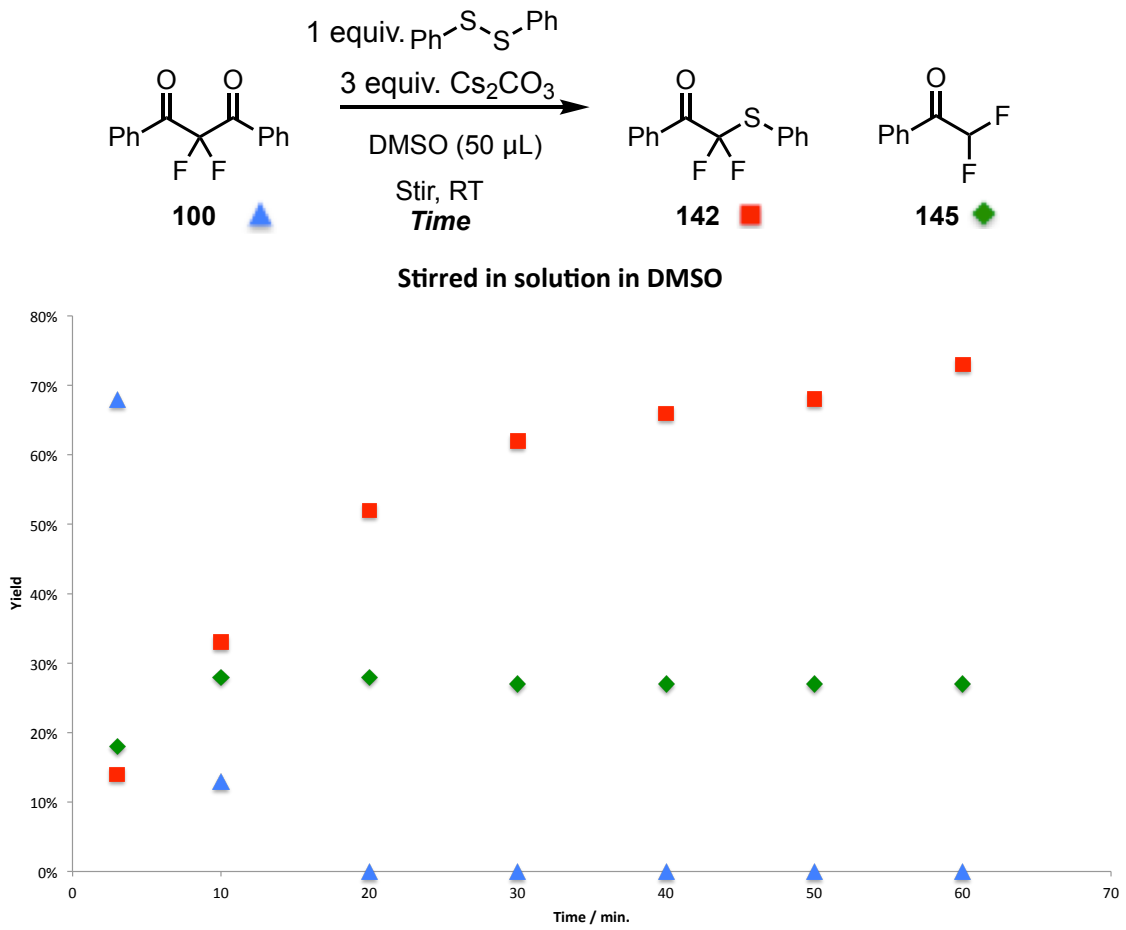


Figure 4.4 Graph of yield against time for solution reaction.

In order to further test this hypothesis, the reaction was performed in solution in DMSO, with the yields measured at different points. In solution, the reagents are dissolved, so there will be no surface effects as in Scheme 4.13. It would therefore be expected that at no time point is any **144** observed. This is the case, with initial consumption of starting material complete within 20 minutes. The major product observed is difluoromethylthioether **142**, as expected in solution, with some of ketone **145** also observed.

Currently, the experimental evidence supporting this hypothesis is still limited to the observed differences in reaction profiles, the trend of polarity in the solvent additives and the effect of different quantities of added DMSO. Further investigations would be required to support or revise this hypothesis and would have to take into account the non-covalent interactions involved, possibly via theoretical simulations. The development of methods for *in situ* monitoring of milled reactions and application to this process would also provide further information of the mechanisms involved.

4.7 Conclusions and Outlook

An example of a reaction where the chemoselectivity is altered by using mechanochemical conditions has been discovered. Although the exact transformation is perhaps of little interest for synthetic chemists, it does provide a proof of concept that alternative reaction pathways can be discovered in the chemical space of mechanochemistry.

It was found that using liquid assisted grinding (LAG), both the quantity and nature of the added liquid could switch the reaction pathway. Using more polar additives (as determined by their dielectric constant), the product observed in solution was obtained, whereas with less polar additives, the product observed under neat milling was observed. The mechanism, including the different reaction pathways, was then investigated, and the ultimate reason for the selectivity differences observed found to be due to different kinetics.

This example is the first example of opening an alternative reaction pathway by using mechanochemistry, with a different reaction happening in solution from the same reagents. If, on further investigation, the physical phenomena giving rise to this alternative selectivity can be confirmed and well understood then it may become possible to predict situations where using mechanochemistry could lead to novel reactions being discovered. Such investigations would require significant collaboration across multiple fields of chemistry.

As this is demonstrating the ability of mechanochemistry to trap a kinetic product, any reaction that features kinetic and thermodynamic product selectivity could perhaps make use of milling to achieve the desired reactions outcome. For example, enolate formation is typically carried out either at low temperatures with a very strong base in order to form the kinetic enolate, or at high temperatures with a weaker base to form the thermodynamic product. An alternative direction for this procedure would be to investigate the use of electrophiles other than a disulfide. For example, perhaps milling the difluorinated diketone **100** with Cs_2CO_3 in the presence of Selectfluor may lead to the trifluoromethylated ketone.

4.8 References

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5 Mechanochemical activation of metals

5.1 Introduction

There are many uses of metals in organic synthesis, particularly as catalysts and activating agents.[1] In terms of being used as synthetic building blocks, organometallic species are usually the synthetic equivalents of choice for nucleophilic-at-carbon synthons. Possibly the most well known example is the Grignard reagents, which are organomagnesium species that react efficiently with electrophiles to form new carbon carbon bonds.[2] Metal catalysts are often also organometallic species, with specialised organic ligands designed to enhance catalytic activity and/or induce enantioselectivity during the transformation.

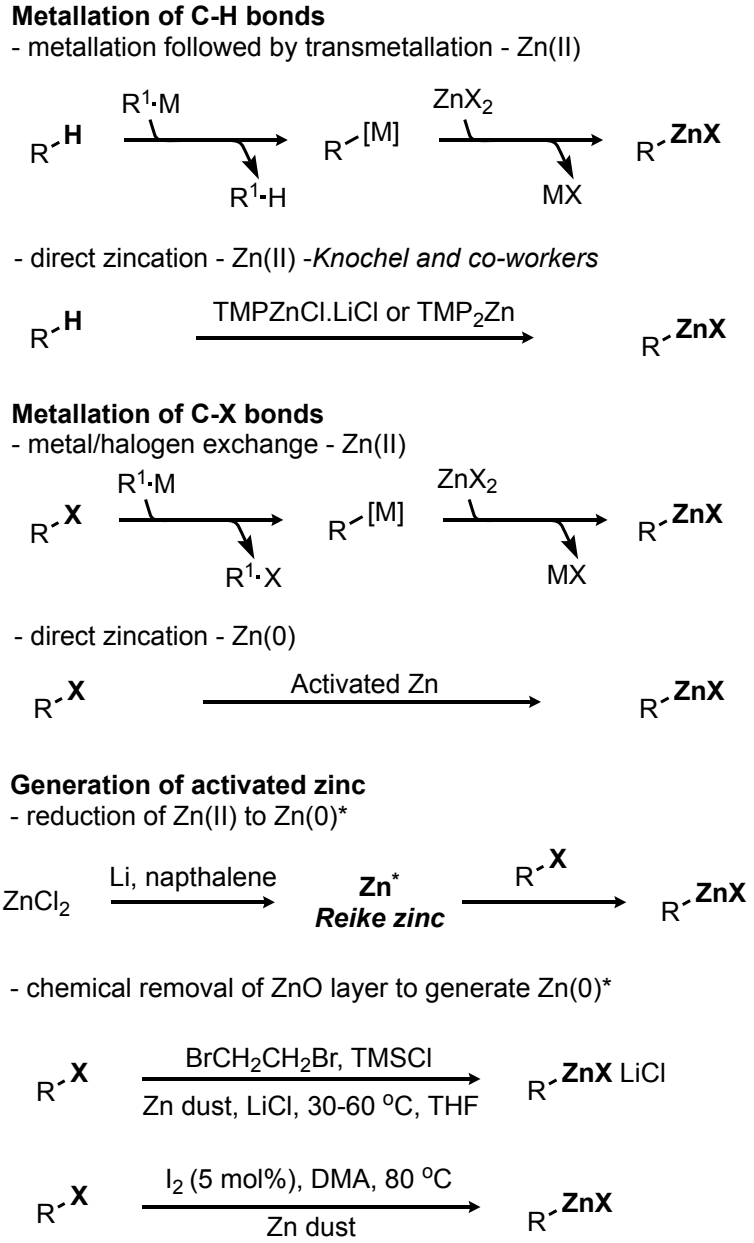
The synthesis of organometallics can be challenging. They are usually air and moisture sensitive and can be extremely reactive. The most straightforward route from the simplest starting materials involves direct oxidative addition of the alkyl halide to the base metal. Although this uses readily available starting materials, in practice this can be challenging. For example, during the synthesis of Grignard reagents from alkyl bromides and magnesium metal, initiating the reaction can be problematic. The main problem is the coating of magnesium oxide on the surface of magnesium metal, which prevents the reactive metal from being exposed to the alkyl halide for oxidative addition. The typical solution to this problem is to "activate" the metal by removing the surface oxide layer, which is often achieved by adding iodine, dibromoethane or other additives.[3] This activation can be a significant problem, especially on large scales, since once initiated the reaction is exothermic and thermal runaways are possible.[4] Another key consideration is the choice of solvent, with Grignard formation being easier in ethereal solvents, since the oxygen can coordinate to the magnesium metal centre, stabilising the organometallic. This coordination also helps dissolve the organometallic species, washing newly formed reagent from the surface of the magnesium metal and revealing fresh reactive metal surface for the reaction to continue. These considerations are well understood for the case of organomagnesium species. However, the synthesis of other organometallics is often more challenging. The relative ease in the synthesis of organomagnesium reagents is due to a balance between how reactive magnesium metal is, leading to fast reaction with alkyl halides, and the facile methods available to remove the surface oxide layer.

Despite the wide use of Grignard reagents, they exhibit poor functional group tolerance and stability. They are very basic, with pKa values of the corresponding alkanes being approximately 50, and so even weakly acidic groups such as alcohols must be protected before a Grignard reaction. They will also react with most electrophilic

centres, including esters, nitriles and alkyl halides. Finally, they are air and moisture sensitive, which can present complications in their handling.

However, other organometallics can offer solutions to some of these problems; indeed, the full suite of metals are needed to achieve selectivity and reactivity across a broad range of capabilities. By varying the metal, the reactivity can be adjusted, which can lead to improved functional group tolerance and stability. For example, organozinc reagents have these improved properties compared to Grignard reagents, although they possess correspondingly decreased reactivity. Unfortunately, few organozinc reagents are commercially available and their synthesis is more challenging than the synthesis of Grignard reagents, leading to the chemistry of organozinc reagents being under-utilised, such as the Negishi cross-coupling reaction.[5] The traditional method to synthesise organozincs and other organometallics is by transmetallation from the corresponding organolithium or organomagnesium, formed either by direct C-H metallation by deprotonation or ortho lithiation, [6] or by oxidative addition from the alkyl halide (Scheme 5.1). [7] However, any advantages gained in terms of functional group tolerance of the new organometallic are lost by transmetallation from these more reactive organolithium or organomagnesium species used as intermediates. For example, it would be impossible to synthesise an organozinc reagent containing an ester by transmetallation from an organolithium or Grignard.

The solution to this problem is to directly synthesise the desired organometallic. For example, the direct zincation of C-H bonds has been developed by Knochel and coworkers, by using specialised zinc-amide bases.[8] Perhaps more attractively, for C-X bonds, is the direct oxidative insertion of Zn(0) from activated zinc metal. Indeed, highly reactive Rieke zinc can be formed by the reduction of $ZnCl_2$ using alkali metals and naphthalene, and will undergo oxidative addition with an alkyl or aryl halide to generate the desired organozinc species (Scheme 5.1).[9] A complementary, and more popular approach to generate activated zinc metal is to remove zinc oxide from the metal surface by chemical reaction or entrainment. This is typically performed by using chemical additives such as TMSCl, 1,2-dibromoethane, bromine or iodine.[10] A further issue arises in the generally poor solubility and oligermerization of organozinc species, causing them to form on the surface of the bulk zinc metal, preventing the exposure of fresh zinc surfaces and reducing the reactivity for subsequent reactions. Knochel and co-workers observed that this limitation can be overcome by the addition of lithium chloride to the reaction mixture.[11]



Scheme 5.1 Methods to synthesise organozinc reagents.

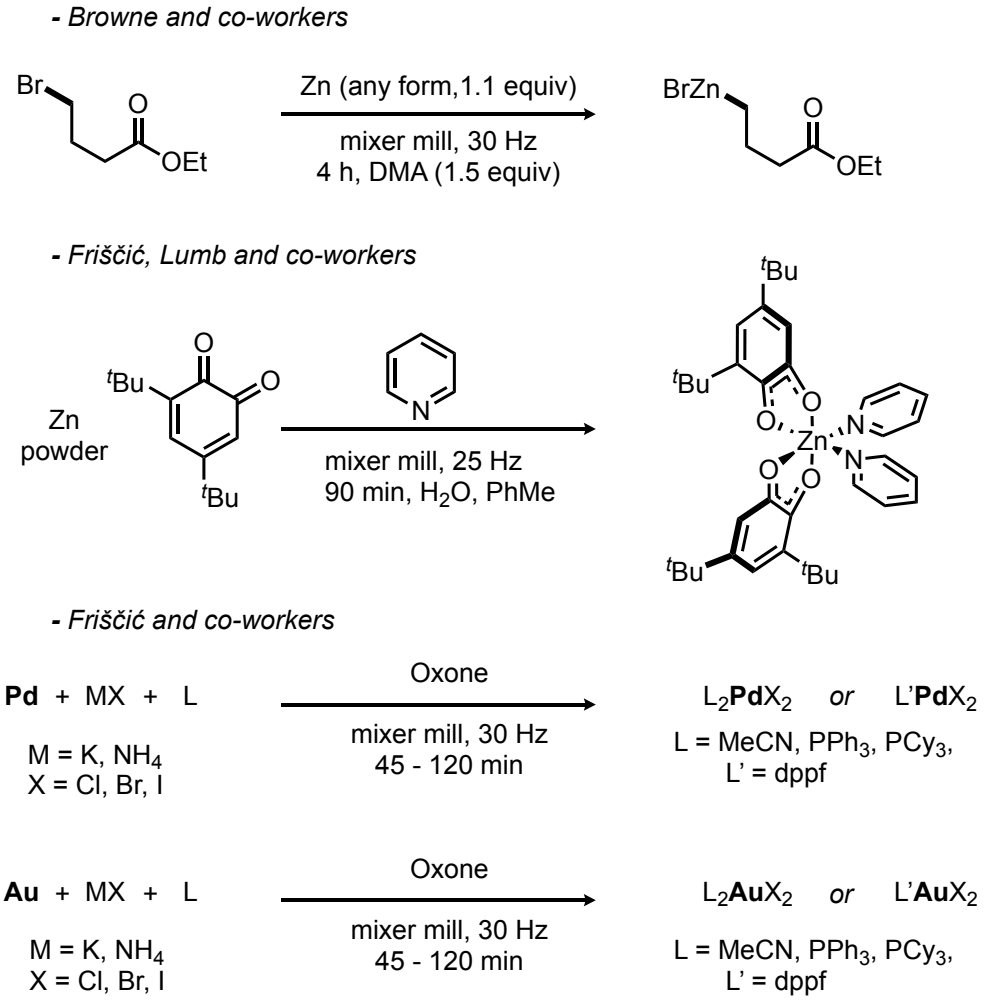
All of these methods require strictly inert conditions and can be unreliable, as well as requiring multiple additives and long reaction times. They are also highly dependent on the form of metal used. An experimentally more straightforward approach to the activation of metals could be to use mechanochemistry.

5.1.1 Mechanochemical direct oxidative addition to base metals

One of the significant issues encountered when attempting to obtain organometallics directly from the base metals and alkyl halides is the presence of a surface layer of

metal oxide. As previously described, activation of these metals typically requires chemical removal of this layer. Under mechanochemical conditions, however, this metal oxide layer may be physically removed, revealing fresh reactive metal surfaces on impact. This idea has been exploited using a pestle and mortar to activate zinc metal.[12] Metals are commercially available in many different forms, which can have a significant impact on their reactivity. However, under milling, any metal form could be ground to a fine powder, suggesting that any commercially available form could be used mechanochemically. Indeed, the forms of metal with the highest surface area to volume ratios (such as fine powders) would have a higher proportion of metal oxide compared to reactive metal.

Previous work in the Browne group developed a mechanochemical process for the activation of zinc metal in order to synthesise organozinc species directly from zinc metal and the corresponding alkyl halide (Scheme 5.2).[13] On milling the alkyl halide with zinc metal and DMA the organozinc reagent could be obtained. Inert conditions were not required and organozinc formation was found to be successful using any commercially available form of zinc. These organozinc reagents were then directly used in the Negishi cross-coupling in a one-pot process.



Scheme 5.2 Examples of mechanochemical activation of metals.

Direct synthesis of metal complexes from base metals under ball milling has also been reported. In 2016, it was reported by Friščić, Lumb and co-workers that milling zinc powder with a quinone and pyridine could form zinc (II) complexes (Scheme 5.2).[14] By changing the pyridine linker used, the authors were able to use this method to form self-assembled metal-organic materials. In a separate report, Friščić and co-workers were able to synthesise palladium (II) and gold (II) complexes directly in a ball mill from the metals, ligands and oxone (Scheme 5.2).[15] These complexes were water-soluble and a palladium complex synthesised by this method was successfully used to catalyse a Suzuki cross-coupling reaction. In a further example of mechanochemical metal activation, Lamaty and co-workers reported that copper - NHC complexes could be directly synthesised in the mill from Cu(0) metal and the desired NHC salt, without addition of a base.[16]

The in situ formation of reactive metal centres has also been demonstrated by the observation that the metallic milling balls can catalyse a reaction. For example, the

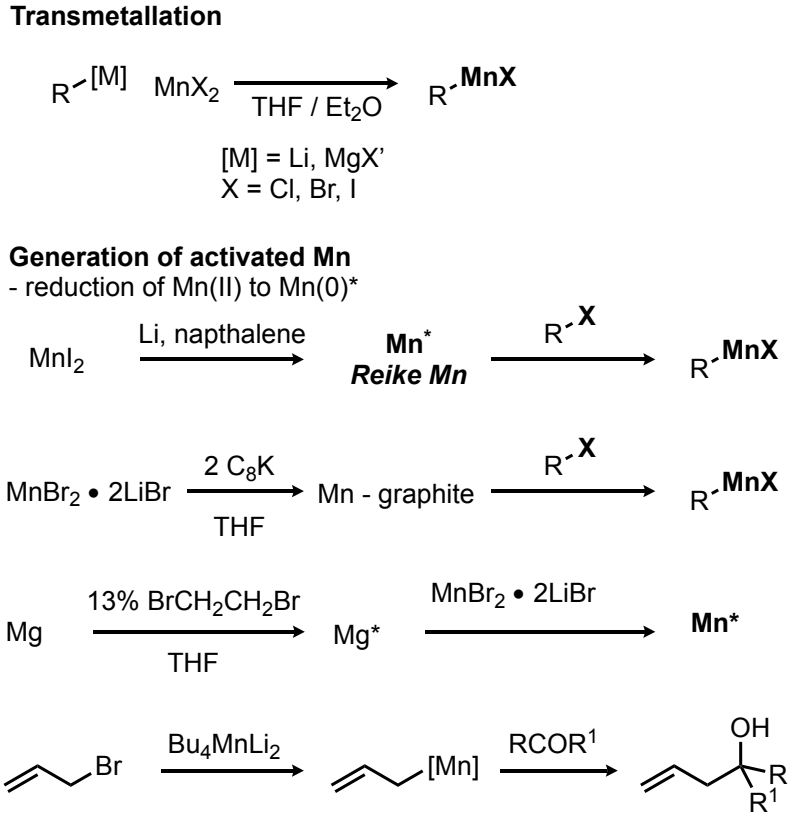
copper catalysed alkynylation of tetrahydroisoquinolines has been performed using copper milling balls as the catalyst.[17] A further demonstration of reactions caused by the presence of metals in the milling balls reports the reduction of arenes using stainless steel milling balls and alkanes.[18] It was demonstrated that the presence of chromium in the balls was vital for this transformation.

As the possibility of synthesising organometallic species in a simple practical method from base metals using mechanochemistry has been demonstrated in the Browne group and by others, attention was turned to manganese. Like organozinc species, organomanganese synthesis is often not straightforward and an improved method for their synthesis would be desirable.[19]

5.1.2 Organomanganese formation

Organomanganese reagents have multiple uses and reactivity in synthesis, such as selective, nucleophilic-at-carbon reagents or as coupling partners in cross-coupling reactions.[19-22] However, they can be challenging to synthesise. By far the most common method used to synthesise organomanganese species is by transmetallation from the corresponding organolithium or organomagnesium (Scheme 5.3).[23] Despite currently being the most reliable method available, this approach has several drawbacks. Firstly, it is a multistep process and therefore is not efficient, forming stoichiometric salts of lithium or magnesium as waste. It also requires strictly inert conditions and synthesis of the required organolithium or organomagnesium is not always straightforward. As discussed previously, there are also drawbacks in terms of functional group tolerance and stability.

A better method would be direct oxidative addition of alkyl halides to manganese metal. This has been achieved from various forms of “activated manganese” (Scheme 5.3). In a similar method to activating zinc, Rieke manganese can also be synthesised by reducing manganese iodide with lithium metal and naphthalene (Scheme 5.3).[24]

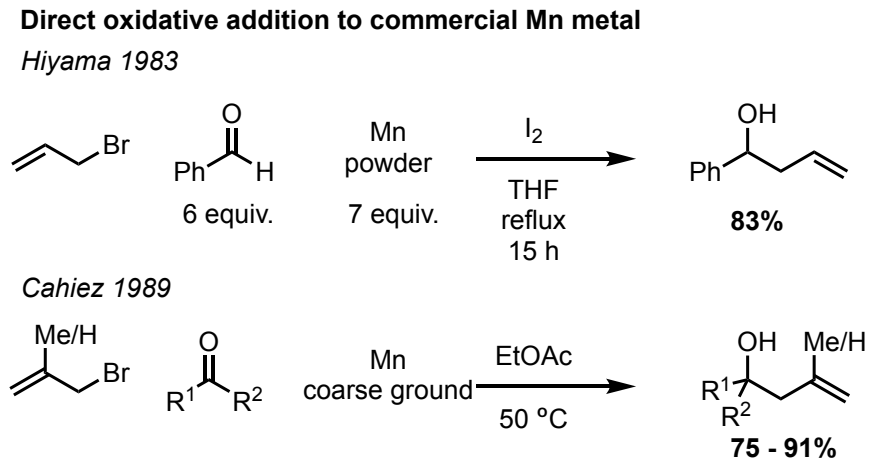


Scheme 5.3 Methods for the synthesis of organomanganese species.

A further method to activate manganese metal was found by Fürstner in 1996. The soluble complex $MnBr_2.2LiBr$ could be reduced by potassium graphite (Scheme 5.3).[25] This activated manganese reacts smoothly with allyl-, alkenyl- and aryl halides and can be used to prepare functionalised organomanganese species, such as those featuring nitriles. An alternative method of generating activated manganese was developed by Oshima and co-workers. This process featured the same starting complex ($MnBr_2.2LiBr$), but reduction was performed using magnesium metal, which was activated by treatment with 1,2-dibromoethane (Scheme 5.3).[26] An alternative to using activated manganese is direct manganese insertion into a carbon-halide bond. This was achieved by Hosomi in 1997 by using Bu_4MnLi_2 as a source of manganese (Scheme 5.3).[27]

Direct oxidative addition of alkyl halides to commercially available manganese metal is of significant interest, due to the improved efficiency and ability to synthesise organomanganese compounds containing more sensitive functional groups. To date, there are very few reports of this transformation (Scheme 5.4). In 1983, it was reported that on treating allyl bromide with benzaldehyde, iodine and manganese powder in THF for 15 hours afforded the addition product in good yield (Scheme 5.4).[28] However, this

process required significant excess reagents to be used and was only successful for allyl bromide.



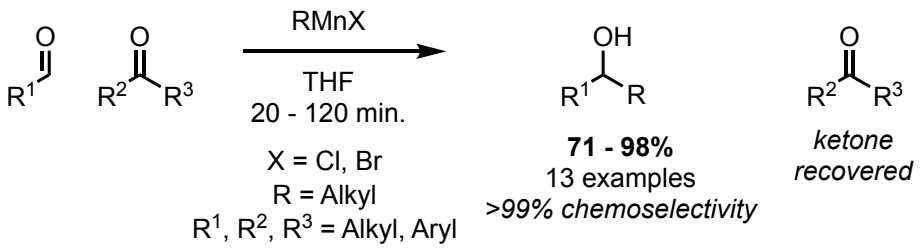
Scheme 5.4 Synthesis of organomanganese reagents from alkyl bromides and commercially available manganese metal.

In 1989, Cahiez and co-workers extended this process to reaction with ketones and methallyl bromide (Scheme 5.4).[29] The choice of solvent was found to be crucial, with ethyl acetate idenitified as the best solvent for this transformation. However, further substitution on the allyl bromide caused the reaction to be unsuccessful. It was also found that aldehydes were not competent electrophiles for this transformation. This observed reactivity is unusual, as aldehydes are more electrophilic than ketones. However, the addition of 10 mol% $ZnCl_2$ enabled aldehydes and further substitution of the allyl bromide to be tolerated. It was proposed that the reactive species was a manganese/zinc couple.

5.1.3 Reactivity of organomanganese reagents

Like other organometallic reagents, organomanganese reagents are nucleophilic at carbon. However, they are more stable and less reactive than other organometallics, such as Grignards or organolithiums. They will react with aldehydes, ketones, carbon dioxide, isocyanates and sulfur dioxide. However, they will not react with nitriles, esters or amides.[19] As well as nucleophilic addition to carbonyls, organomanganese compounds can also be used as substrates for cross-coupling reactions.

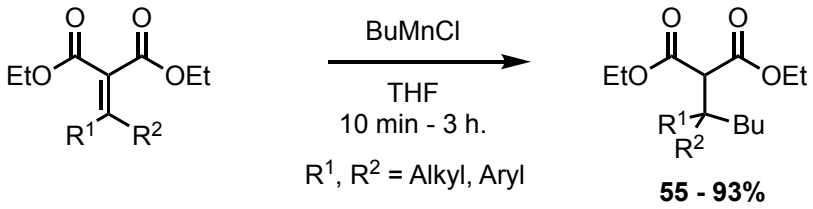
An early example demonstrating the utility of organomanganese reagents describes chemoselective addition to aldehydes in the presence of ketones (Scheme 5.5).[30]



Scheme 5.5 Chemoselective addition of organomanganese to aldehydes.

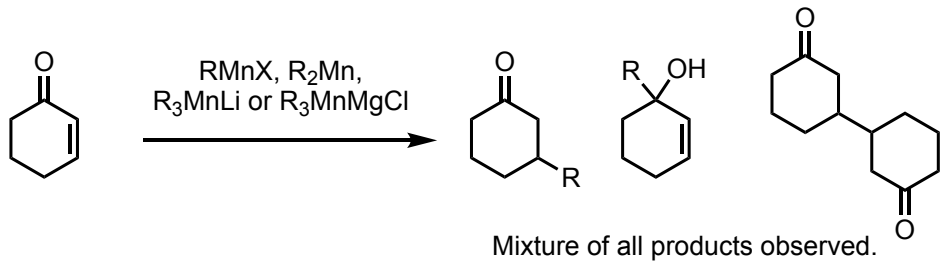
Prior to this example, the best performing class of reagents for this chemoselective transformation were organotitaniums.[31]

Organomanganese reagents behave as soft nucleophiles, as demonstrated by Cahiez and Alami in 1989.[32] It was reported that butyl manganese chloride reacted smoothly with various alkylidenemalonic esters (Scheme 5.6).



Scheme 5.6 Selective 1,4-addition of butylmanganese chloride to alkylidenemalonate esters.

It is interesting to note that this selective 1,4-addition is not observed for reactions with unsaturated ketones (Scheme 5.7).



Scheme 5.7 Reaction of cyclohexenone with a variety of organomanganese reagents.

It was reported that on treating cyclohexenone with a range of organomanganese reagents, three different products were obtained (Scheme 5.7).[33] After attempting this reaction with different types of organomanganese reagents, the exact ratios between the three different products varied, but reaction conditions were not found that lead to selective formation of one product. As well as the desired 1,4-addition product, some 1,2-addition was observed, as well as the product from β reductive dimerization. This was unexpected and had not been achieved by any kind of organometallic reagent.

This kind of transformation is known photochemically[34], and has recently been achieved using a titanium catalyst.[35] The exact ratio of the different products depended on the nature of the organomanganese reagent used and the solvent.

5.2 Results and discussion

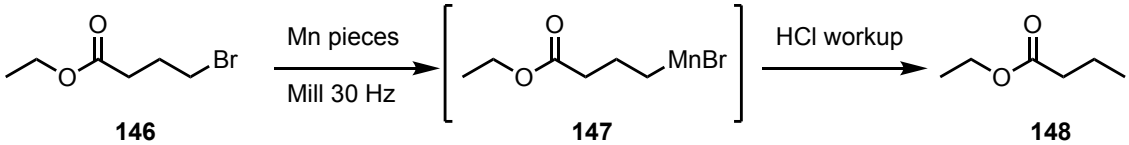
5.2.1 Mechanochemical formation of organomanganese reagents

Initial investigations into the possibility of forming organomanganese reagents directly from manganese metal and alkyl halides were performed in a mixer mill.

The formation of the organometallic was analysed by the same method previously used in the Browne group to investigate the formation of organozincs.[13] Ethyl-4-bromobutyrate **146** was chosen as a model substrate because, if this method was successful, an organomanganese species containing an ester would have been directly synthesised. As discussed previously, by current state of the art methods this remains challenging. Bromoester **146** was milled with manganese metal under various conditions, then the reaction mixture was stirred with HCl to hydrolyse any organomanganese **147** formed, and a GC yield and conversion from starting material was determined (Table 5.1). Pleasingly, after milling **146** for 3 hours with manganese metal, the yield was determined as 28%, with 100% conversion of starting material (Table 5.1, Entry 3). Milling for longer times does not yield a significant improvement. However, Increasing the quantity of manganese to two equivalents did show some improvement to the yield (Table 5.1, Entry 5). Next, the addition of different additives was explored, with DMA chosen initially. In our previous work, it was found that DMA significantly improved the formation of organozinc species. Co-ordinating ligands or solvents are known to improve the stability of organomanganese species.[36] The formation of organomanganese was sensitive to the quantity of DMA added, with the highest yield obtained for one equivalent (Table 5.1, Entry 9). Lithium chloride was investigated as an additive, since when forming organomanganese reagents by transmetallation from organolithiums to $MnCl_2$, it is present as a byproduct. Lithium chloride has also been used to enhance the reactivity of other organometallics, such as the turbo Grignard reagents.[37] This was found not to have a significant effect on the outcome of the reaction (Table 5.1, Entries 13-14). Tetrahydrofuran (THF) was also investigated as an additive, since this is the solvent most commonly used when performing reactions with organomanganese reagents, with no significant improvement in the yield (Table 5.1, Entry 15). However, a mixture containing THF and LiCl was found to increase the yield to that similar to the addition of DMA (Table 5.1, Entry 17). Increased milling time was unable to increase the yield significantly, despite a higher

conversion of starting material (Table 5.1, Entry 24). Other solvents were also screened (Table 5.1, Entries 19 - 23), without any improvement in the yield.

Table 5.1 Initial results on mechanochemical organomanganese formation.



146 **147** **148**

Entry	Mn equiv.	Time / h.	Additive (equiv.)	Conversion of **146**[a]	Yield **148**[a]
1	1.1	1	-	14%	0%
2	1.1	2	-	46%	2%
3	1.1	3	-	100%	28%
4	1.1	4	-	100%	33%
5	2	3	-	100%	43%
6	3	3	-	100%	26%
7	1.1	3	DMA (0.5)	77%	23%
8	1.1	3	DMA (0.75)	75%	25%
9	1.1	3	DMA (1.0)	80%	37%
10	1.1	3	DMA (1.25)	67%	30%
11	1.1	3	DMA (1.5)	84%	16%
12	1.1	3	DMA (2.0)	N. D.[b]	N.D.[b]
13	1.1	3	LiCl (1.0)	52%	21%
14	1.1	3	LiCl (2.0)	33%	12%
15	1.1	3	THF (1.0)	69%	20%
16	1.1	3	THF (2.0)	N. D.[b]	N.D.[b]
17	1.1	3	THF (1.0) / LiCl (1.0)	75%	36%
18	2	3	DMA (1.0)	82%	34%
19	1.1	3	DMF (1.0)	75%	28%
20	1.1	3	DMSO (1.0)	N. D.[b]	N.D.[b]
21	1.1	3	EtOAc (1.0)	0%	0%
22	1.1	3	NMP (1.0)	81%	23%
23	1.1	4	DMA (1.0)	88%	33%
24	1.1	4	THF (1.0) / LiCl (1.0)	97%	38%

[a] Measured by GC. [b]Milling vessel leaked during reaction.

The larger quantities of solvents sometimes led to the milling jar leaking, perhaps due to a build up in pressure (Table 5.1, Entries 12, 16). These reactions were repeated,

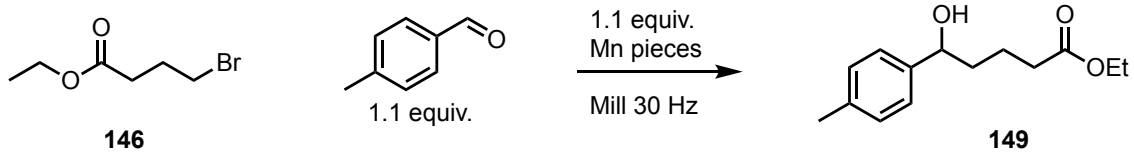
with the same outcome. Interestingly, there were also problems with leaking when one equivalent of DMSO was used (Table 5.1, Entry 20), which also occurred on repetition. Possible decomposition of DMSO to dimethyl sulfide could have occurred, which, as a gas, could lead to a build up of pressure inside the milling vessel.

At this point, the highest yields observed resulted from milling with two equivalents of manganese for three hours (Table 5.1, Entry 5). However, with high stoichiometric ratio of manganese being undesirable, the optimal conditions were chosen as milling with 1.1 equivalents of manganese and one equivalent of DMA (Table 5.1, Entry 9) or with one equivalent of THF and LiCl (Table 5.1, Entry 17). However, the conversion of starting material remained high. This suggests that the organomanganese is being formed, but without any external reagent to react with, it decomposes. It was therefore proposed that an external electrophile should be added to the reaction mixture.

5.2.2 Initial results

As alkylmanganese reagents are reported to react smoothly with aldehydes in solution, the first reaction attempted was with tolaldehyde. However, to date there is no report of an organomanganese reagent featuring an ester.

Table 5.2 Attempts at mechanochemical reaction of organomanganese with tolaldehyde.



146 **149**

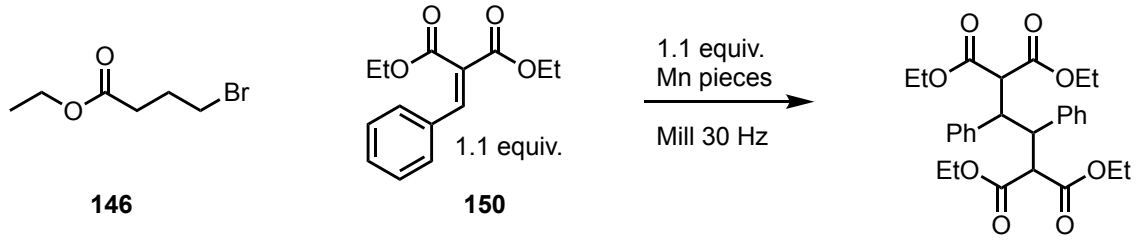
Entry	Mn equiv.	Time / h.	Additive (equiv.)	Yield 149
1	1.1	3	DMA (1.0)	0%
2	1.1	3	THF (1.0) / LiCl (1.0)	0%

On addition of tolaldehyde to the optimal conditions for the formation of organomanganese **147**, no addition product **149** was identified in the reaction mixture by GC-MS (Table 5.2), with only starting materials observed.

The possibility of reaction with alkylidenemalonate esters was then investigated. The optimal conditions from Table 5.1 were applied, with the addition of 1.1 equivalents of diethylbenzylidenemalonate **150** (Table 5.3). There was significant conversion of starting material with THF / LiCl, but not to the expected 1,4-addition product. The main

product was isolated and identified as **151** in 66% yield (Table 5.3, Entry 2). On increasing the reaction time, this product could also be obtained using DMA as an additive. This reductive dimerisation product is similar to the reactivity previously observed between organomanganese reagents and cyclohexenone[33], but with better selectivity, as only the dimerised product was observed for the alkylidenemalonate ester.

Table 5.3 Attempts at mechanochemical reaction of organomanganese with diethylbenzylidenemalonate **150**.



146 **150** **151**

Entry	Mn equiv.	Time / h.	Additive (equiv.)	Yield 151[a]
1	1.1	3	DMA (1.0)	0%
2	1.1	3	THF (1.0) / LiCl (1.0)	66%
3	1.1	4	DMA (1.0)	31%
4	1.1	5	DMA (1.0)	42%

[a] Isolated yield.

As this reactivity was unexpected, a number of control experiments were performed to establish which additives are required for the dimerisation to occur.

It was found that the dimerisation did not occur only by milling of reactant **150** (Table 5.4, Entry 1). Likewise, milling the same reaction mixture without manganese did not lead to any product formation (Table 5.4, Entry 2). This demonstrates that manganese is required, however on milling with only manganese no reactivity was observed (Table 5.4, Entries 3 - 4). Further experiments demonstrate that THF, LiCl and Mn are required for this dimerisation to occur (Table 5.4, Entry 8). However, the isolated yield is significantly lower than when bromoester **146** is present (Table 5.4, Entry 2).

Table 5.4 Control experiments on dimerisation of **150**.

150 **151**

Entry	Reagents (equiv.)	Yield 151
1	-	0%
2	LiCl (1.0), THF (1.0), ethyl-4-bromobutyrate (1.0)	0%
3	Mn (1.1)	0%
4	Mn (0.5)	0%
5	Mn (1.1), LiCl (1.0)	0%
6	Mn (1.1), ethyl-4-bromobutyrate (1.0)	0%
7	Mn (1.1), ethyl-4-bromobutyrate (1.0), LiCl (1.0)	0%
8	Mn (1.1), THF (1.0), LiCl (1.0)	30%
9	Mn (1.0), THF (1.0), ethyl-4-bromobutyrate (1.0)	0%

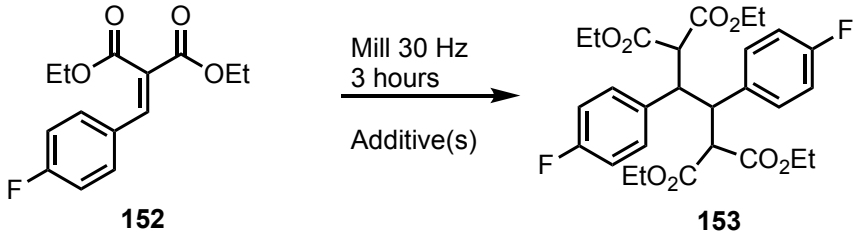
This is interesting, as it suggests that an organomanganese species is not required for the dimerisation to occur, but that if one can be formed, it significantly enhances the reactivity. Further investigations are required to probe how this reaction proceeds are necessary in order to understand the mechanism and what intermediates are involved.

The literature precedents for this type of reductive alkene dimerisation are relatively few. The currently known methods all make use of single electron transfer conditions, such as electrochemical processes.[38] There are also reports of similar transformations using samarium diiodide[39] and a recent report of alkene dimerisation using a palladium catalyst in the presence of an alcohol.[40] However, manganese is not currently known to mediate reductive dimerisation, although Mn(III) salts can perform single electron oxidations.[41]

5.2.3 Scope

In order to probe this reactivity further, the scope of the dimerisation was briefly investigated. Arylidenemalonate ester **152** was synthesised by Knoevenagel condensation of diethyl malonate with 4-fluorobenzaldehyde. Diester **152** was then subjected to the reaction conditions identified for the dimerisation of **150** (Table 5.3).

Table 5.5 Dimerisation of **152**.

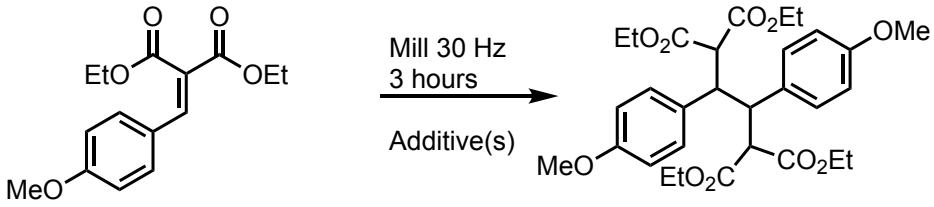


152 **153**

Entry	Additive (equiv.)	Yield 153
1	Mn (1.1), THF (1.0), LiCl (1.0)	0%
2	Mn (1.0), THF (1.0), LiCl (1.0), ethyl-4-bromobutyrate (1.0)	37%

It was found that dimerisation to **153** occurred in the presence of all additives with an isolated yield of 37%. As **152** features an electron deficient aromatic ring, an example with an electron rich aromatic ring was tested. The arylidenemalonate ester **154** derived from anisaldehyde was subjected to the same reaction conditions (Table 5.6). Under the same reaction conditions, that were successful for the dimerisation of **150** and **152**, no conversion to **154** was observed, with only starting material obtained after the reaction. If the reaction mechanism involves single electron transfer to the alkylidenemalonate, then this result is to be expected. A more electron rich substrate would undergo single electron reduction slower than a more electron poor substrate.

Table 5.6 Attempts at dimerisation of **154**.

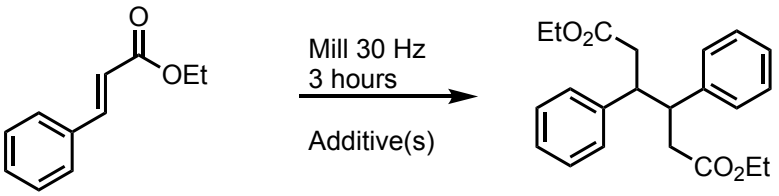


154 **155**

Entry	Additive (equiv.)	Yield 155
1	Mn (1.1), THF (1.0), LiCl (1.0)	0%
2	Mn (1.0), THF (1.0), LiCl (1.0), ethyl-4-bromobutyrate (1.0)	0%

A range of different activated alkenes were then synthesised and applied to the reaction conditions. Electron withdrawing groups were chosen with varying Hammett parameters in order to probe any electronic effects on the reaction outcome. The unsaturated monoester **156** was subjected to milling under comparable reaction conditions, and no reactivity was observed (Table 5.7).

Table 5.7 Attempts at dimerisation of **156**.

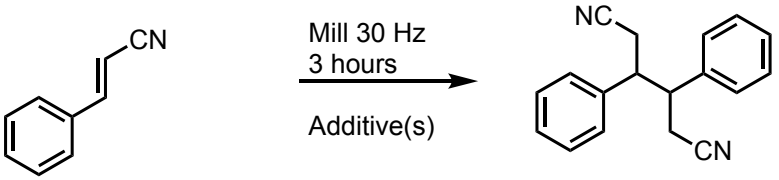


156 **157**

Entry	Additive (equiv.)	Yield 157
1	Mn (1.1), THF (1.0), LiCl (1.0)	0%
2	Mn (1.0), THF (1.0), LiCl (1.0), ethyl-4-bromobutyrate (1.0)	0%

The unsaturated nitrile **158** was also subjected to these reaction conditions (Table 5.8). It was found that using a mononitrile as the electron-withdrawing group was not sufficient for activating the alkene towards this dimerisation process.

Table 5.8 Attempts at dimerisation of mononitrile **158**.

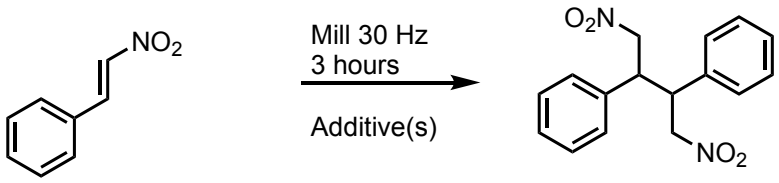


158 **159**

Entry	Additive (equiv.)	Yield 159
1	Mn (1.1), THF (1.0), LiCl (1.0)	0%
2	Mn (1.0), THF (1.0), LiCl (1.0), ethyl-4-bromobutyrate (1.0)	0%

A further test of functional groups that are able to activate the alkene towards manganese mediated dimerisation was performed with nitroalkene **160** (Table 5.9). Although the expected product **161** was not observed, the starting material could not be recovered from the reaction mixture in this case. However, most of the material was lost on rotary evaporation, demonstrating that nitroalkene **160** decomposed to volatile materials on being subjected to these conditions.

Table 5.9 Attempts at dimerisation of mononitrile **160**.

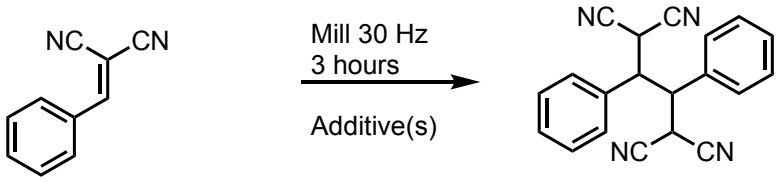


160 **161**

Entry	Additive (equiv.)	Yield 161
1	Mn (1.1), THF (1.0), LiCl (1.0)	0%
2	Mn (1.0), THF (1.0), LiCl (1.0), ethyl-4-bromobutyrate (1.0)	0%

As alkenes activated by one electron withdrawing group are unreactive towards dimerisation under the conditions investigated, the reactivity of dinitrilealkene **162** was investigated (Table 5.10). This substrate was, however, also found to be unreactive under these mechanochemical conditions, with only starting material observed after milling.

Table 5.10 Attempts at dimerisation of dinitrile **162**.

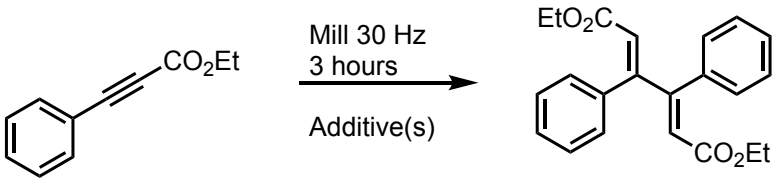


162 **163**

Entry	Additive (equiv.)	Yield 163
1	Mn (1.1), THF (1.0), LiCl (1.0)	0%
2	Mn (1.0), THF (1.0), LiCl (1.0), ethyl-4-bromobutyrate (1.0)	0%

As a further initial search for reactive functional groups the propargyl ester **164** was used as a substrate (Table 5.11). This was synthesised by Sonogashira coupling from the corresponding ethyl propiolate and iodobenzene. This reaction attempt also failed to furnish any product, with only starting materials obtained at the end of the milling time.

Table 5.11 Attempts at dimerisation of propargyl ester **164**.



164 **165**

Entry	Additive (equiv.)	Yield 165
1	Mn (1.1), THF (1.0), LiCl (1.0)	0%
2	Mn (1.0), THF (1.0), LiCl (1.0), ethyl-4-bromobutyrate (1.0)	0%

In summary, the observed dimerisation of diethylarylidenemalonates under mechanochemical conditions with manganese metal and various additives could not be extended to other examples of electron deficient alkenes. None of the alkenes activated by one electron-withdrawing group were reactive, suggesting that possibly two activating groups are required. However, even dinitrile **162** was unreactive, despite being more electron-withdrawing than diester **150** (Table 5.12). This suggests that the success of the reaction may depend on a different property of the substrate.

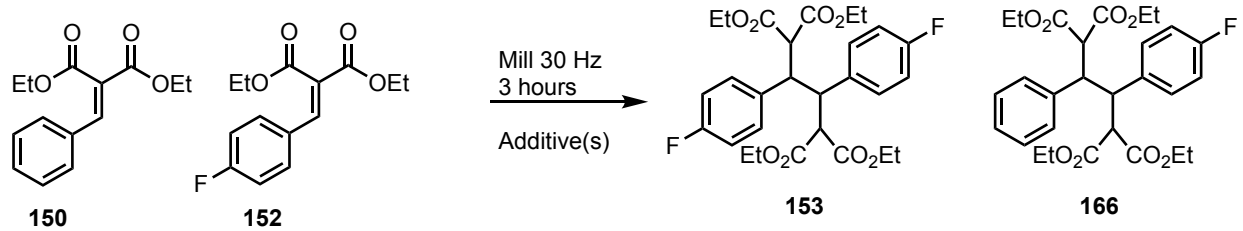
Table 5.12 Hammett parameters for substituents tested.[42]

Substituent	Hammett σ_{para} parameter for benzoic acid ionisation
$-NO_2$	0.778
-CN	0.660
$-CO_2Et$	0.45
-F	0.062
-H	0
-OMe	-0.268

If the mechanism involves the single electron reduction of the substrate, more important a parameter than how electron-withdrawing the substrates are is the reduction potential of the substrates.

In order to probe the possible utility of this process an attempt at cross coupling different alkenes was performed. The two alkenes found that exhibited reactivity towards dimerisation (**150** and **152**) were both subjected to the milling reaction conditions in a 1:1 mixture (Table 5.13).

Table 5.13 Cross coupling of **150** with **152**.



150 0.5 mmol

152 0.5 mmol

153

166

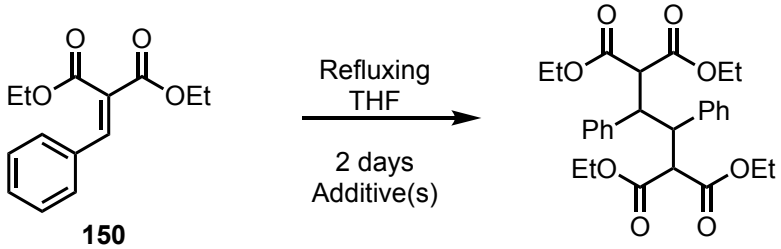
Entry	Additive (equiv.)	Yield 153	Yield 166
1	Mn (1.1), THF (1.0), LiCl (1.0)	0%	0%
2	Mn (1.0), THF (1.0), LiCl (1.0), ethyl-4-bromobutyrate (1.0)	38%[a, b]	36%[a, c]

[a]Isolated as a mixture of **153** and **166**. [b] Relative to 0.25 mmol. [c] Relative to 0.5 mmol.

It was found that cross coupling was possible on milling, with a mixture of **153** and **166** isolated and the ratio determined by ^{19}F NMR spectroscopy. The homocoupled product of **150** with **150** was not observed. However, a significant quantity of the fluorinated dimer was also obtained, so the selectivity is fairly poor for the desired cross-coupled product.

As a control experiment, it was investigated whether mechanochemical conditions were required for the desired transformation. A mixture of diethylbenzylidenemalonate **150** with manganese powder and lithium chloride in refluxing THF for 2 days yielded only the starting materials (Table 5.14). Likewise, a mixture containing the same reagents and ethyl-4-bromobutyrate under reflux for 2 days also failed to yield any of dimer **151**.

Table 5.14 Attempts at the dimerisation of **150** in refluxing THF.



150

151

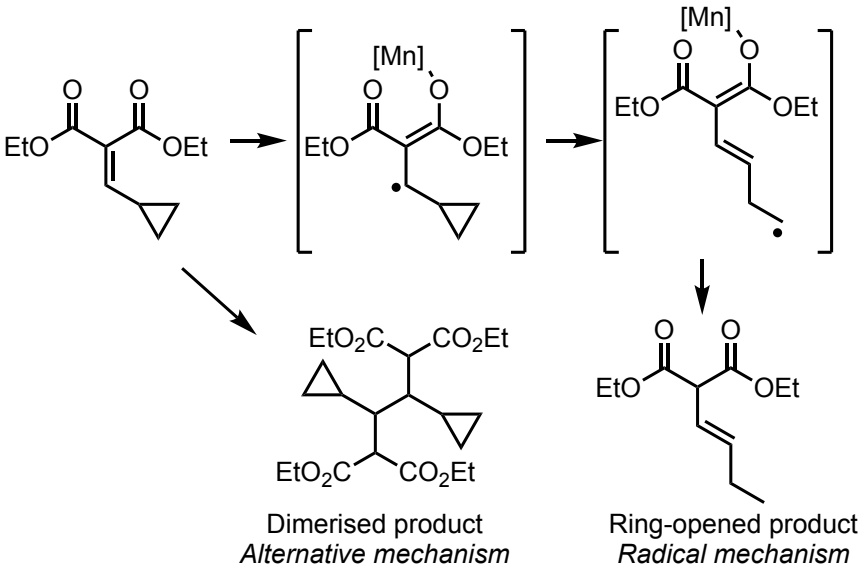
Entry	Additive (equiv.)	Yield 151
1	Mn (1.1), LiCl (1.0)	0%
2	Mn (1.0), LiCl (1.0), ethyl-4-bromobutyrate (1.0)	0%

This result suggests that the mechanical action in the ball mill is required, possibly to expose reactive surfaces of manganese metal.

5.2.4 Conclusion and outlook

Initial investigations into the formation and reaction of an organomanganese reagent were performed under ball milling conditions. Following on from previous work in the Browne group into organozinc reagents, ethyl-4-bromobutyrate was milled with manganese metal and it was found that the most promising reaction conditions included THF and LiCl. However, on addition of diethylbenzylidenemalonate, which was expected to undergo conjugate addition with the organomanganese reagent, a different reaction occurred. Under these conditions, a reductive dimerisation of the alkene occurred in the ball mill, with the unsaturated diester exhibiting umpolung reactivity. This transformation could also be achieved for the electron poor diethyl-(4-fluoro)-benzylidenemalonate and the reductive cross coupled product could also be obtained from these two different arylidenemalonate esters. Other less-activated alkenes were not competent substrates in this reaction. The reactivity observed in the ball mill could not be reproduced in refluxing THF.

These initial results are interesting, and demonstrate a novel manganese mediated reaction manifold. However, a significant amount of further work is required to further develop and understand this reactivity. As other electrophilic, electron-deficient alkenes could not be transformed in this process, this suggests that the mechanism may not be ionic, but radical. Future work could focus on establishing a reasonable mechanism for this transformation, including the role of each additive. To test for the formation of radicals, a radical trapping experiment from the cyclopropane derivative would be interesting (Scheme 5.8).



Scheme 5.8 Envisaged possible products from cyclopropane derivative giving information about the mechanism.

Addition of other radical trapping agents, such as TEMPO could also be used to help determine the mechanism. This experiment could give information about possible radical intermediates and therefore single electron transfers occurring during the dimerisation process. As both the dimerisation and cross-coupling processes observed require reduction, one or more of the additives must be being oxidised. Experiments carefully analysing side products could help elucidate the mechanism and role of the additives. Kinetic studies varying the concentration of the different additives would also help.

Once a mechanism that explains the observations can be proposed, then it may be possible to predict reactive substrates for the observed transformation. It may also be possible to predict other possible transformations using similar reaction conditions.

Assuming that the mechanism is found to involve single electron reduction of the alkene by manganese metal, this would be the first demonstration of such reactivity using manganese. A range of more synthetically useful substrates could then have their reactivity in this process predicted by measuring their reduction potentials using cyclic voltammetry. It would also be interesting to test if the previously observed reactivity with cyclohexenone and organomanganese reagents in solution (to yield 1,2-addition, 1,4-addition and dimerisation, Scheme 5.7) occurs mechanochemically, or if this can be achieved selectively.

Turning attention back to the original aim, of synthesising and reacting organomanganese reagents in the ball mill, is also important. The initial attempts presented in this chapter using ethyl-4-bromobutyrate are complicated by the presence of an ester, with no such organomanganese reagents previously reported. It would therefore be interesting to investigate the mechanochemical synthesis of organomanganese reagents that are known, such as from butyl bromide or allyl bromide. These substrates may form the organomanganese reagent more successfully and react reliably with electrophiles such as aldehydes.

The texture of the reaction mixture when forming the organomanganese reagent could also be an important parameter to optimise. As all the reagents added are liquids, except for the manganese metal, it would be of interest to investigate the addition of a grinding auxiliary.

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6 Experimental

6.1 General Methods

All chemicals were obtained from commercial sources and used without further purification unless stated otherwise. Dry solvents were obtained from a Braun MB SPS-800 solvent purification system fitted with the recommended columns.

^{1}H, ^{19}F and ^{13}C NMR spectra were obtained on Bruker 300 Avance II, Bruker 400 MHz and Bruker 500 MHz spectrometers with chloroform-d, MeCN-d3 or DMSO-d6 as deuterated solvents. The obtained chemical shifts δ are reported in ppm and are referenced to the residual solvent signal (7.26 and 77.16 ppm for ^{1}H and ^{13}C respectively). Spin-spin coupling constants *J* are given in Hz and refer to apparent multiplicities rather than true coupling constants. Data are reported as: chemical shift, multiplicity and integration.

High resolution mass spectral (HRMS) data were obtained on a Thermo Scientific LTQ Orbitrap XL by the EPSRC UK National Mass Spectrometry Facility at Swansea University or on a Waters MALDI-TOF mx at Cardiff University. Spectra were obtained using electron impact ionization (EI), chemical ionization (CI), positive electrospray (ES), pneumatically-assisted electrospray (pNSI) or atmospheric solids analysis probe (ASAP+).

Infrared spectra were recorded on a Shimadzu IR-Affinity-1S FTIR spectrometer.

Melting points were measured using a Gallenkamp apparatus and are reported uncorrected.

The ball mill used for sections **6.2** and **6.3** was a Retsch MM 400 mixer mill. Unless otherwise stated, mechanochemical reactions were performed in 10 mL stainless steel jars with one stainless steel ball of mass 4 g. The longest time that this mill can be programmed to run for is 99 minutes. In order to run longer reaction times the mill was started, then additional time added to the timer in order to ensure that the mill was running continuously for the desired reaction time.

The ball mill used for sections **6.4** and **6.5** was an InSolidoTech IST500 mixer mill. Unless otherwise stated, mechanochemical reactions were performed in 14 mL stainless steel jars with one stainless steel ball of mass 4 g at a milling frequency of 30 Hz.

6.2 Mechanochemical Fluorination

6.2.1 Conventional solution phase reactions

Monofluorination

To a solution of Selectfluor (0.708 g, 2 mmol) in acetonitrile (20 mL) was added the 1,3-dicarbonyl (1 mmol). α,α,α -Trifluorotoluene (0.041 mL, 0.33 mmol) was added as an NMR standard and the reaction mixture was stirred at room temperature, monitoring by ^{19}F NMR. When the reaction was complete, the solvent was removed under reduced pressure. Water (20 mL) and dichloromethane (20 mL) were added and the aqueous layer further extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed to yield the product. ^{19}F NMR spectra were measured again to confirm that the ratio of products had not changed during extraction.

Difluorination

To a solution of Selectfluor (0.708 g, 2 mmol) in acetonitrile (20 mL) was added the 1,3-dicarbonyl (1 mmol) and sodium carbonate (0.106 g, 1 mmol). α,α,α -Trifluorotoluene (0.041 mL, 0.33 mmol) was added as an NMR standard (δ = -63 ppm) and the reaction mixture was stirred at room temperature, monitoring by ^{19}F NMR spectroscopy. When the reaction was complete, the solvent was removed under reduced pressure. Water (20 mL) and dichloromethane (20 mL) were added and the aqueous layer further extracted with dichloromethane (20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed to yield the product. ^{19}F NMR spectra were measured again to confirm that the ratio of products had not changed during extraction.

6.2.2 Study of yield against time with and without LAG

6.2.3 Neat grinding conditions

To a 10 mL stainless steel jar was added Selectfluor (0.142 g, 0.2 mmol), dibenzoylmethane (0.045 g, 0.2 mmol) and a stainless steel ball (mass 4.0 g). The ball mill was run at 30 Hz for the appropriate time. The contents of the jar were transferred to a flask, washing with chloroform. α,α,α-Trifluorotoluene (0.041 mL, 0.33 mmol) was added and the mixture filtered through a plug of cotton wool into an NMR tube. ^{19}F NMR spectra were measured and the yield determined by comparing the integrals of the products to the integrals of trifluorotoluene. This process was repeated for each jar over different time intervals (Table 6.1).

Table 6.1 Neat grinding kinetic results

Time / min	Yield Mono / %	Yield Di / %
5	7	0
30	53	4
45	78	9
60	87	11
90	76	24
120	61	38
180	57	43

Liquid-Assisted-Grinding (LAG) conditions

To a 10 mL stainless steel jar was added Selectfluor (0.142 g, 0.2 mmol), dibenzoylmethane (0.045 g, 0.2 mmol), acetonitrile (0.125 mL) and a stainless steel ball (mass 4.0 g). The ball mill was run at 30 Hz for the appropriate time. The contents of the jar were transferred to a flask, washing with chloroform. α,α,α-Trifluorotoluene (0.041 mL, 0.33 mmol) was added and the mixture filtered through a plug of cotton wool into an NMR tube. ^{19}F NMR spectra were measured and the yield determined by comparing the integrals of the products to the integrals of trifluorotoluene. This process was repeated for each jar over different time intervals (Table 6.2).

Table 6.2 LAG kinetic results

Time / min	Yield Mono / %	Yield Di / %
5	12	0
45	47	0
90	75	0
120	100	0
180	95	3

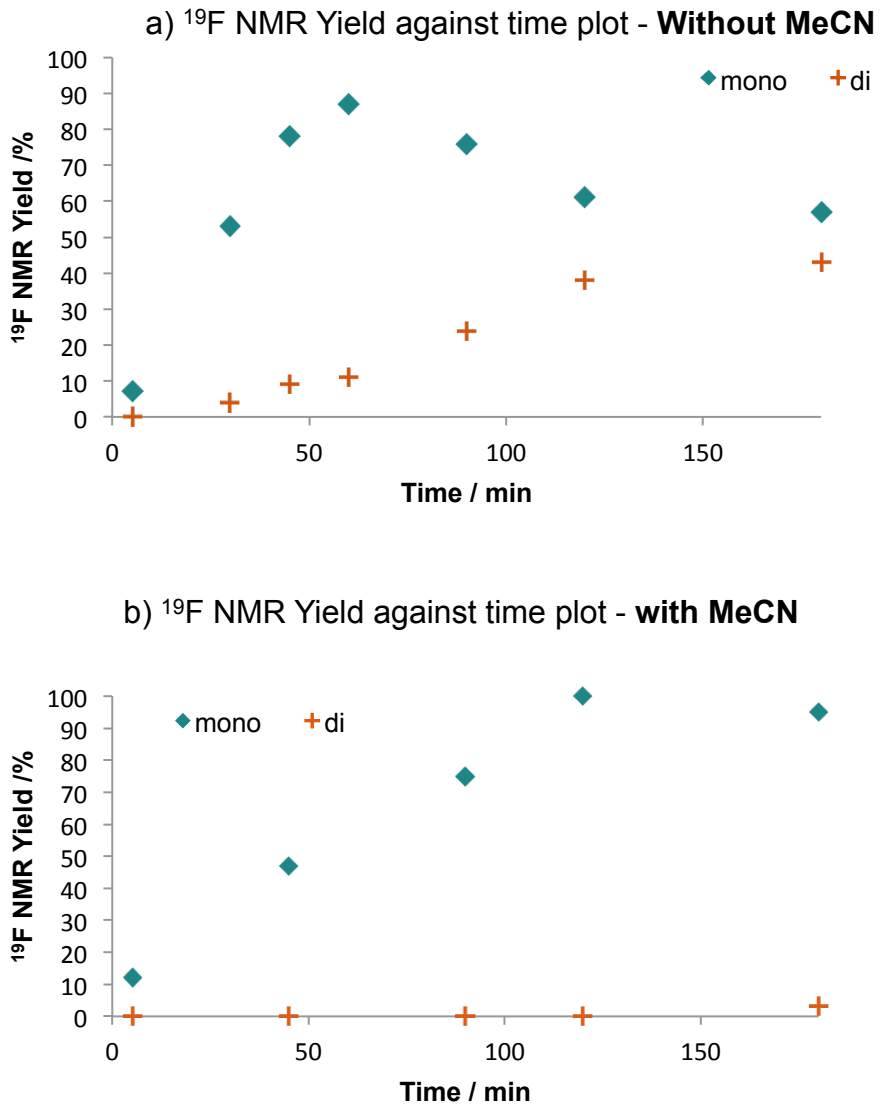
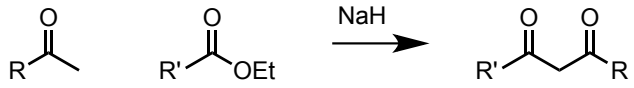


Figure 6.1 Yields of mono- and difluorinated products at different times a) without and b) with acetonitrile

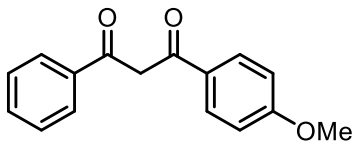
6.2.4 Synthesis of 1,3-diketones



General Procedure 1 (GP1)

Following a modified literature procedure[1], the corresponding ester (20 mmol, 2 equiv) and NaH (1.2 g, 28 mmol, 2.8 equiv, 60% in mineral oil) were dissolved in dry THF (20 mL) in oven-dried glassware under N_2. A solution of the corresponding ketone (10 mmol) in dry THF (20 mL) was added slowly and the reaction mixture, heated to reflux and stirred overnight. The reaction mixture was quenched with aqueous HCl (25 mL, 1 M) and dichloromethane (50 mL). The aqueous layer was extracted with dichloromethane (2 x 20 mL) and the combined organic phase washed with brine (20 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the crude product. This was further purified by recrystallization from EtOH to give the clean product.

1-(4-methoxyphenyl)-3-phenylpropane-1,3-dione[2]



Prepared according to **GP1,** 0.915 g, 3.6 mmol, 18%, off-white powder. Analytical data is in agreement with the literature.[2]

^{1}H NMR (300 MHz, $CDCl_3$, enol form) δ 8.05 – 7.93 (m, 4H, Ar-H), 7.58 – 7.42 (m, 3H, Ar-H), 6.99 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.80 (s, 1H, enol), 3.89 (s, 3H, -C**H**$_3$).

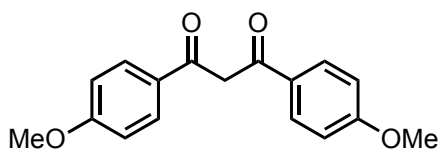
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 186.4 (**C**=O), 184.2 (**C**=O), 175.7 (Ar), 163.4 (Ar), 135.7 (Ar), 132.3 (Ar), 129.5 (Ar), 128.8 (Ar), 127.2 (Ar), 114.1 (Ar), 92.5 (**C**H$_2$), 55.7 (**C**H$_3$).

IR: 1587, 1437, 1296, 1257, 1182, 1020, 766, 702, 694 cm^{-1}

HRMS (EI+) [$C_{16}H_{14}O_3$]: calc. 254.0943, found 254.0948

mp: 129 - 130 °C (ethanol)

1,3-bis(4-methoxyphenyl)propane-1,3-dione, 102SM[3]



Prepared according to **GP1,** 2.410 g, 8.45 mmol, 85%, yellow crystals. Analytical data is in agreement with the literature.[3]

^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ 7.96 (d, *J* = 8.7 Hz, 4H, Ar-H), 6.98 (d, *J* = 8.7 Hz, 4H, Ar-H), 6.73 (s, 1H, enol), 3.88 (s, 6H, -C**H**$_3$).

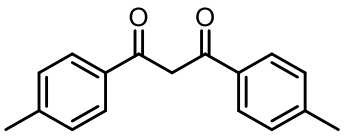
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 185.0 (**C**=O), 163.0 (Ar), 129.0 (Ar), 128.5 (Ar), 114.0 (Ar), 91.5 (-**C**H_2), 55.5 9 (**C**H_3).

HRMS (EI+) [$C_{17}H_{16}O_4$]: calc. 284.1049, found 284.1053.

IR: 1587, 1437, 1256, 1227, 1167, 1110, 1018, 835, 777, 575, 507, 473 cm^{-1}.

mp: 111 - 113 °C (ethanol)

1,3-di-p-tolylpropane-1,3-dione, 103SM



Prepared according to **GP1,** 1.686 g, 6.6 mmol, 33%, yellow needles.

^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ 7.89 (d, *J* = 8.1 Hz, 4H, Ar-H), 7.29 (d, *J* = 8.0 Hz, 4H, Ar-H), 6.81 (s, 1H, enol), 2.43 (s, 6H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 185.6 (**C**=O), 143.3 (Ar), 133.0 (Ar), 129.5 (Ar), 127.3 (Ar), 92.6 (-**C**H_2), 21.8 (-**C**H_3).

IR: 1522, 1477, 1182, 1121, 1055, 1015, 768, 474 cm^{-1}.

HRMS (EI+) [$C_{17}H_{16}O_2$]: calc. 252.1150, found 252.1154

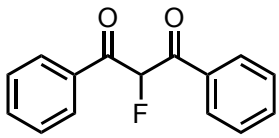
mp: 127 - 128 °C (ethanol)

6.2.5 Mechanochemical monofluorination of 1,3-diketones

General procedure 2 (GP2)

To a 10 mL stainless steel jar was added the 1,3-diketone (1 mmol), Selectfluor (0.708 g, 2 mmol) and acetonitrile (0.125 mL). A stainless steel ball of mass 4.0 g was added and the mixture milled at 30 Hz for 2 hours. The resulting powder was transferred into a flask, washing the residue with chloroform (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-Trifluorotoluene (0.041 mL, 0.33 mmol) was added as an NMR standard (δ = -63 ppm) and ^{19}F NMR spectra of the crude mixture were measured to determine the product ratio and conversion. The solvent and α,α,α-trifluorotoluene were removed under reduced pressure to yield the product. ^{19}F NMR spectra were measured again to confirm that the ratio of products had not changed after evaporation of the solvent.

2-fluoro-1,3-diphenylpropane-1,3-dione, 99[4]



Prepared according to **GP2**, 236 mg, 0.98 mmol, 98%, 50:1 mono:di, yellow solid. Analytical data is in agreement with the literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 4H, Ar-H), 7.65 – 7.59 (m, 2H, Ar-H), 7.53 – 7.45 (m, 4H, Ar-H), 6.54 (d, *J* = 49.2 Hz, 1H, -C**H**F).

^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 191.3 (d, *J* = 20.2 Hz, **C**=O), 134.7 (Ar), 133.7 (d, *J* = 2.0 Hz, Ar), 130.0 (d, *J* = 3.5 Hz, Ar), 128.9 (Ar), 96.7 (d, *J* = 199.0 Hz, -**C**HF).

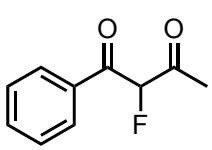
^{19}F NMR (376 MHz, $CDCl_3$) δ -186.88 (d, *J* = 48.9 Hz).

IR: 1697, 1672, 1593, 1448, 1282, 1097, 1022, 1001, 966, 867, 779, 705, 680, 553, 457 cm^{-1}

HRMS (EI+): [$C_{15}H_{11}O_2F + NH_4$] calc. 260.1081, found 260.1083

mp: 74-76 °C (chloroform)

2-fluoro-1-phenylbutane-1,3-dione, 101[4]



Prepared according to **GP2**, 180 mg, 0.99 mmol, 99%, 5:1 mono:di, purple oil. Analytical data is in agreement with the literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.61 – 7.48 (m, 1H, Ar-H), 7.39 (t, *J* = 7.6 Hz, 2H, Ar-H), 5.86 (d, *J* = 50.0 Hz, 1H, -C**H**F), 2.23 (s, 3H, -C**H**$_3$).

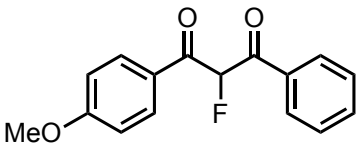
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.6 (d, *J* = 23.9 Hz, **C**=O), 190.3 (d, *J* = 19.0 Hz, **C**=O), 134.6 (Ar), 133.5 (d, *J* = 1.3 Hz, Ar), 129.7 (d, *J* = 3.0 Hz, Ar), 128.8 (Ar), 96.5 (d, *J* = 198.0 Hz, -**C**HF), 25.9 (-**C**H$_3$).

^{19}F NMR (376 MHz, $CDCl_3$) δ -189.58 (d, *J* = 50.1 Hz).

IR: 1734, 1692, 1597, 1450, 1360, 1275, 1204, 1179, 1101, 959, 689 cm^{-1}.

HRMS (EI+) [$C_{10}H_9O_2F$] calc. 180.0587, found 180.0589

2-fluoro-1-(4-methoxyphenyl)-3-phenylpropane-1,3-dione, 102



Prepared according to **GP2**, 225 mg, 0.83 mmol, 83%, 40:1 mono:di, yellow solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, 4H, Ar-H), 7.54 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.41 (t, *J* = 7.5 Hz, 2H, Ar-H), 6.88 (d, *J* = 8.3 Hz, 2H, Ar-H), 6.51 (d, *J* = 49.2 Hz, 1H, -C**H**F), 3.78 (s, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 191.5 (d, *J* = 20.2 Hz, **C**=O), 189.3 (d, *J* = 19.8 Hz, **C**=O), 164.6 (Ar), 134.4 (Ar), 133.6 (d, *J* = 1.9 Hz, Ar), 132.3 (d, *J* = 3.6 Hz, Ar), 129.7 (d, *J* = 3.3 Hz, Ar), 128.7 (Ar), 126.5 (d, *J* = 2.1 Hz, Ar), 114.0 (Ar), 96.5 (d, *J* = 198.1 Hz, -**C**HF), 55.5 (-**C**H$_3$).

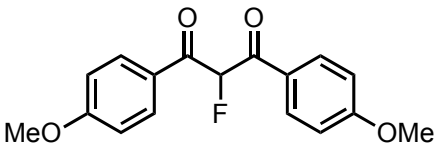
^{19}F NMR (376 MHz, CDCl3) δ -186.37 (d, *J* = 49.2 Hz).

IR: 1672, 1595, 1510, 1256, 1024, 841, 750, 691 cm^{-1}.

HRMS (EI+): [$C_{16}H_{13}O_3F$] calc. 272.0849, found 272.0845

mp: 37 - 39 °C (chloroform)

2-fluoro-1,3-bis(4-methoxyphenyl)propane-1,3-dione, 103[5]



Prepared according to **GP2**, 295 mg, 0.98 mmol, 98%, 50:1 mono:di, yellow crystals. Analytical data is in agreement with the literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.5 Hz, 4H, Ar-H), 6.90 (d, *J* = 8.5 Hz, 4H, Ar-H), 6.45 (d, *J* = 49.3 Hz, 1H, -C**H**F), 3.81 (s, 6H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 189.6 (d, *J* = 19.9 Hz, **C**=O), 164.6 (Ar), 132.4 (d, *J* = 3.5 Hz, Ar), 126.6 (d, *J* = 2.0 Hz, Ar), 114.0 (Ar), 97.8 (d, *J* = 191.9 Hz, -**C**HF), 55.6 (-**C**H$_3$).

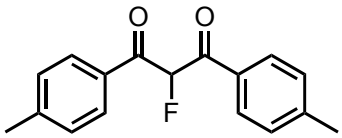
^{19}F NMR (376 MHz, $CDCl_3$) δ -185.98 (d, *J* = 49.3 Hz).

IR: 1667, 1589, 1572, 1508, 1244, 1169, 1096, 1022, 961, 835, 567, 513 cm^{-1}.

HRMS (EI+) [$C_{17}H_{15}O_4F$] calc. 302.0954, found 302.0961

mp: 94 - 95 °C (chloroform)

2-fluoro-1,3-di-p-tolylpropane-1,3-dione, 104



Prepared according to **GP2**, 202 mg, 0.75 mmol, 75%, 29:1 mono:di, yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.5 Hz, 4H, Ar-H), 7.13 (d, *J* = 8.5 Hz, 4H, Ar-H), 6.50 (d, *J* = 49.2 Hz, 1H, -C**H**F), 2.43 (s, 6H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.8 (d, *J* = 20.0 Hz, **C**=O), 145.7 (Ar), 131.1 (d, *J* = 1.9 Hz, Ar), 130.0 (d, *J* = 3.4 Hz, Ar), 129.5 (Ar), 96.7 (d, *J* = 198.3 Hz, -**C**HF), 21.8 (-**C**H$_3$).

^{19}F NMR (376 MHz, $CDCl_3$) δ -186.72 (d, *J* = 49.2 Hz).

IR: 1695, 1603, 1287, 1233, 1184, 1090, 959, 876, 824, 752, 556 cm^{-1}.

HRMS (EI+): [$C_{17}H_{15}O_2F$] calc. 270.1056, found 270.1051

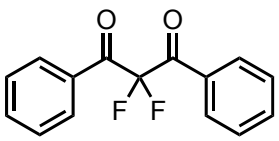
mp: 88 - 89 °C (chloroform)

6.2.6 Mechanochemical difluorination of 1,3-diketones

General Procedure 3 (GP3)

To a 10 mL stainless steel jar was added the 1,3-diketone (1 mmol), Selectfluor (0.708 g, 2 mmol) and sodium carbonate (0.106 g, 1 mmol). A stainless steel ball of mass 4.0 g was added and the mixture milled at 30 Hz for 2 hours. The resulting powder was transferred into a flask, washing the residue with chloroform (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-Trifluorotoluene (0.041 mL, 0.33 mmol) was added as a NMR standard (δ = -63 ppm) and ^{19}F NMR spectra of the crude mixture were measured to determine the product ratio and conversion. The solvent and α,α,α-trifluorotoluene were removed under reduced pressure to yield the product. ^{19}F NMR spectra were measured again to confirm that the ratio of products had not changed after evaporation of the solvent.

2,2-difluoro-1,3-diphenylpropane-1,3-dione, 100[6]



Prepared according to **GP3**, 242 mg, 0.93 mmol, 93%, 17:1 di:mono, brown crystals. Analytical data is in agreement with the literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.5, 1.0 Hz, 4H, Ar-H), 7.71 – 7.65 (m, 2H, Ar-H), 7.55 – 7.50 (m, 4H, Ar-H).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 187.4 (t, *J* = 27.0 Hz, **C**=O), 135.1 (Ar), 131.6 (t, *J* = 1.5 Hz, Ar), 130.3 (t, *J* = 2.5 Hz, Ar), 129.0 (Ar), 112.7 (t, *J* = 266.0 Hz, -**C**F$_2$).

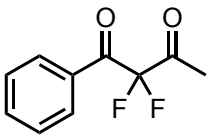
^{19}F NMR (376 MHz, $CDCl_3$) δ -102.66 (s, 2F).

IR 1693, 1595, 1577, 1448, 1305, 1251, 1188, 1155, 1136, 1101, 999, 941, 887, 771, 719, 694, 678, 663, 569, 522, 435, 422 cm^{-1}

HRMS (EI+): $[C_{15}H_{10}F_2O_2]$ $[M+NH_4]^+$ calc. 278.0987, found 278.0988.

mp: 58 – 60 °C.

2,2-difluoro-1-phenylbutane-1,3-dione, 105[7]



Prepared according to **GP3**, 185 mg, 0.93 mmol, 93%, >50:1 di:mono, red oil. Analytical data is in agreement with the literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.55 (t, *J* = 6.8 Hz, 1H, Ar-H), 7.40 (t, *J* = 7.4 Hz, 2H, Ar-H), 2.31 (s, 3H, -C**H**$_3$).

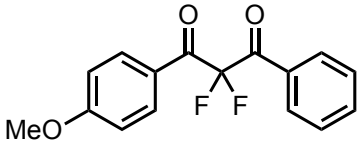
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 196.0 (**C**=O), 187.6 (**C**=O), 135.2 (Ar), 131.4 (Ar), 130.1 (t, *J* = 2.7 Hz, Ar), 129.0 (Ar), 111.3 (t, *J* = 266.5 Hz, -**C**F_2), 25.0 (-**C**H_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ -108.97 (s).

IR: 1753, 1697, 1597, 1450, 1361, 1292, 1111, 1080, 891, 837, 712, 685 cm^{-1}.

HRMS (EI+) $[C_{10}H_8O_2F_2]$ calc. 198.0492, found 198.0495

2,2-difluoro-1-(4-methoxyphenyl)-3-phenylpropane-1,3-dione, 106



Prepared according to **GP3**, 270 mg, 0.93 mmol, 93%, >50:1 di:mono, orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.03 (m, 3H, Ar-H), 8.01 - 7.94 (m, 1H, Ar-H), 7.60 (t, *J* = 7.1 Hz, 1H, Ar-H), 7.46 (t, *J* = 7.3 Hz, 2H, Ar-H), 7.00 - 6.88 (m, 2H, Ar-H), 3.83 (s, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 187.5 (t, *J* = 26.8 Hz, **C**=O), 185.6 (t, *J* = 26.6 Hz, **C**=O), 165.1 (Ar), 134.9 (Ar), 132.9 (t, *J* = 2.6 Hz, Ar), 132.2 (Ar), 130.3 (t, *J* = 2.5 Hz, Ar), 128.9 (Ar), 127.0 (Ar), 114.3 (Ar), 113.0 (t, *J* = 265.3 Hz, -**C**F_2), 55.6 (-**C**H_3).

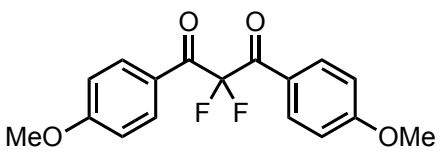
^{19}F NMR (376 MHz, $CDCl_3$) δ -102.38 (s).

IR: 1589, 1508, 1182, 1092, 1020, 840, 766, 503 cm^{-1}.

HRMS (EI+) $[C_{16}H_{12}O_3F_2]$ calc. 290.0755, found 290.0749.

mp: 35 - 36 °C (chloroform)

2,2-difluoro-1,3-bis(4-methoxyphenyl)propane-1,3-dione, 107



Prepared according to **GP3**, 219 mg, 0.68 mmol, 68%, >50:1 di:mono, orange crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 4H, Ar-H), 6.81 (d, *J* = 8.4 Hz, 4H, Ar-H), 3.73 (s, 6H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 185.7 (t, *J* = 26.5 Hz, **C**=O), 165.1 (Ar), 132.9 (t, *J* = 2.6 Hz, Ar), 124.6 (Ar), 114.3 (Ar), 113.2 (t, *J* = 264.5 Hz, -**C**F_2), 55.6 (-**C**H_3).

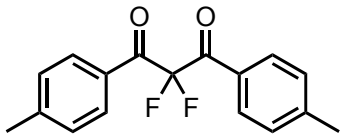
^{19}F NMR (376 MHz, $CDCl_3$) δ -102.36 (s).

IR: 1676, 1593, 1508, 1256, 1126, 1020, 847, 781, 573 cm^{-1}.

HRMS (EI+) [$C_{17}H_{14}O_4F_2$] calc. 320.0860, found 320.0863.

mp: 68 - 69 °C (chloroform)

2,2-difluoro-1,3-di-p-tolylpropane-1,3-dione, 108



Prepared according to **GP3**, 274 mg, 0.95 mmol, 95%, 8:1 di:mono, orange crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.9 Hz, 4H, Ar-H), 7.14 (d, *J* = 7.9 Hz, 4H, Ar-H), 2.27 (s, 6H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 186.9 (t, *J* = 26.7 Hz, **C**=O), 146.5 (Ar), 130.4 (t, *J* = 2.6 Hz, Ar), 129.7 (Ar), 129.2 (Ar), 112.9 (t, *J* = 265.6 Hz, -**C**F_2), 21.9 (-**C**H_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ -102.65 (s).

IR: 1688, 1603, 1244, 1159, 1125, 1094, 939, 880, 766, 573, cm^{-1}.

HRMS (pNSI+) [$C_{17}H_{14}O_2F_2$ + H] calc. 289.1035, found 289.1035

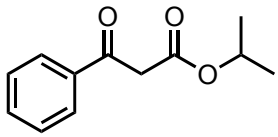
mp: 84 °C (chloroform)

6.2.7 Synthesis of β-ketoesters

General Procedure 4 (GP4)

Following a modified literature procedure[8]; an aqueous sodium hydroxide solution (1 M, 50 mL) was added to ethylbenzoylacetate (8.7 mL, 50 mmol) . This mixture was stirred overnight at room temperature then transferred to a separating funnel. It was washed with dichloromethane (3 x 10 mL) and the aqueous layer acidified to pH 1 by the addition of aqueous HCl (3 M). The precipitate was collected by suction filtration and dried under vacuum to yield benzoylacetic acid (6.325 g, 39 mmol, 78%), which was used without further purification. A solution of this acid (1.640 g, 10 mmol) and the corresponding alcohol (10 mmol) in acetonitrile (20 mL) was prepared. To this solution was added a solution of dicyclohexylcarbodiimide (2.063 g, 10 mmol) and 4-dimethylaminopyridine (0.061 g, 0.5 mmol) in acetonitrile (10 mL) under rapid stirring. This mixture was stirred overnight at room temperature then directly dry loaded onto silica and purified by flash column chromatography eluting with 40-60 petroleum ether and ethyl acetate to yield the desired product.

Isopropyl 3-oxo-3-phenylpropanoate, 112SM



Prepared according to **GP4**. 1.820 g, 8.8 mmol, 88%, yellow oil. 3:1 keto:enol

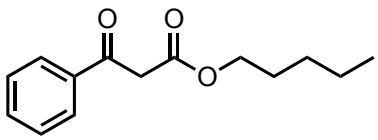
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.59 (s, enol), 7.86 (t, *J* = 7.7 Hz, 2H, Ar-H), 7.67 (t, *J* = 11.0 Hz, enol), 7.57 – 7.44 (m, 1H, Ar-H), 7.43 – 7.28 (m, 2H, Ar-H), 5.55 (s, enol), 5.06 (sep, *J* = 6.2 Hz, enol), 4.99 (sep, *J* = 6.3 Hz, 1H, -C**H**Me_2), 3.87 (s, 2H, -C**H**$_2$), 1.22 (d, *J* = 6.3 Hz, enol), 1.14 (d, *J* = 6.3 Hz, 6H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 192.7 (**C**=O), 167.1 (**C**=O), 133.7 (Ar), 128.8 (Ar), 128.5 (Ar), 126.1 (Ar), 69.1 (**C**H_2), 46.4 (-**C**HMe_2), 22.0 (-**C**H_3).

IR: 1732, 1684, 1265, 1200, 1103, 689 cm^{-1}.

HRMS (ES+) [$C_{12}H_{14}O_3$ + Na] calc. 229.0841, found 229.0849.

Pentyl 3-oxo-3-phenylpropanoate, 113SM



Prepared according to **GP4**. 0.760 g, 4.9 mmol, 49%, yellow oil. 2.5:1 keto:enol

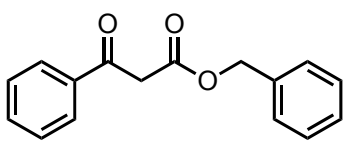
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.59 (s, enol), 7.93 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.77 (d, *J* = 7.8 Hz, enol), 7.57 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.52 – 7.35 (m, 2H, Ar-H), 5.66 (s, enol), 4.19 (t, *J* = 6.7 Hz, enol), 4.13 (t, *J* = 6.7 Hz, 2H, -C**H**$_2$O), 3.98 (s, 2H, -C**H**$_2$), 1.69 - 1.70 (m, enol), 1.64 – 1.52 (m, 2H, -C**H**$_2$), 1.36 (dd, *J* = 8.5, 5.3 Hz, enol), 1.31 – 1.16 (m, 4H, -C**H**$_2$C**H**$_2$-), 0.91 (t, *J* = 6.6 Hz, enol), 0.85 (t, *J* = 6.7 Hz, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 192.6 (**C**=O), 173.4 (enol), 171.5 (**C**=O), 167.6 (enol), 136.1 (Ar), 133.8 (Ar), 133.5 (Ar), 131.3 (Ar), 128.8 (Ar), 128.6 (Ar), 128.5 (Ar), 126.1 (Ar), 87.4 (enol), 65.7 (enol), 64.6 (-**C**H_2), 46.1(-**C**H_2O), 28.5 (enol), 28.2 (-**C**H_2), 28.1 (enol), 27.9 (-**C**H_2), 22.4 (enol), 22.3 (-**C**H_2), 14.1 (enol), 14.0 (-**C**H_3).

IR: 1738, 1686, 1450, 1411, 1263, 1190, 1144, 978, 775, 754, 687 cm^{-1}.

HRMS (ES+) [$C_{14}H_{18}O_3$ + Na] calc. 257.1154, found 257.1144

Benzyl 3-oxo-3-phenylpropanoate, 114SM[9]



Prepared according to **GP4**. 2.176 g, 8.6 mmol, 86%, yellow oil. 10:3 keto:enol

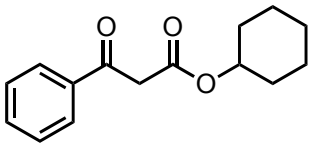
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.48 (s, enol), 7.90 (d, *J* = 8.0 Hz, enol), 7.86 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.72 (d, *J* = 7.9 Hz, enol), 7.51 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.44 – 7.24 (m, 7H, Ar-H), 5.68 (s, enol), 5.19 (s, enol), 5.13 (s, 2H, -C**H**$_2$), 3.98 (s, 2H, -C**H**$_2$).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 192.3 (**C**=O), 167.4 (**C**=O), 135.4 (Ar), 133.8 (Ar), 128.8 (Ar), 128.6 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 67.1 (-**C**H_2), 45.9 (-**C**H_2).

IR: 1738, 1682, 1263, 1182, 1140, 752, 689 cm^{-1}.

HRMS (ES+) [$C_{16}H_{14}O_3$ + Na] calc. 277.0841, found 277.0842

Cyclohexyl 3-oxo-3-phenylpropanoate, 115SM



Prepared according to **GP4**. 2.135 g, 8.7 mmol, 87%, yellow oil. 2.5:1 keto:enol

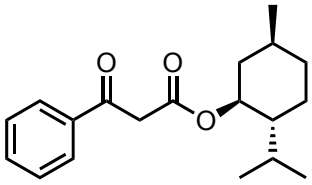
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.70 (s, enol), 7.94 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.77 (d, *J* = 7.8 Hz, enol), 7.57 (t, *J* = 7.4 Hz, enol), 7.52 – 7.37 (m, 3H, Ar-H), 5.66 (s, enol), 4.95 – 4.88 (m, enol), 4.88 – 4.79 (m, 1H, -C**H**O-), 3.97 (s, 2H, -C**H**$_2$), 2.09 – 1.10 (m, 10H, (-C**H**$_2$-)$_5$).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 192.7 (**C**=O), 166.9 (**C**=O), 133.6 (Ar), 128.7 (Ar), 128.5 (Ar), 126.0 (Ar), 87.9 (-**C**HO-), 73.8 (-**C**H_2), 46.4 (-**C**H_2), 31.3 (-**C**H_2), 25.3 (-**C**H_2), 23.5 (-**C**H_2).

IR: 2936, 2859, 1732, 1684, 1449, 1263, 1194, 1013, 756, 689 cm^{-1}.

HRMS (ES+) [$C_{15}H_{18}O_3$ + Na] calc. 269.1154, found 269.1154

(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl3-oxo-3-phenylpropanoate, 116SM



Prepared according to **GP4**. 1.697 g, 5.6 mmol, 56%, yellow crystals. 2.5:1 keto:enol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.62 (s, enol), 7.85 (t, *J* = 11.1 Hz, 2H), 7.68 (d, *J* = 7.5 Hz, enol), 7.47 (t, *J* = 7.4 Hz, 1H), 7.40 – 7.25 (m, 4H), 5.56 (s, enol), 4.74 (td, *J* = 10.8, 4.3 Hz, enol), 4.63 (td, *J* = 10.9, 4.3 Hz, 1H), 3.86 (q, *J* = 15.4 Hz, 2H), 2.03 – 1.75 (m, 1H), 1.71 – 1.48 (m, 3H), 1.45 – 1.14 (m, 2H), 1.0 - 0.65 (m, 10H), 0.59 (d, *J* = 6.9 Hz, 2H).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 192.5, 167.1, 133.6, 128.7, 128.5, 126.0, 87.7, 75.5, 74.1, 47.1, 34.1, 31.3, 26.3, 25.9, 23.6, 23.2, 22.0.

IR: 2957, 2932, 2866, 1630, 1576, 1406, 1223, 1182, 1080, 810, 772, 689 cm^{-1}.

HRMS (ES+) [$C_{19}H_{26}O_3$ + Na] calc. 325.1780, found 325.1776

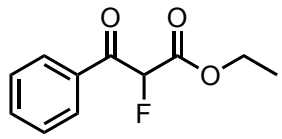
mp: 40 °C (dichloromethane)

6.2.8 Mechanochemical monofluorination of *β*-ketoesters

General Procedure 5 (GP5)

To a 10 mL stainless steel jar was added the *β*-ketoester (1 mmol), selectfluor (0.708 g, 2 mmol), sodium chloride (twice the total mass of substrate and selectfluor) and acetonitrile (0.25 mL). The ball was added and the mixture milled at 30 Hz for 2 hours. The resulting powder was transferred into a flask, washing the residue with chloroform (about 40 mL). The insoluble material was removed by gravity filtration. The solvent was removed under reduced pressure to yield the product. The selectivity ratio was determined by ^{19}F NMR spectroscopy.

Ethyl 2-fluoro-3-oxo-3-phenylpropanoate, 110[4]



Prepared according to **GP5**. 0.201 g, 0.96 mmol, 96%, 12.5:1 mono:di, dark red liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.64 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.51 (t, *J* = 7.8 Hz, 2H, Ar-H), 5.86 (d, *J* = 48.9 Hz, 1H, -C**H**F-), 4.30 (q, *J* = 6.8 Hz, 2H, -C**H**$_2$), 1.26 (t, *J* = 7.1 Hz, 3H, -C**H**$_3$).

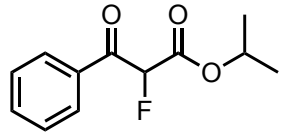
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 189.7 (d, *J* = 20.2 Hz, **C**=O), 165.1 (d, *J* = 24.2 Hz, **C**=O), 134.7 (Ar), 133.5 (Ar), 129.7 (d, *J* = 3.4 Hz, Ar), 129.0 (Ar), 90.2 (d, *J* = 197.7 Hz, -**C**HF), 62.7 (-**C**H_2), 14.1 (-**C**H_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ -190.29 (d, *J* = 48.8 Hz).

IR: 2983, 1759, 1693, 1597, 1448, 1371, 1242, 1095, 686 cm^{-1}

HRMS (ASAP+) [$C_{11}H_{11}O_3F$ + H] calc. 211.0770, found 211.0773

Isopropyl 2-fluoro-3-oxo-3-phenylpropanoate, 112



Prepared according to **GP5**. 0.182 g, 0.81 mmol, 81%, 15:1 mono:di, light brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.64 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.50 (t, *J* = 7.4 Hz, 2H, Ar-H), 5.83 (d, *J* = 48.9 Hz, 1H, -C**H**F), 5.20 – 5.10 (m, 1H, -OC**H**Me$_2$), 1.28 (d, *J* = 6.2 Hz, 3H, -C**H**$_3$), 1.18 (d, *J* = 6.2 Hz, 3H, -C**H**$_3$).

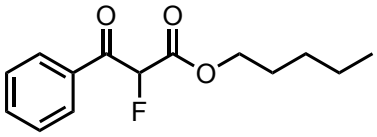
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 189.8 (d, *J* = 20.1 Hz, **C**=O), 164.6 (d, *J* = 24.1 Hz, **C**=O), 134.6 (Ar), 129.6 (d, *J* = 3.3 Hz, Ar), 128.9 (Ar), 128.6 (d, *J* = 26.3 Hz, Ar), 90.3 (d, *J* = 197.4 Hz, -**C**HF), 71.1 (-O**C**HMe$_2$), 21.7 (-**C**H_3)$_2$.

^{19}F NMR (376 MHz, $CDCl_3$) δ -190.28 (d, *J* = 48.9 Hz).

IR: 2984, 1755, 1692, 1597, 1449, 1098, 689 cm^{-1}

HRMS (ASAP+) [$C_{12}H_{13}O_3F$ + H] calc. 225.0927, found 225.0922

Pentyl 2-fluoro-3-oxo-3-phenylpropanoate, 113



Prepared according to **GP5**. 0.239 g, 0.95 mmol, 95%, 16:1 mono:di, pale red oil.

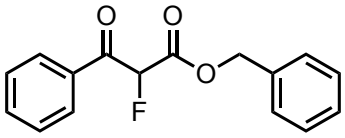
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.63 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.49 (t, *J* = 7.6 Hz, 2H, Ar-H), 5.88 (d, *J* = 48.8 Hz, 1H, -C**H**F), 4.22 (sep, *J* = 5.1 Hz, 2H, -OC**H**$_2$), 1.64 – 1.54 (m, 2H, -C**H**$_2$), 1.30 – 1.14 (m, 4H, -C**H**$_2$), 0.82 (t, *J* = 6.8 Hz, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 189.6 (d, *J* = 20.0 Hz, **C**=O), 165.0 (d, *J* = 24.2 Hz, **C**=O), 134.6 (Ar), 133.5 (d, *J* = 1.9 Hz, Ar), 129.6 (d, *J* = 3.3 Hz, Ar), 128.9 (Ar), 90.1 (d, *J* = 197.3 Hz, -**C**HF), 66.8 (-O**C**H$_2$), 28.1 (-**C**H$_2$), 27.8 (-**C**H$_2$), 22.2 (-**C**H$_2$), 13.9 (-**C**H$_3$).

^{19}F NMR (376 MHz, $CDCl_3$) δ -190.61 (d, *J* = 48.8 Hz).

IR: 1759, 1694, 1597, 1449, 1240, 1099, 959, 880, 689 cm^{-1}.

Benzyl 2-fluoro-3-oxo-3-phenylpropanoate, 114[9]



Prepared according to **GP5**. 0.239 g, 0.88 mmol, 88%, 7:1 mono:di, dark yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.63 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.47 (t, *J* = 7.4 Hz, 3H, Ar-H), 7.31 (s, 4H, Ar-H), 5.92 (d, *J* = 48.7 Hz, 1H, -C**H**F), 5.31 – 5.21 (m, 2H, -OC**H**$_2$).

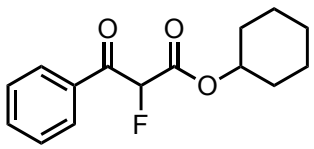
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 189.5 (d, *J* = 20.2 Hz, **C**=O), 164.9 (d, *J* = 24.3 Hz, **C**=O), 134.7 (Ar), 134.5 (Ar), 129.7 (d, *J* = 3.4 Hz, Ar), 129.1 (d, *J* = 4.9 Hz, Ar), 129.0 (Ar), 128.8 (Ar), 128.7 (Ar), 128.5 (Ar), 90.1 (d, *J* = 198.1 Hz, -**C**HF), 68.2 (-O**C**H$_2$).

^{19}F NMR (376 MHz, $CDCl_3$) δ -190.39 (d, *J* = 48.6 Hz).

IR: 1761, 1688, 1597, 1449, 1101, 955, 743, 687, 586 cm^{-1}

HRMS (EI+): [$C_{16}H_{13}O_3F$] calc. 272.0849, found 272.0850

Cyclohexyl 2-fluoro-3-oxo-3-phenylpropanoate, 115



Prepared according to **GP5**. 0.199 g, 0.75 mmol, 75%, 17:1 mono:di, yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.63 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.50 (t, *J* = 7.5 Hz, 2H, Ar-H), 5.85 (d, *J* = 48.9 Hz, 1H, -C**H**F), 4.96 – 4.90 (m, 1H, -OC**H**-), 1.91 – 1.15 (m, 10H, (-C**H**$_2$-)$_5$).

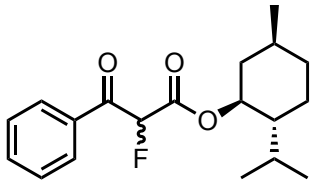
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 189.8 (d, *J* = 20.0 Hz, **C**=O), 164.5 (d, *J* = 24.2 Hz, **C**=O), 134.6 (Ar), 133.6 (d, *J* = 1.9 Hz, Ar), 129.6 (d, *J* = 3.3 Hz, Ar), 128.9 (Ar), 90.2 (d, *J* = 197.1 Hz, -**C**HF), 75.6 (-O**C**H-), 31.3 (-**C**H$_2$), 31.1 (-**C**H$_2$), 23.2 (-**C**H$_2$).

^{19}F NMR (376 MHz, $CDCl_3$) δ -190.44 (d, *J* = 49.0 Hz).

IR: 2936, 2860, 1755, 1690, 1597, 1449, 1236, 1007, 689 cm^{-1}

HRMS (EI+): [$C_{15}H_{17}O_3F$] calc. 264.1162, found 264.1161

(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-2-fluoro-3-oxo-3-phenylpropanoate, 116



Prepared according to **GP5**. 0.288 g, 0.90 mmol, 90%, 20:1 mono:di, dr 56:44, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, *J* = 6.2 Hz, 2H, Ar-H), 7.61 (t, *J* = 6.8 Hz, 1H, Ar-H), 7.47 (t, *J* = 7.2 Hz, 2H, Ar-H), 5.83 (m, 1H, -C**H**F), 4.94 – 4.55 (m, 1H, -OC**H**-), 1.87 – 0.36 (m,18H).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 189.6 (d, *J* = 21 Hz, **C**=O), 189.4 (d, *J* = 20 Hz, **C**=O), 164.5 (d, *J* = 23 Hz, **C**=O), 164.4 (d, *J* = 24 Hz, **C**=O), 134.5 (Ar), 134.4 (Ar), 133.4 (Ar), 129.5 (Ar), 129.47 (Ar), 129.41 (Ar), 129.38 (Ar), 128.78 (Ar), 90.3 (d, *J* = 198 Hz, -**C**HF), 90.1 (d, *J* = 198 Hz, -**C**HF), 46.7 (-**C**H_2), 40.5 (-**C**H_2), 33.9 (-**C**H_2), 31.4 (-**C**H_2), 25.6 (-**C**H_2), 22.9 (-**C**H_2), 21.9 (-**C**H_2), 20.5 (-**C**H_3), 16.1 (-**C**H_3), 15.5 (-**C**H_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ -189.94 (d, *J* = 48.8 Hz), -190.52 (d, *J* = 48.7 Hz).

IR: 2955, 2870, 1755, 1694, 1449, 1238, 1096, 953, 910, 689 cm^{-1}.

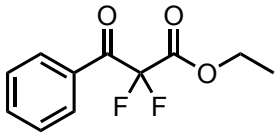
HRMS (ES+) [$C_{19}H_{25}O_3F$ + Na] calc. 343.1685, found 343.1683

6.2.9 Mechanochemical difluorination of *β*-ketoesters

General Procedure 6 (GP6)

To a 10 mL stainless steel jar was added the *β*-ketoester (1 mmol), selectfluor (0.708 g, 2 mmol), sodium carbonate (0.106 g, 1 mmol) and sodium chloride (twice the total mass of substrate and selectfluor). The ball was added and the mixture milled at 30 Hz for 2 hours. The resulting powder was transferred into a flask, washing the residue with chloroform (about 40 mL). The insoluble material was removed by gravity filtration. The solvent was removed under reduced pressure to yield the product. The selectivity ratio was determined by ^{19}F NMR spectroscopy.

Ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate, 111[7]



Prepared according to **GP6**. 0.227 g, 1 mmol, 100%, 7:1 di:mono, yellow-green liquid.

^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.68 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.5 Hz, 2H, Ar-H), 4.39 (q, *J* = 7.1 Hz, 2H, -OC**H**$_2$), 1.32 (t, *J* = 7.2 Hz, 3H, -C**H**$_3$).

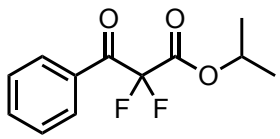
^{13}C {^1H} NMR (101 MHz, $CDCl_3$) δ 185.6 (t, *J* = 30.3 Hz, **C**=O), 162.0 (t, *J* = 30.6 Hz, **C**=O), 135.2 (Ar), 131.2 (Ar), 130.1 (t, *J* = 2.7 Hz, Ar), 129.1 (Ar), 109.9 (t, *J* = 264.6 Hz, -**C**F_2), 63.9 (-O**C**H_2), 14.0 (-**C**H_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.61 (s).

IR: 1770, 1697, 1597, 1450, 1371, 1307, 1255, 1155, 1097, 1001, 921, 684, 582 cm^{-1}

HRMS (ASAP+) [$C_{11}H_{10}O_3F_2$ + H] calc. 229.0676, found 229.0680

Isopropyl 2,2-difluoro-3-oxo-3-phenylpropanoate, 117



Prepared according to **GP6.** 0.187 g, 0.77 mmol, 77%, >50:1 di:mono, light yellow liquid.

^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.67 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.52 (t, *J* = 7.7 Hz, 2H, Ar-H), 5.29 – 5.14 (m, 1H, -OC**H**Me_2), 1.29 (d, *J* = 6.3 Hz, 6H, -(C**H**$_3$)$_2$).

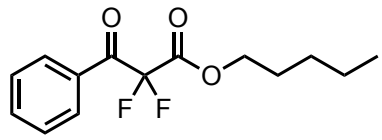
^{13}C {^1H} NMR (101 MHz, $CDCl_3$) δ 185.7 (t, *J* = 27.5 Hz, **C**=O), 161.5 (t, *J* = 30.3 Hz, **C**=O), 135.2 (Ar), 131.3 (t, *J* = 1.9 Hz, Ar), 130.0 (t, *J* = 2.7 Hz, Ar), 129.1 (Ar), 109.7 (t, *J* = 264.5 Hz, -**C**F_2), 72.5 (-O**C**HMe_2), 21.5 (-**C**H_3)$_2$.

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.93 (s).

IR: 2988, 1769, 1599, 1450, 1307, 1260, 1159, 1092, 922, 831, 685, 584 cm^{-1}

HRMS (EI+): [$C_{12}H_{12}O_3F_2$] calc. 242.0755, found 242.0753

Pentyl 2,2-difluoro-3-oxo-3-phenylpropanoate, 118



Prepared according to **GP6**. 0.239 g, 0.89 mmol, 89%, 5:1 di:mono, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.67 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.52 (t, *J* = 7.6 Hz, 2H, Ar-H), 4.34 - 4.19 (m, 2H, -OC**H**$_2$), 1.73 – 1.52 (m, 2H, -C**H**$_2$), 1.45 – 1.12 (m, 4H, -C**H**$_2$), 0.85 (t, *J* = 6.8 Hz, 3H, -C**H**$_3$).

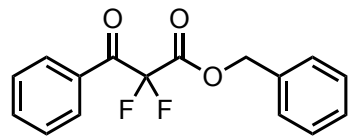
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 185.5 (t, *J* = 27.5 Hz, **C**=O), 162.0 (t, *J* = 30.6 Hz, **C**=O), 135.2 (Ar), 134.6 (Ar), 130.0 (t, *J* = 2.7 Hz, Ar), 129.1 (Ar), 109.9 (t, *J* = 264.4 Hz, -**C**F$_2$), 67.9 (-**C**H$_2$), 28.0 (-**C**H$_2$), 27.7 (-**C**H$_2$), 22.2 (-**C**H$_2$), 13.9 (-**C**H$_3$).

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.62 (s).

IR: 2957, 2932, 2868, 1632, 1614, 1450, 1406, 1256, 1200, 1080, 959, 810, 773, 725, 689 cm^{-1}

HRMS (ASAP+) [$C_{13}H_{16}O_3F_2$ + H] calc. 271.1146, found 271.1144

Benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate, 119[9]



Prepared according to **GP6**. 0.218 g, 0.75 mmol, 75%, >50:1 di:mono, light yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.66 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.48 (t, *J* = 7.7 Hz, 2H, Ar-H), 7.36 – 7.28 (m, *J* = 5.7 Hz, 5H, Ar-H), 5.34 (s, 2H, -C**H**$_2$).

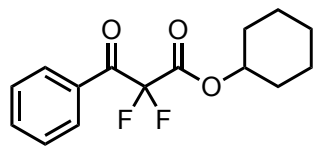
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 185.4 (t, *J* = 27.4 Hz, **C**=O), 161.8 (t, *J* = 30.7 Hz, **C**=O), 135.2 (Ar), 133.9 (Ar), 131.1 (t, *J* = 1.9 Hz, Ar), 130.0 (t, *J* = 2.7 Hz, Ar), 129.1 (Ar), 129.1 (Ar), 128.8 (Ar), 128.6 (Ar), 109.9 (t, *J* = 265.1 Hz, -**C**F$_2$), 69.2 (-**C**H$_2$).

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.40 (s, *J* = 9.2 Hz).

IR: 1773, 1697, 1597, 1450, 1304, 1263, 1155, 1099, 920, 793, 745, 685 cm^{-1}

HRMS (EI+): [$C_{16}H_{12}O_3F_2$] calc. 290.0755, found 290.0752

Cyclohexyl 2,2-difluoro-3-oxo-3-phenylpropanoate, 120



Prepared according to **GP6**. 0.234 g, 0.83 mmol, 83%, 16:1 di:mono, light yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.67 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.52 (t, *J* = 7.6 Hz, 2H, Ar-H), 5.04 – 4.95 (m, 1H, -OC**H**-), 1.90 – 1.18 (m, 10H, (-CH$_2$-)$_5$).

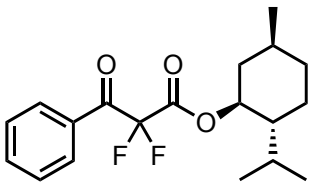
^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 185.6 (t, *J* = 27.4 Hz, **C**=O), 161.4 (t, *J* = 30.4 Hz, **C**=O), 135.1 (Ar), 131.3 (t, *J* = 1.7 Hz, Ar), 130.0 (t, *J* = 2.7 Hz, Ar), 129.1 (Ar), 109.7 (t, *J* = 264.2 Hz, -**C**F$_2$), 77.0 (-O**C**H-), 31.0 (-**C**H$_2$), 25.2 (-**C**H$_2$), 23.3 (-**C**H$_2$).

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.90 (s).

IR: 2940, 2862, 1769, 1697, 1597, 1450, 1306, 1258, 1161, 1101, 1003, 930, 826, 685, 407 cm^{-1}

HRMS (EI+): [$C_{15}H_{16}O_3F_2$] calc. 282.1068, found 282.1067

(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-2,2-difluoro-3-oxo-3-phenylpropanoate, 121



Prepared according to **GP6**. 0.263 g, 0.78 mmol, 78%, 2.25:1 di:mono, orange liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 7.90 (m, 2H, Ar-H), 7.72 – 7.55 (m, 1H, Ar-H), 7.55 – 7.37 (m, 2H, Ar-H), 4.91 – 4.65 (m, 1H, -OC**H**-), 2.10 – 0.38 (m, 18H).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 185.3 (t, *J* = 27.3 Hz, **C**=O), 161.5 (t, *J* = 30.0 Hz, **C**=O), 135.0 (Ar), 129.8 (t, *J* = 2.6 Hz, Ar), 129.5 (t, *J* = 8.9 Hz, Ar), 129.0 (Ar), 90.3 (t, *J* = 197.4 Hz, -**C**F_2), 78.7 (-O**C**H-), 46.6 (-**C**H_2), 40.0 (-**C**H_2), 33.9 (-**C**H_2), 31.4 (-**C**H_2), 25.9 (-**C**H_2), 23.1 (-**C**H_2), 21.9 (-**C**H_3), 20.6 (-**C**H_3), 15.8 (-**C**H_3).

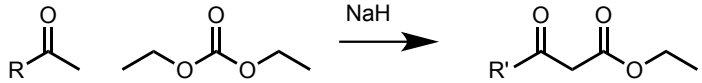
^{19}F NMR (376 MHz, $CDCl_3$) δ -107.37 (d, *J* = 284.5 Hz), -108.58 (d, *J* = 284.5 Hz).

IR: 2957, 1765, 1695, 1599, 1450, 1369, 1308, 908, 687 cm^{-1}

HRMS (EI+): [$C_{19}H_{24}O_3F_2$] calc. 338.1694, found 338.1696

6.3 Mechanochemical one-pot, two step synthesis of fluorinated pyrazolones

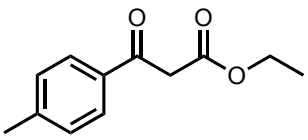
6.3.1 Synthesis of β-ketoesters



General Procedure 7 (GP7)

Following a literature procedure[10]: to a suspension of NaH (1.2 g, 30 mmol, 60% in mineral oil) in dry THF (10 mL) was added diethyl carbonate (4.85 mL, 40 mmol) in oven-dried glassware under N_2. A solution of the corresponding ketone (10 mmol) in dry THF (5 mL) was added slowly and the reaction mixture heated under reflux for 6 hours. The reaction mixture was quenched with glacial acetic acid (1 mL) and HCl (10%, 20 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phase washed with saturated sodium hydrogen carbonate (10 mL), water (10 mL) and brine (10 mL). The combined organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield the crude product. This was purified by flash column chromatography on silica gel (gradient elution EtOAc in petroleum ether (0-25%)).

Ethyl 3-oxo-3-(*p*-tolyl)propanoate, 130SM[11]



Prepared according to **GP7** with further purification by short-path distillation (190 °C, 7 mbar); 0.583 g, 2.8 mmol, 28%, yellow oil. 1:3.7 enol:keto.

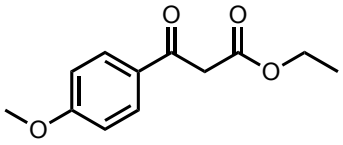
^{1}H NMR (400 MHz; $CDCl_3$): δ 12.60 (s, enol 1H), 7.86 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.69 (d, *J* = 8.1, enol 2H), 7.29 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.24 (d, *J* = 7.9 Hz, enol 2H), 5.65 (s, enol 1H), 4.27 (q, *J* = 7.1 Hz, enol 2H), 4.23 (q, *J* = 7.1 Hz, 2H, -OC**H**$_2$), 3.98 (s, 2H, -C**H**$_2$), 2.44 (s, 3H, -C**H**$_3$), 2.41 (s, enol 3H), 1.35 (t, *J* = 7.1 Hz, enol 3H), 1.28 (t, *J* = 7.1 Hz, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz; $CDCl_3$): δ 192.2, 173.4, 171.7, 167.8, 144.8, 141.8, 133.7, 130.8, 129.6, 129.4, 128.8, 126.1, 86.8, 61.6, 60.4, 46.1, 21.8, 21.6, 14.5, 14.2.

IR: 2980, 1736, 1682, 1265, 1182, 1144, 808 cm^{-1}.

HRMS (AP+): $[C_{12}H_{14}O_3 + H]^+$ calc. 207.1021, found 207.1024.

Ethyl 3-(4-methoxyphenyl)-3-oxopropanoate, 131SM[12]



Prepared according to **GP7** with further purification by short-path distillation (200 °C, 8 mbar); 0.434 g, 2.0 mmol, 20%, colourless oil. 1:18 enol:keto.

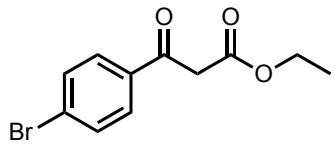
^{1}H NMR (400 MHz; $CDCl_3$): δ 12.63 (s, enol 1H), 7.93 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.74 (d, *J* = 9.1 Hz, enol 2H, Ar-H), 6.95 (m, 2H, -C**H**$_2$), 5.58 (s, enol 1H), 4.25 (q, *J* = 7.1 Hz, enol 2H), 4.22 (q, *J* = 7.1 Hz, 2H, -C**H**$_2$) 3.94 (s, 2H, -C**H**$_2$), 3.88 (s, 3H, -C**H**$_3$), 3.85 (s, enol 3H), 1.33 (t, *J* = 7.1 Hz, enol 3H), 1.26 (t, *J* = 7.1 Hz, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz; $CDCl_3$): δ 191.1 (**C**=O), 167.9 (**C**=O), 164.1 (Ar), 131.0 (Ar), 129.3 (Ar), 114.1 (Ar), 61.6 (-O**C**H$_2$), 55.7 (-O**C**H$_3$), 46.0 (-**C**H$_2$), 14.2 (-**C**H$_3$).

IR: 2980, 1734, 1674, 1597, 1256, 1024, 843 cm^{-1}.

HRMS (pNSI+): $[C_{12}H_{14}O_4 + H]^+$ calc. 223.0965, found 223.0964.

Ethyl 3-(4-bromophenyl)-3-oxopropanoate, 133SM[12]



Prepared according to **GP7**; 2.395 g, 8.8 mmol, 88%, yellow oil. 1:2.2 enol:keto.

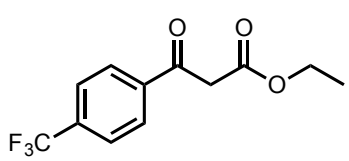
^{1}H NMR (400 MHz; $CDCl_3$): δ 12.56 (s, enol 1H), 7.81 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.63 (m, 2H, Ar-H), 7.55 (d, *J* = 8.6 Hz, enol 2H), 5.64 (s, enol 1H), 4.30 (q, *J* = 7.3 Hz, enol 2H), 4.18 (q, *J* = 7.3 Hz, 2H, -OC**H**$_2$), 3.95 (s, 2H, -C**H**$_2$), 1.33 (t, *J* = 7.1 Hz, enol 3H), 1.25 (t, *J* = 7.1 Hz, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz; $CDCl_3$): δ 191.6, 173.2, 170.3, 167.3, 134.9, 132.5, 132.3, 131.9, 130.1, 129.2, 127.7, 125.9, 87.9, 61.8, 60.6, 46.1, 14.4, 14.2.

IR: 2980, 1734, 1686, 1585, 1260, 1194, 995, 800 cm^{-1}.

HRMS (pNSI+): $[C_{11}H_{11}O_3Br + H]^+$ calc. 270.9964, found 270.9957.

Ethyl 3-oxo-3-(4-(trifluoromethyl)phenyl)propanoate, 132SM[13]



Prepared according to **GP7**; 1.701 g, 6.5 mmol, 65%, yellow oil. 3:2 enol:keto.

^{1}H NMR (400 MHz; $CDCl_3$): δ 12.57 (s, enol 1H), 8.06 (m, 2H, Ar-H), 7.88 (m, enol 2H), 7.76 (m, 2H, Ar-H), 7.68 (m, enol 2H), 5.72 (s, enol 1H), 4.31 (q, *J* = 7.1 Hz, enol 2H), 4.19 (q, *J* = 7.1 Hz, 2H, -OC**H**$_2$) 4.01 (s, 2H, -C**H**$_2$), 1.39 (t, *J* = 7.1 Hz, enol 3H), 1.21 (t, *J* = 7.1 Hz, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz; $CDCl_3$): δ 191.7, 173.0, 169.5, 167.1, 138.7, 136.9, 135.0 (q, *J* = 32.7 Hz), 132.8 (q, *J* = 32.7 Hz), 129.0, 126.5, 125.9 (q, *J* = 3.7 Hz), 125.6 (q, *J* =

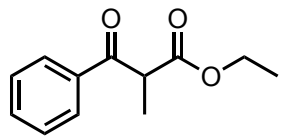
3.7 Hz), 123.9 (q, *J* = 272.7 Hz), 123.6 (q, *J* = 272.7 Hz), 89.1, 61.8, 60.7, 46.2, 14.30, 14.10.

^{19}F NMR (376 MHz; $CDCl_3$): δ -62.9 (s, enol 3F), -63.2 (s, 3F).

IR: 2980, 1744, 1695, 1616, 1319, 1260, 1111, 1065, 853, 802 cm^{-1}.

HRMS (pNSI+): $[C_{12}H_{11}F_3O_3 + H]^+$ calc. 261.0733, found 261.0736.

Ethyl 2-methyl-3-oxo-3-phenylpropanoate, 140SM[11]



Following a literature procedure[14]: To a suspension of sodium hydride (0.788 g, 19.5 mmol, 60% in mineral oil) in dry THF (20 mL) was added dropwise ethylbenzoylacetate (3.75 g, 19.5 mmol). When the gas evolution stopped, methyl iodide (1.2 mL, 19.5 mmol) was added slowly. The reaction mixture was stirred for a further 20 hours at room temperature then quenched with a saturated aqueous solution of ammonium chloride (30 mL). The phases were separated and the aqueous phase further extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed to yield the product as a yellow oil (4.01 g, 99%).

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.98 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.58 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.49-7.45 (m, 2H, Ar-H), 4.37 (q, *J* = 7.1 Hz, 1H, -C**H**Me-), 4.14 (q, *J* = 7.1 Hz, 2H, -OC**H**$_2$-), 1.49 (d, *J* = 7.1 Hz, 3H, -C**H**$_3$), 1.16 (t, *J* = 7.1 Hz, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (101 MHz; $CDCl_3$): δ 196.0 (**C**=O), 171.0 (**C**=O), 136.0 (Ar), 133.6 (Ar), 128.8 (Ar), 128.7 (Ar), 61.5 (-O**C**H$_2$-), 48.5 (-**C**H-), 14.1 (-**C**H$_3$), 13.9 (-**C**H$_3$).

IR: 2980, 1734, 1684, 1375, 957 cm^{-1}.

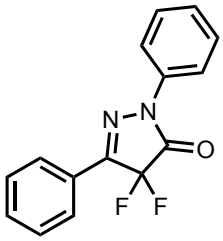
HRMS (pNSI+): $[C_{12}H_{14}O_3 + H]^+$ calc. 207.1016, found 207.1014.

6.3.2 Multistep one pot mechanochemical synthesis of fluorinated pyrazolones

General procedure 8 (GP8)

To a 10 mL stainless steel jar was added the β-ketoester (1 mmol), the hydrazine (1 mmol), sodium chloride (six times the total mass of reagents) and glacial acetic acid (30 µL, 0.5 mmol). The ball was added and the mixture milled at 30 Hz for 40 minutes. Following this initial grinding period, Selectfluor (0.708 g, 2 mmol) and sodium carbonate (0.133 g, 1.25 mmol) were added to the reaction mixture. The jar was hand sealed and milled for a further 60 minutes at 30 Hz (Scheme S1). The resulting powder was transferred into a flask, washing the residue with dichloromethane (approximately 40 mL). The insoluble material was removed by filtration. The solvent was removed under reduced pressure to yield the crude product. This was purified by flash column chromatography on silica gel (gradient elution EtOAc (0-5%) in petroleum ether).

4,4-Difluoro-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one, 129[15]



Prepared according to **GP8**. 0.205 g, 0.75 mmol, 75%, orange powder.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.98 (m, 4H, Ar-H), 7.52 (m, 5H, Ar-H), 7.30 (t, *J* = 7.4 Hz, 1H, Ar-H).

^{13}C {^{1}H} NMR (126 MHz; $CDCl_3$): δ 159.3 (t, *J* = 29 Hz, **C**=O), 149.8 (t, *J* = 25 Hz, **C**=N), 136.8 (Ar), 132.3 (Ar), 129.3 (Ar), 129.2 (Ar), 126.8 (Ar), 126.5 (Ar), 126.4 (Ar), 118.8 (Ar), 109.2 (t, *J* = 265 Hz, -**C**F_2).

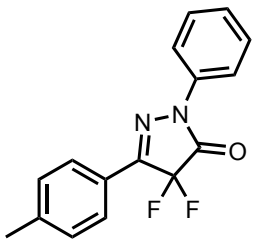
^{19}F NMR (376 MHz; $CDCl_3$): δ -115.7 (s).

IR: 1736, 1491, 1410, 1179, 1101, 756, 737, 664, 631 cm^{-1}.

HRMS (AP+): $[C_{15}H_{10}N_2F_2O + H]^+$ calc. 273.0839, found 273.0842.

mp: 77-78 °C (ethyl acetate).

4,4-Difluoro-2-phenyl-5-(*p*-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one, 130



Prepared according to **GP8**. 0.238 g, 0.83 mmol, 83%, Yellow powder.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.95 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.87 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.48 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.33 (m, 3H, Ar-H), 2.45 (s, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (126 MHz; $CDCl_3$): δ 159.3 (t, *J* = 30 Hz, **C**=O), 149.9 (t, *J* = 21 Hz, **C**=N), 143.2 (Ar), 136.9 (Ar), 130.1 (Ar), 129.2 (Ar), 126.8 (Ar), 126.4 (Ar), 123.7 (Ar), 118.8 (Ar), 109.3 (t, *J* = 258 Hz, -**C**F_2), 21.8 (-**C**H_3).

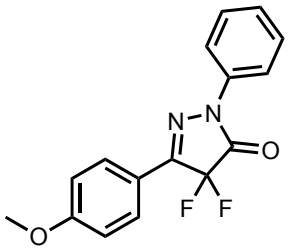
^{19}F NMR (471 MHz; $CDCl_3$): δ -115.4 (s).

IR: 1738, 1493, 1261, 1103, 743, 689 cm^{-1}.

HRMS (AP+): $[C_{16}H_{12}N_2F_2O + H]^+$ calc. 287.0996, found 287.0999.

mp: 112-113 °C (ethyl acetate).

4,4-Difluoro-5-(4-methoxyphenyl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, 131



Prepared according to **GP8**. 0.224 g, 0.74 mmol, 74%, Yellow powder.

^{1}H NMR (500 MHz; $CDCl_3$): δ 7.94 (m, 4H, Ar-H), 7.47 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.29 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.02 (d, *J* = 8.9 Hz, 2H, Ar-H), 3.89 (s, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (126 MHz; $CDCl_3$): δ 162.9 (Ar), 159.2 (t, *J* = 31 Hz, **C**=O), 149.7 (t, *J* = 21 Hz, **C**=N), 137.0 (Ar), 129.2 (Ar), 128.8 (Ar), 126.4 (Ar), 119.01 (Ar), 118.86 (Ar), 114.9 (Ar), 109.5 (t, *J* = 258 Hz, -**C**F_2), 55.7 (-**C**H_3).

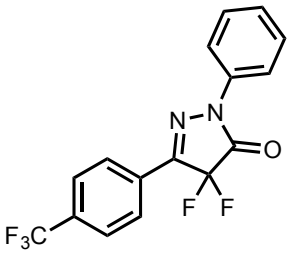
^{19}F NMR (471 MHz; $CDCl_3$): δ -115.1 (s).

IR: 1734, 1520, 1497, 1180, 1099, 833, 687 cm^{-1}.

HRMS (AP+): $[C_{16}H_{12}F_2N_2O_2 + H]^+$ calc. 303.0945, found 303.0941.

mp: 105-106 °C (ethyl acetate).

4,4-Difluoro-2-phenyl-5-(4-(trifluoromethyl)phenyl)-2,4-dihydro-3*H*-pyrazol-3-one, 132



Prepared according to **GP8**. 0.137 g, 0.40 mmol, 40%, Orange powder.

^{1}H NMR (400 MHz; $CDCl_3$): δ 8.10 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.93 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.79 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.50 (t, *J* = 8.4 Hz, 2H, Ar-H), 7.32 (m, 1H, Ar-H).

^{13}C {^{1}H} NMR (101 MHz; $CDCl_3$): δ 159.1 (t, *J* = 30 Hz, **C**=O), 148.5 (t, *J* = 22 Hz, **C**=N), 136.6 (Ar), 133.7 (q, *J* = 33 Hz, Ar), 129.6 (Ar), 129.4 (Ar), 127.1 (Ar), 126.9 (Ar), 126.4 (q, *J* = 4 Hz, Ar), 123.6 (q, *J* = 274 Hz, -**C**F_3), 119.0 (Ar), 108.7 (t, *J* = 259 Hz, -**C**F_2).

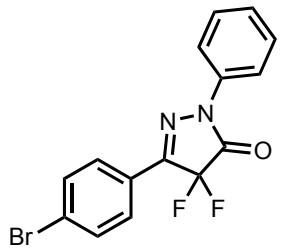
^{19}F NMR (376 MHz; $CDCl_3$): δ -63.2 (s, 3F), -116.2 (s, 2F).

IR: 1742, 1493, 1400, 1321, 1167, 1065, 1015, 934, 825, 733 cm^{-1}.

HRMS (ASAP+): $[C_{16}H_9N_2F_5O + H]^+$ calc.341.0713, found 341.0718.

mp: 112-113 °C (ethyl acetate).

5-(4-Bromophenyl)-4,4-difluoro-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, 133



Prepared according to **GP8**. 0.187 g, 0.53 mmol, 53%, Yellow powder.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.92 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.83 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.67 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.48 (m, 2H, Ar-H), 7.31 (t, *J* = 7.2 Hz, 1H, Ar-H).

^{13}C {^{1}H} NMR (126 MHz; $CDCl_3$): δ 159.1 (t, *J* = 30 Hz, **C**=O), 149.0 (t, *J* = 21 Hz, **C**=N), 136.6 (Ar), 132.7 (Ar), 129.3 (Ar), 128.1 (Ar), 127.2 (Ar), 126.7 (Ar), 125.2 (Ar), 118.9 (Ar), 108.9 (t, *J* = 259 Hz, -**C**F_2).

^{19}F NMR (471 MHz; $CDCl_3$): δ -115.8 (s).

IR: 2980, 1740, 1587, 1487, 1256, 1393, 1098, 1069, 934, 745, 685 cm^{-1}.

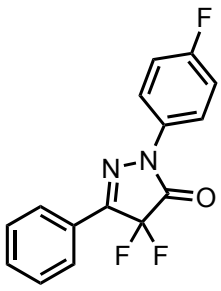
HRMS (AP+): $[C_{15}H_9N_2F_2OBr + H]^+$ calc. 350.9945, found 350.9945.

mp: 123-124 °C (ethyl acetate).

General Procedure 9 (GP9)

Diethyl ether (10 mL) and sodium hydroxide solution (10 mL, 0.5 M) were added to the hydrazine hydrochloride (2 mmol) and shaken until dissolved. The layers were separated and the aqueous layer further extracted with diethyl ether (2 x 10 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent removed to yield the hydrazine. To a 10 mL stainless steel jar was added ethylbenzoyl acetate (0.192 g, 1 mmol), the hydrazine (1 mmol), sodium chloride (six times the total mass of reagents) and glacial acetic acid (30 µL, 0.5 mmol). The ball was added and the mixture milled at 30 Hz for 40 minutes. Following this intial grinding period, Selectfluor (0.708 g, 2 mmol) and sodium carbonate (0.133 g, 1.25 mmol) were directly added to the reaction mixture. The jar was hand sealed and milled for a further 60 minutes at 30 Hz. The resulting powder was transferred into a flask, washing the residue with dichloromethane (about 40 mL). The insoluble material was removed by filtration. The solvent was removed under reduced pressure to yield the crude product. This was purified by flash column chromatography on silica gel (gradient elution EtOAc (0-5%) in petroleum ether).

4,4-Difluoro-2-(4-fluorophenyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, 134



Prepared according to **GP9**. 0.193 g, 0.67 mmol, 67%. Orange powder.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.97 - 7.92 (m, 4H, Ar-H), 7.56-7.51 (m, 3H, Ar-H), 7.19-7.14 (m, 2H, Ar-H).

^{13}C {^{1}H} NMR (101 MHz; $CDCl_3$): δ 160.8 (d, *J* = 248 Hz, -**C**F), 159.1 (t, *J* = 30 Hz, **C**=O), 150.0 (t, *J* = 21 Hz, **C**=N), 132.9 (Ar), 132.5 (Ar), 129.4 (Ar), 126.9 (Ar), 126.3 (t, *J* = 2 Hz, Ar), 120.7 (d, *J* = 8 Hz, Ar), 116.1 (d, *J* = 23 Hz, Ar), 109.2 (t, *J* = 260 Hz, -**C**F_2).

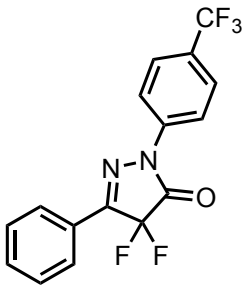
^{19}F NMR (376 MHz; $CDCl_3$): δ -114.8 (s, 1F), -115.6 (s, 2F).

IR: 2980, 1742, 1508, 1225, 1107, 1067, 831, 737, 687 cm^{-1}.

HRMS (ASAP+): $[C_{15}H_9N_2OF_3 + H]^+$ calc. 291.0745, found 291.0745.

mp: 92-93 °C (ethyl acetate).

4,4-Difluoro-5-phenyl-2-(4-(trifluoromethyl)phenyl)-2,4-dihydro-3*H*-pyrazol-3-one, 135



Prepared according to **GP9**. 0.127 g, 0.37 mmol, 37%. Yellow powder.

^{1}H NMR (400 MHz; $CDCl_3$): δ 8.13 (d, *J* = 6.8 Hz, 2H, Ar-H), 8.00 (d, *J* = 6.0 Hz, 2H, Ar-H), 7.74 (d, *J* = 6.8 Hz, 2H, Ar-H), 7.58 (m, 3H, Ar-H).

^{13}C {^{1}H} NMR (126 MHz; $CDCl_3$): δ 159.5 (t, *J* = 30 Hz, **C**=O), 150.3 (t, *J* = 21 Hz, **C**=N), 139.5 (Ar), 132.8 (Ar), 129.5 (Ar), 128.2 (q, *J* = 33 Hz, Ar), 127.0 (Ar), 126.6 (q, *J* = 4 Hz, Ar), 126.0 (Ar), 123.0 (q, *J* = 272 Hz, -**C**F_3), 118.4 (Ar), 109.0 (t, *J* = 259 Hz, -**C**F_2).

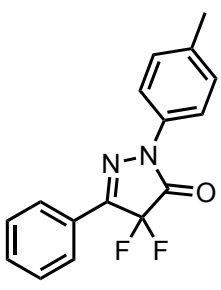
^{19}F NMR (471 MHz; $CDCl_3$): δ -62.3 (s, 3F), -115.0 (s, 2F).

IR: 1751, 1618, 1518, 1406, 1319, 1159, 1109, 1061, 841, 739, 687, 635, 592 cm^{-1}.

HRMS (ASAP+): $[C_{16}H_9N_2F_5O + H]^+$ calc. 341.0713, found 341.0706.

mp: 84-85 °C (ethyl acetate).

4,4-Difluoro-5-phenyl-2-(*p*-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one, 136



Prepared according to **GP9**. 0.169 g, 0.59 mmol, 59%. Brown powder.

^{1}H NMR (400 MHz; $CDCl_3$): δ 8.00 (d, *J* = 6.0 Hz, 2H, Ar-H), 7.84 (d, *J* = 6.4 Hz, 2H, Ar-H), 7.56 (m, 3H, Ar-H), 7.29 (m, 2H, Ar-H), 2.42 (s, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (126 MHz; $CDCl_3$): δ 159.2 (t, *J* = 30 Hz, **C**=O), 149.7 (t, *J* = 21 Hz, **C**=N), 136.5 (Ar), 135.2 (Ar), 134.4 (Ar), 132.3 (Ar), 129.8 (Ar), 129.3 (Ar), 126.8 (Ar), 118.9 (Ar), 109.2 (t, *J* = 259 Hz, -**C**F_2), 21.2 (-**C**H_3).

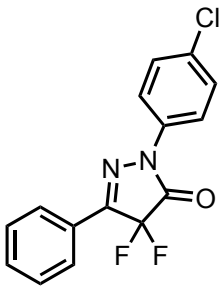
^{19}F NMR (471 MHz; $CDCl_3$): δ -115.8 (s).

IR: 2980, 1754, 1512, 1402, 1256, 1067, 937, 816, 739, 664, 640, 598, 513 cm^{-1}.

HRMS (pNSI+): $[C_{16}H_{12}F_2N_2O + H]^+$ calc. 287.0990, found 287.0992.

mp: 80-81 °C (ethyl acetate).

2-(4-Chlorophenyl)-4,4-difluoro-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, 137



Prepared according to **GP9**. 0.205 g, 0.67 mmol, 67%. Yellow powder.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.97 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.91 (m, 2H, Ar-H), 7.53 (m, 3H, Ar-H), 7.44 (m, 2H, Ar-H).

^{13}C {^{1}H} NMR (101 MHz; $CDCl_3$): δ 159.2 (t, *J* = 30 Hz, **C**=O), 150.1 (t, *J* = 21 Hz, **C**=N), 135.4 (Ar), 132.6 (Ar), 131.8 (Ar), 129.4 (Ar), 129.3 (Ar), 126.9 (Ar), 126.2 (t, *J* = 2 Hz, Ar), 119.9 (Ar), 109.1 (t, *J* = 260 Hz, -**C**F_2).

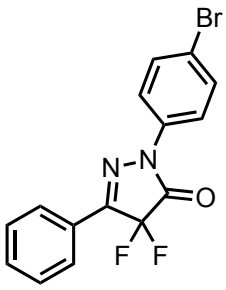
^{19}F NMR (376 MHz; $CDCl_3$): δ -115.3 (s).

IR: 1742, 1493, 1402, 1016, 1111, 737, 687 cm^{-1}.

HRMS (ASAP+): $[C_{15}H_9N_2F_2OCl + H]^+$ calc. 307.0450, found 307.0459.

mp: 79-80 °C (ethyl acetate).

2-(4-Bromophenyl)-4,4-difluoro-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, 138



Prepared according to **GP9**. 0.246 g, 0.70 mmol, 70%. Orange powder.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.98 (d, *J* = 6.8 Hz, 2H, Ar-H), 7.87 (d, *J* = 9.2 Hz, 2H, Ar-H), 7.58-7.52 (m, 5H, Ar-H).

^{13}C {^{1}H} NMR (101 MHz; $CDCl_3$): δ 159.1 (t, *J* = 30 Hz, **C**=O), 150.1 (t, *J* = 21 Hz, **C**=N), 135.8 (Ar), 132.6 (Ar), 132.3 (Ar), 129.4 (Ar), 126.9 (Ar), 126.1 (t, *J* = 2 Hz, Ar), 120.1 (Ar), 119.6 (Ar), 109.1 (t, *J* = 260 Hz, -**C**F_2).

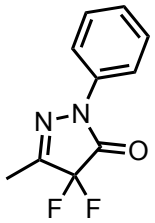
^{19}F NMR (376 MHz; $CDCl_3$): δ -115.3 (s).

IR: 1745, 1489, 1400, 1254, 1103, 739, 683 cm^{-1}.

HRMS (ASAP+): $[C_{15}H_9N_2F_2OBr + H]^+$ calc. 350.9945, found 350.9930.

mp: 79-80 °C (ethyl acetate)

4,4-Difluoro-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, 139[16]



Prepared according to **GP8**. 0.064 g, 0.30 mmol, 30%. Red oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.86 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.48-7.44 (m, 2H, Ar-H), 7.28 (t, *J* = 7.4 Hz, 1H, Ar-H), 2.32 (t, *J* = 1.3 Hz, 3H, -C**H**$_3$).

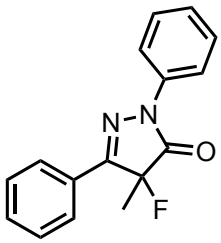
^{13}C {^{1}H} NMR (101 MHz; $CDCl_3$): δ 159.2 (t, *J* = 30 Hz, **C**=O), 152.0 (t, *J* = 23 Hz, **C**=N), 136.7 (Ar), 129.2 (Ar), 126.3 (Ar), 118.6 (Ar), 108.1 (t, *J* = 258 Hz, -**C**F$_2$), 11.9 (-**C**H$_3$).

^{19}F NMR (376 MHz; $CDCl_3$): δ -122.4 (s).

IR: 2980, 1748, 1501, 1373, 1254, 1146, 1111, 754, 731, 689, 648 cm^{-1}.

HRMS (ASAP+): $[C_{10}H_8N_2OF_2 + H]^+$ calc. 211.0683, found 211.0687.

4-Fluoro-4-methyl-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one, 140



Prepared according to modified **GP8** using 1 equivalent of Selectfluor. 0.126 g, 0.47 mmol, 47%. Orange powder.

^{1}H NMR (400 MHz; $CDCl_3$): δ 8.02-7.99 (m, 4H, Ar-H), 7.54-7.53 (m, 3H, Ar-H), 7.52-7.48 (m, 2H, Ar-H), 7.28 (t, *J* = 7.6 Hz, 1H, Ar-H), 1.91 (d, *J* = 22.4 Hz, 3H, -C**H**$_3$).

^{13}C {^{1}H} NMR (126 MHz; $CDCl_3$): δ 168.9 (d, *J* = 22 Hz, **C**=O), 155.8 (d, *J* = 14 Hz, **C**=N), 137.6 (Ar), 131.4 (Ar), 129.2 (Ar), 129.1 (Ar), 128.7 (d, *J* = 2 Hz, Ar), 126.8 (d, *J* = 2 Hz, Ar), 125.9 (Ar), 119.0 (Ar), 93.7 (d, *J* = 195 Hz, -**C**FMe), 21.6 (d, *J* = 27 Hz, -**C**H$_3$).

^{19}F NMR (471 MHz; $CDCl_3$): δ -163.8 (q, *J* = 23.1 Hz).

IR: 1724, 1593, 1395, 1177, 1117, 745, 683 cm^{-1}.

HRMS (pNSI+): $[C_{16}H_{13}ON_2F + H]^+$ calc. 269.1085, found 269.1086.

mp: 73-74 °C (ethyl acetate).

6.4 Using mechanochemistry to alter reaction pathway

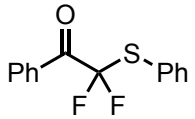
6.4.1 Liquid Assisted Grinding (LAG) Screen

2,2-difluoro-1,3-diphenylpropane-1,3-dione (0.065 g, 0.25 mmol), diphenyl disulfide (0.055 g, 0.25 mmol), cesium carbonate (0.244 g, 0.75 mmol) and the liquid additive were added to a 14 mL stainless steel jar and a ball added. The mixture was milled for one hour and the resulting mixture transferred into a flask by manually removing the material with a spatula and washing with ethyl acetate (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-trifluorotoluene (0.020 mL, 0.16 mmol) was added as a standard and ^{19}F NMR spectra of the crude mixture were measured to determine the yields of different products.

6.4.2 Optimum conditions for synthesis of 142. General procedure 10 (GP10).

2,2-difluoro-1,3-diphenylpropane-1,3-dione (0.065 g, 0.25 mmol), cesium carbonate (0.244 g, 0.75 mmol), diphenyl disulfide (0.055 g, 0.25 mmol) and DMSO (0.050 mL) were added to a 14 mL stainless steel jar and charged with one stainless steel ball (10 mm, 4.1 g). The reaction mixture was milled at 30 Hz for one hour. The resulting mixture was transferred into a flask by manually removing the material with a spatula and washing with ethyl acetate (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-trifluorotoluene (0.020 mL, 0.16 mmol) was added as a NMR standard and ^{19}F NMR spectra of the crude mixture were measured and the yield determined to be 62%. The mixture was then added to a separating funnel with distilled water (40 mL). The aqueous layer was extracted with ethyl acetate (2 x 40 mL). The organic layers were combined and washed with brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield the crude product. This was purified by flash column chromatography with gradient elution (0 - 10% ethyl acetate in petroleum ether) to yield the product as a colourless oil (0.038 g, 0.14 mmol, 56%).[17]

2,2-difluoro-1-phenyl-2-(phenylthio)ethan-1-one, 142



^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.5 Hz, 2H, Ar-H), 7.68 – 7.60 (m, 3H, Ar-H), 7.55 – 7.44 (m, 3H, Ar-H), 7.39 (t, J = 7.3 Hz, 2H, Ar-H).

^{13}C {^1H} NMR (101 MHz, $CDCl_3$) δ 185.3 (t, *J* = 28.0 Hz, **C**=O), 136.8 (Ar), 134.8 (Ar), 131.2 (Ar), 130.6 (Ar), 130.5 (t, *J* = 2.5 Hz, Ar), 129.4 (Ar), 128.8 (Ar), 124.8 (Ar), 123.8 (t, *J* = 291.0 Hz, -**C**F_2).

^{19}F NMR (376 MHz, CDCl3) δ -77.20 (s, 2F).

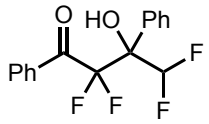
IR 1701, 1597, 1577, 1473, 1448, 1440, 1307, 1269, 1188, 1130, 1056, 1024, 1001, 983, 933, 883, 823, 779, 748, 709, 682, 665, 640, 594, 497, 441, 406 cm^{-1}.

HRMS (EI+): [$C_{14}H_{10}F_2OS$] calc. 264.0420, found 264.0426.

6.4.3 Optimum conditions for synthesis of 144. General Procedure 11 (GP11)

2,2-difluoro-1,3-diphenylpropane-1,3-dione (0.065 g, 0.25 mmol), cesium carbonate (0.244 g, 0.75 mmol), and diphenyl disulfide (0.055 g, 0.25 mmol) were added to a 14 mL stainless steel jar and charged with one stainless steel ball (10 mm, 4.1 g). The reaction mixture was milled at 30 Hz for one hour. The resulting mixture was transferred into a flask by manually removing the material with a spatula and washing with ethyl acetate (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-trifluorotoluene (0.020 mL, 0.16 mmol) was added as a NMR standard and ^{19}F NMR spectra of the crude mixture were measured and the yield determined to be 88%. The mixture was then added to a separating funnel with distilled water (40 mL). The aqueous layer was extracted with ethyl acetate (2 x 40 mL). The organic layers were combined and washed with brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield the crude product. This was purified by flash column chromatography with gradient elution (0 - 10% ethyl acetate in petroleum ether) to yield the product as a yellow oil (0.028 g, 0.09 mmol, 72%).

2,2,4,4-tetrafluoro-3-hydroxy-1,3-diphenylbutan-1-one, 144



^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.5, 1.1 Hz, 2H, Ar-H), 7.81 – 7.57 (m, 3H, Ar-H), 7.55 – 7.37 (m, 5H, Ar-H), 6.43 (t, *J* = 54.5 Hz, 1H, -CF_2**H**), 4.32 (s, 1H, -O**H**).

^{13}C {^1H} NMR (101 MHz, CDCl3) δ 190.5 (t, *J* = 29.5 Hz, **C**=O), 134.9 (Ar), 132.6 (t, J = 2.5 Hz, Ar), 132.6 (Ar), 130.4 (t, J = 3.5 Hz, Ar), 129.4 (Ar), 128.7 (Ar), 128.6 (Ar), 127.0 (Ar), 115.2 (t, *J* = 267.0 Hz, -**C**F_2), 114.0 (tt, *J* = 250.0, 3.0 Hz, -**C**F_2), 78.1 (t, *J* = 23.0 Hz, -**C**OHPh-).

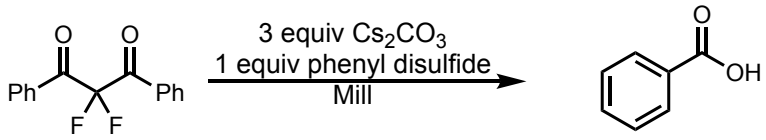
^{19}F NMR (376 MHz, CDCl3) δ -105.41 (dt, *J* = 293.5, 8.0 Hz, 1F), -106.63 (dt, *J* = 293.5, 9.3 Hz, 1F), -128.59 (ddt, *J* = 289.3, 54.1, 8.6 Hz, 1F), -130.31 (dddd, *J* = 289.4, 54.9, 10.0, 7.5 Hz, 1F).

IR 3458, 1694, 1597, 1450, 1278, 1161, 1132, 1097, 1070, 846, 808, 744, 711, 553 cm^{-1}.

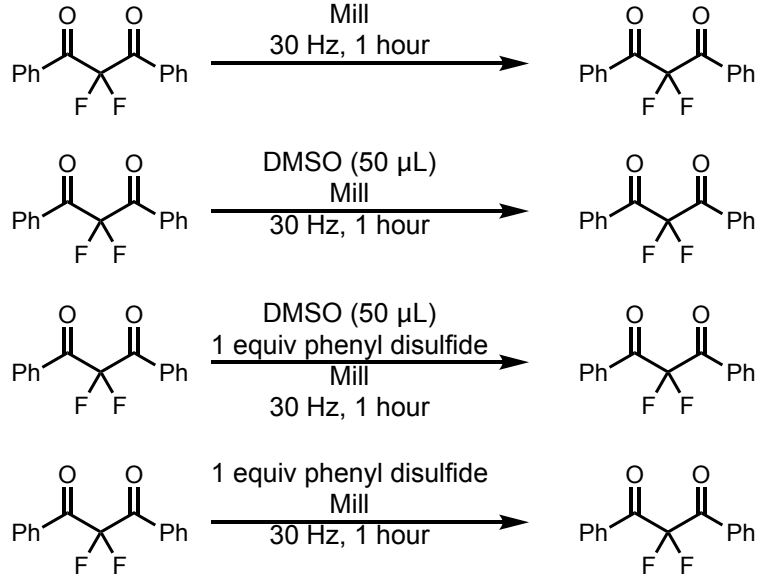
HRMS (EI+): [$C_{16}H_{12}F_4O_2$] calc. 312.0773, found 312.0772.

6.4.4 Procedures for mechanistic experiments

6.4.5 Testing fragmentation

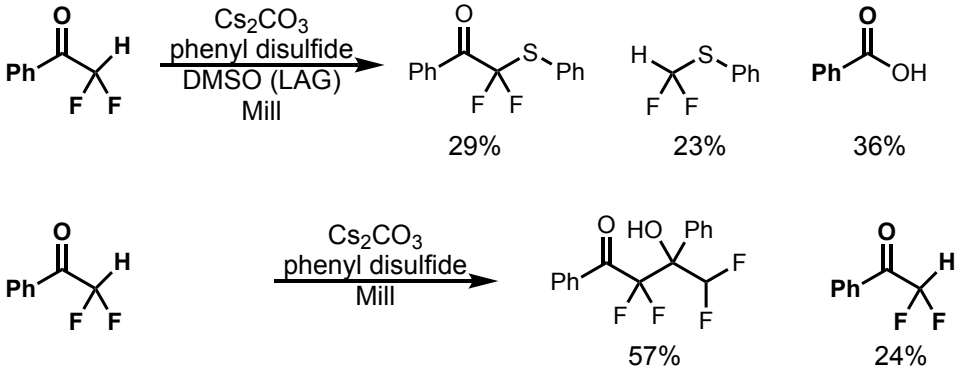


2,2-difluoro-1,3-diphenylpropane-1,3-dione (0.065 g, 0.25 mmol), cesium carbonate (0.244 g, 0.75 mmol) and diphenyl disulfide (0.055 g, 0.25 mmol) were added to a 14 mL stainless steel jar and charged with one stainless steel ball (10 mm, 4.1 g). The reaction mixture was milled at 30 Hz for one hour. The residue was then transferred into a separating funnel, washing with dichloromethane (30 mL) and water (30 mL). The layers were separated and the aqueous layer further extracted with dichloromethane (2 x 30 mL). The aqueous phase was acidified to pH 1 with HCl (1 M) then extracted with dichloromethane (3 x 30 mL). This organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield benzoic acid (0.026 g, 0.21 mmol, 84%).



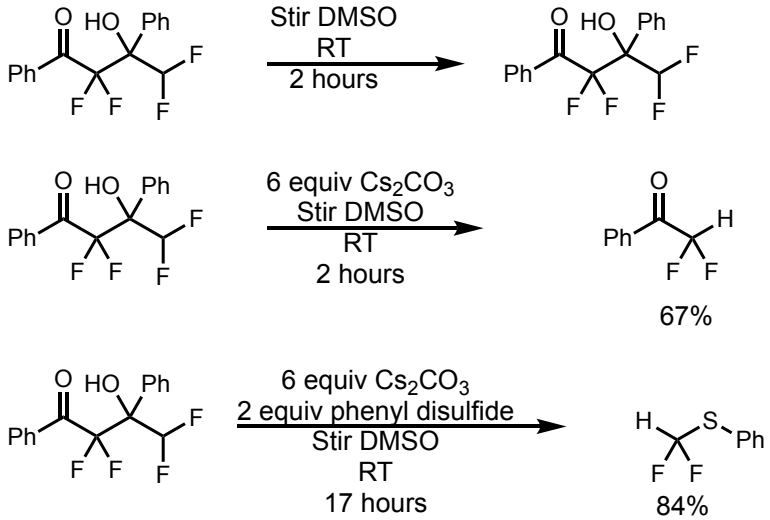
2,2-difluoro-1,3-diphenylpropane-1,3-dione (0.065 g, 0.25 mmol) and the specified additive(s) were added to a 14 mL stainless steel jar and charged with one stainless steel ball (10 mm, 4.1 g). The reaction mixture was milled at 30 Hz for one hour. The resulting mixture was transferred into a flask by manually removing the material with a spatula and washing with ethyl acetate (approximately 40 mL). The insoluble material was removed by gravity filtration and ^{19}F NMR spectra of the crude mixture were measured. In all cases the only peak observed was due to the starting material.

6.4.6 Testing intermediate



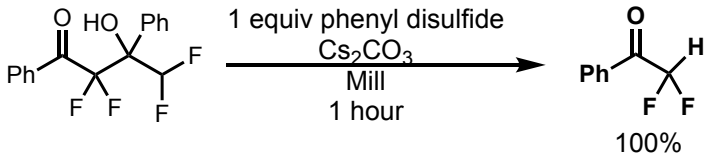
2,2-difluoro-1-phenylethan-1-one (0.039 g, 0.25 mmol), cesium carbonate (0.244 g, 0.75 mmol), DMSO (0.050 mL, where applicable) and diphenyl disulfide (0.055 g, 0.25 mmol) were added to a 14 mL stainless steel jar and charged with one stainless steel ball (10 mm, 4.1 g). The reaction mixture was milled at 30 Hz for one hour. The resulting mixture was transferred into a flask by manually removing the material with a spatula and washing with ethyl acetate (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-trifluorotoluene (0.020 mL, 0.16 mmol) was added as a NMR standard and ^{19}F NMR spectra of the reaction mixture were measured to determine the yields. To measure the quantity of benzoic acid (for the LAG case), the residue was then transferred into a separating funnel, washing with dichloromethane (30 mL) and water (30 mL). The layers were separated and the aqueous layer further extracted with dichloromethane (2 x 30 mL). The aqueous phase was acidified to pH 1 with HCl (1 M) then extracted with dichloromethane (3 x 30 mL). This organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield benzoic acid (0.011 g, 0.09 mmol, 36%).

6.4.7 Testing reversibility in solution

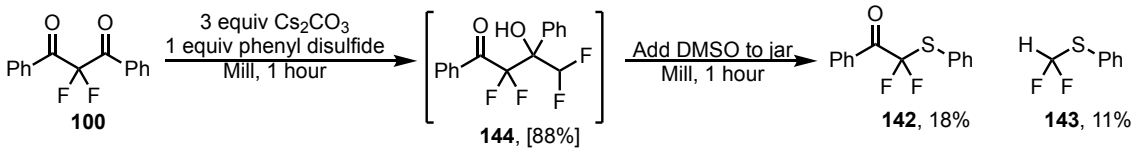


A mixture of 2,2,4,4-tetrafluoro-3-hydroxy-1,3-diphenylbutan-1-one (0.037 g, 0.12 mmol), other reagents (see scheme above) in DMSO (1 mL) was stirred at room temperature for the required time. α,α,α-trifluorotoluene (0.020 mL, 0.16 mmol) was added as a NMR standard and ^{19}F NMR spectra of the reaction mixture were measured to determine the yields.

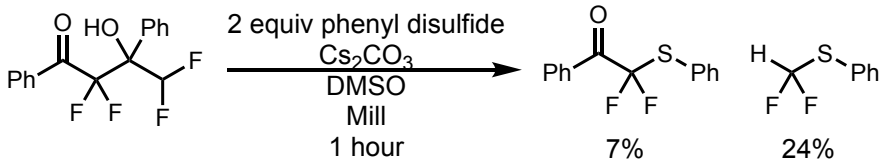
6.4.8 Testing reversibility in ball mill



2,2,4,4-tetrafluoro-3-hydroxy-1,3-diphenylbutan-1-one (0.037 g, 0.12 mmol), diphenyl disulfide (0.055 g, 0.25 mmol) and cesium carbonate (0.244 g, 0.75 mmol) were added to a 14 mL stainless steel jar and a stainless steel ball (10 mm, 4.1 g) added. The mixture was milled for one hour. The resulting mixture was transferred into a flask by manually removing the material with a spatula and washing with ethyl acetate (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-trifluorotoluene (0.020 mL, 0.16 mmol) was added as a NMR standard and ^{19}F NMR spectra of the reaction mixture were measured to determine the yield.



2,2-difluoro-1,3-diphenylpropane-1,3-dione (0.065 g, 0.25 mmol), cesium carbonate (0.244 g, 0.75 mmol), and diphenyl disulfide (0.055 g, 0.25 mmol) were added to a 14 mL stainless steel jar and charged with one stainless steel ball (10 mm, 4.1 g). The reaction mixture was milled at 30 Hz for one hour. The jar was opened, DMSO (0.050 mL) added and the mixture further milled for one hour. The mixture was milled for one hour. The resulting mixture was transferred into a flask by manually removing the material with a spatula and washing with ethyl acetate (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-trifluorotoluene (0.020 mL, 0.16 mmol) was added as a NMR standard and ^{19}F NMR spectra of the reaction mixture were measured to determine the yields.



2,2-difluoro-1,3-diphenylpropane-1,3-dione (0.065 g, 0.25 mmol), cesium carbonate (0.244 g, 0.75 mmol), diphenyl disulfide (0.055 g, 0.25 mmol) and DMSO (50 µL) were added to a 14 mL stainless steel jar and charged with one stainless steel ball (10 mm, 4.1 g). The reaction mixture was milled at 30 Hz for one hour. The resulting mixture was transferred into a flask by manually removing the material with a spatula and washing with ethyl acetate (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-trifluorotoluene (0.020 mL, 0.16 mmol) was added as a NMR standard and ^{19}F NMR spectra of the reaction mixture were measured to determine the yields.

6.4.9 Effect of time on yield for LAG reaction

The reactions were run as in GP10 but for different times.

Time / min	Yield 142	Yield 144	Yield 145
10	13%	22%	35%
20	27%	26%	27%
30	43%	12%	20%
40	53%	10%	17%
50	57%	0%	8%
60	62%	0%	5%

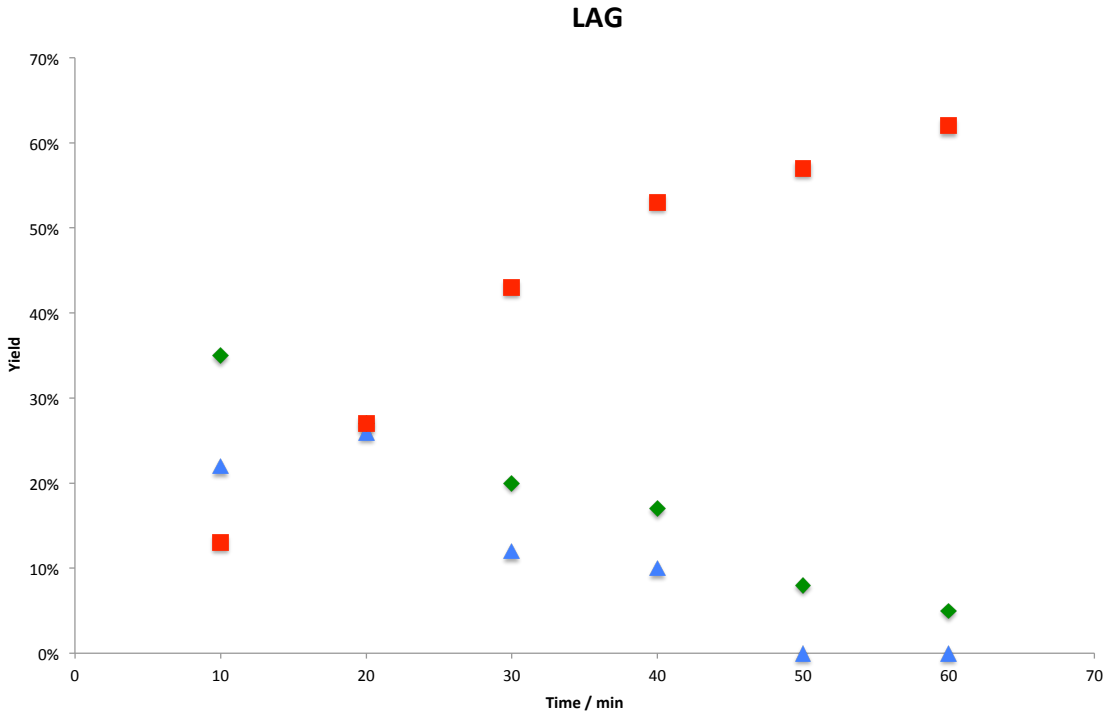


Figure 6.2 Effect of time on yield under LAG conditions

6.4.10 Effect of time on yield for neat grinding reaction

The reactions were run as in GP11 but for different times.

Time / hours	Yield 142	Yield 144	Yield 145
1	0%	88%	10%
2	10%	24%	33%
4	18%	24%	21%
6	26%	18%	7%
8	27%	14%	8%

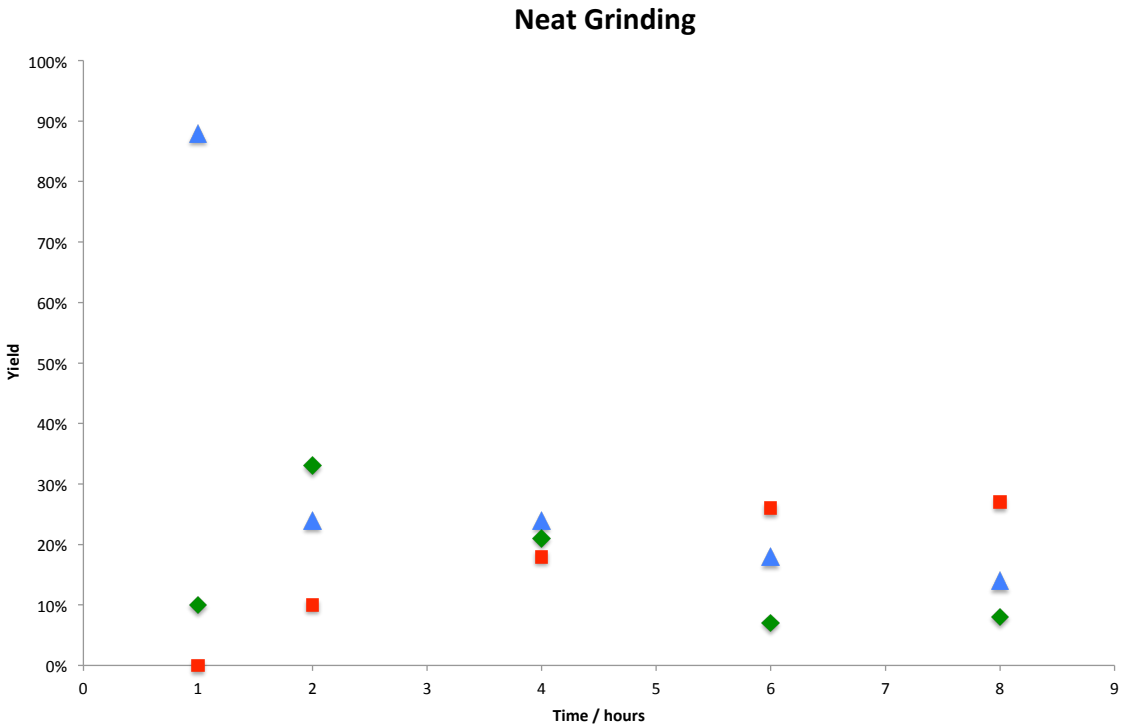


Figure 6.3 Effect of time on yield under neat milling

6.4.11 Effect of quantity of DMSO on yield after 10 minutes

2,2-difluoro-1,3-diphenylpropane-1,3-dione (0.065 g, 0.25 mmol), cesium carbonate (0.244 g, 0.75 mmol), diphenyl disulfide (0.055 g, 0.25 mmol) and the relevant quantity of DMSO were added to a 14 mL stainless steel jar and charged with one stainless steel ball (10 mm, 4.1 g). The reaction mixture was milled at 30 Hz for 10 minutes. The resulting mixture was transferred into a flask by manually removing the material with a spatula and washing with ethyl acetate (approximately 40 mL). The insoluble material was removed by gravity filtration. α,α,α-trifluorotoluene (0.020 mL, 0.16 mmol) was added as a NMR standard and ^{19}F NMR spectra of the crude mixture were measured and the yield determined.

DMSO / µL	Yield 142	Yield 144	Yield 145
0	29%	50%	0%
25	45%	24%	5%
50	35%	22%	13%
100	16%	16%	48%
150	9%	12%	59%

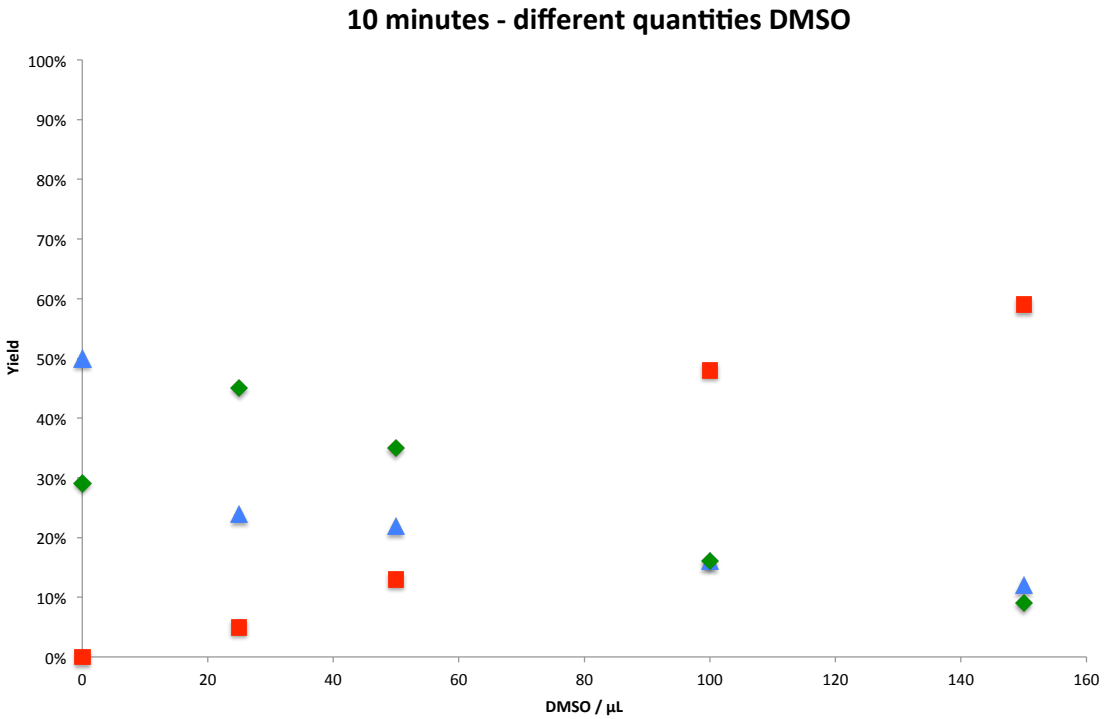


Figure 6.4 Effect of quantity of added DMSO on yield after milling for 10 minutes.

6.4.12 Effect of time on yield in solution

2,2-difluoro-1,3-diphenylpropane-1,3-dione (0.520 g, 2 mmol.), cesium carbonate (1.952 g, 6 mmol), diphenyl disulfide (0.440 g, 2 mmol) and DMSO (10 mL) were added to a flask, which was stirred at room temperature. α,α,α-trifluorotoluene (0.160 mL, 1.3 mmol) was added as a NMR standard. After stirring for the desired time, a sample was removed from the reaction mixture and filtered through cotton wool into an NMR tube. ^{19}F NMR spectra of this mixture were measured and the yields determined.

Time / min	Yield 100	Yield 142	Yield 145
3	68%	14%	18%
10	13%	33%	28%
20	0%	52%	28%
30	0%	62%	27%
40	0%	66%	27%
50	0%	68%	27%
60	0%	73%	27%

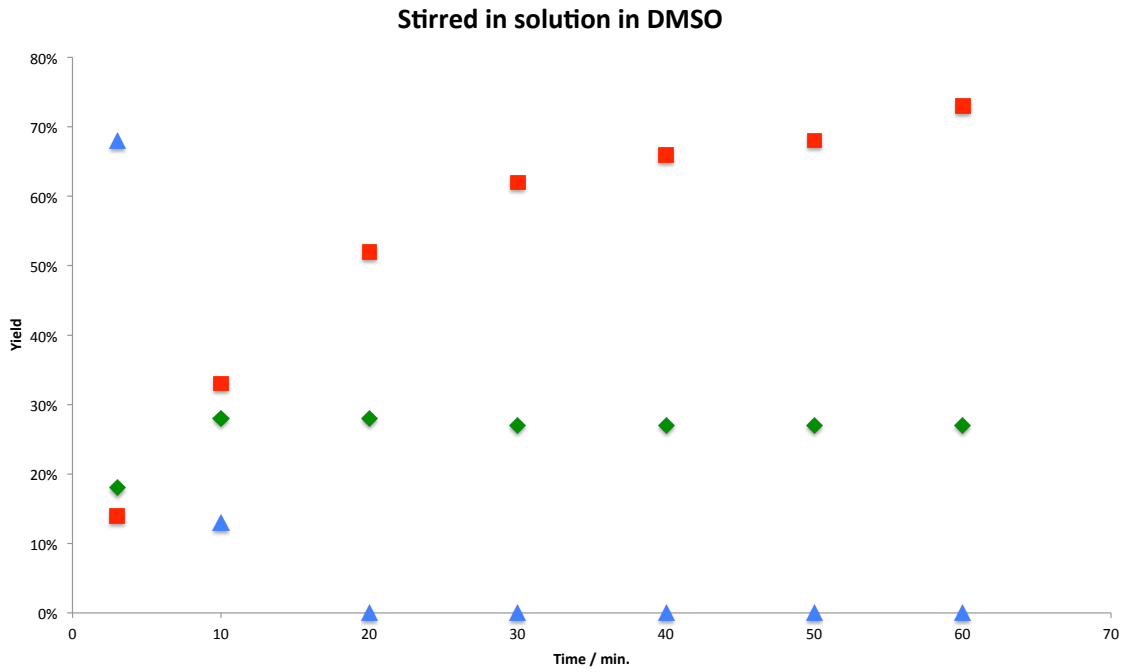
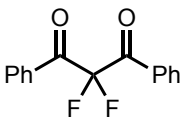


Figure 6.5 Effect of time on yield in solution.

6.4.13 Synthesis of Starting Materials

2,2-difluoro-1,3-diphenylpropane-1,3-dione, 100



To dibenzoylmethane (5.6 g, 25 mmol), Selectfluor (17.7 g, 50 mmol) and sodium carbonate (5.3 g, 50 mmol) was added acetonitrile (250 mL). This mixture was stirred at room temperature for 72 h. The solvent was removed under reduced pressure, the residue dissolved in water (150 mL) and dichloromethane (150 mL) and transferred to a separating funnel. The layers were separated and the aqueous layer further extracted with dichloromethane (2 x 100 mL). The combined organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield the crude product. Hot hexane was added until most of the residue was dissolved, with a dark, insoluble impurity remaining. The solution in hot hexane was transferred to another flask and left to cool to room temperature.

Colourless crystals of pure product were obtained and collected by vacuum filtration, washing on the filter with hexane to yield the desired product (4.69 g, 18 mmol, 72%).[18]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.5, 1.0 Hz, 4H, Ar-H), 7.71 – 7.65 (m, 2H, Ar-H), 7.55 – 7.50 (m, 4H, Ar-H).

^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 187.4 (t, *J* = 27.0 Hz, **C**=O), 135.1 (Ar), 131.6 (t, *J* = 1.5 Hz, Ar), 130.3 (t, *J* = 2.5 Hz, Ar), 129.0 (Ar), 112.7 (t, *J* = 266.0 Hz, -**C**F_2).

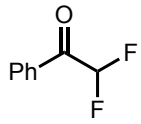
^{19}F NMR (376 MHz, $CDCl_3$) δ -102.66 (s, 2F).

IR 1693, 1595, 1577, 1448, 1305, 1251, 1188, 1155, 1136, 1101, 999, 941, 887, 771, 719, 694, 678, 663, 569, 522, 435, 422 cm^{-1}

HRMS (EI+): [$C_{15}H_{10}F_2O_2$] $[M+NH_4]^+$ calc. 278.0987, found 278.0988.

mp: 58 – 60 °C (hexane).

2,2-difluoro-1-phenylethan-1-one, 145



Prepared according to a modified literature procedure.[19] To ethylbenzoylacetate (4.3 mL, 4.77 g, 25 mmol) was added aqueous sodium hydroxide (1 M, 25 mL) and the mixture stirred at room temperature for 20 hours. The mixture was transferred to a separating funnel and the aqueous layer washed with dichloromethane (3 x 10 mL). The aqueous layer was acidified to pH 1 with HCl (1 M). The precipitate was collected by vacuum filtration, washing on the filter with water to yield benzoylacetic acid (2.545 g, 15.5 mmol, 62%), which was used without further purification.

To benzoylacetic acid (2.545 g, 15.5 mmol) was added Selectfluor (13.718 g, 38.75 mmol) and acetonitrile (100 mL). A reflux condenser was fitted and the mixture heated to 60 °C and stirred for 67 hours. The solvent was removed under reduced pressure. Water (50 mL) and dichloromethane (50 mL) were added to the residue and the mixture transferred to a separating funnel. The layers were separated and the aqueous layer further extracted with dichloromethane (2 x 50 mL). The combined organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to yield the crude product. This was further purified by flash column chromatography with gradient elution (0 - 10% Ethyl acetate in petroleum ether) to yield the product as a colourless oil (1.146 g, 7.35 mmol, 47%).[19]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.70 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.56 (t, *J* = 7.9 Hz, 2H, Ar-H), 6.32 (t, *J* = 53.5 Hz, 1H, -CF_2**H**).

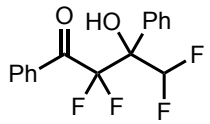
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 187.6 (t, *J* = 25.5 Hz, **C**=O), 134.9 (Ar), 131.5 (t, *J* = 2.0 Hz, Ar), 129.7 (t, *J* = 2.5 Hz, Ar), 129.0 (Ar), 111.2 (t, *J* = 254.0 Hz, -**C**F_2H).

^{19}F NMR (471 MHz, $CDCl_3$) δ -121.94 (d, *J* = 53.5 Hz, 2F).

IR 1707, 1597, 1579, 1450, 1348, 1288, 1055, 1001, 972, 933, 862, 761, 700, 682, 657, 572, 553, 468 cm^{-1}.

HRMS (EI+): [$C_8H_6F_2O$] calc. 156.0387, found 156.0385.

2,2,4,4-tetrafluoro-3-hydroxy-1,3-diphenylbutan-1-one, 144



2,2-difluoro-1,3-diphenylpropane-1,3-dione (0.065 g, 0.25 mmol), diphenyl disulfide (0.055 g, 0.25 mmol) and cesium carbonate (0.244 g, 0.75 mmol) were added to a 14 mL stainless steel jar and a ball added. The mixture was milled for one hour. The residue was then transferred into a separating funnel, washing with ethyl acetate (30 mL) and water (30 mL). The layers were separated and the aqueous layer further extracted with ethyl acetate (2 x 30 mL). The combined organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. This reaction and workup procedure was repeated ten times and the crude material combined and purified by flash column chromatography with gradient elution (0 - 10% ethyl acetate in petroleum ether) to yield the product as a yellow oil (0.240 g, 0.77 mmol, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.5, 1.1 Hz, 2H, Ar-H), 7.81 – 7.57 (m, 3H, Ar-H), 7.55 – 7.37 (m, 5H, Ar-H), 6.43 (t, *J* = 54.5 Hz, 1H, -CF_2**H**), 4.32 (s, 1H, -O**H**).

^{13}C {^{1}H} NMR (101 MHz, CDCl3) δ 190.5 (t, *J* = 29.5 Hz, **C**=O), 134.9 (Ar), 132.6 (t, J = 2.5 Hz, Ar), 132.6 (Ar), 130.4 (t, J = 3.5 Hz, Ar), 129.4 (Ar), 128.7 (Ar), 128.6 (Ar), 127.0 (Ar), 115.2 (t, *J* = 267.0 Hz, -**C**F_2), 114.0 (tt, *J* = 250.0, 3.0 Hz, -**C**F_2), 78.1 (t, *J* = 23.0 Hz, -**C**OHPh-).

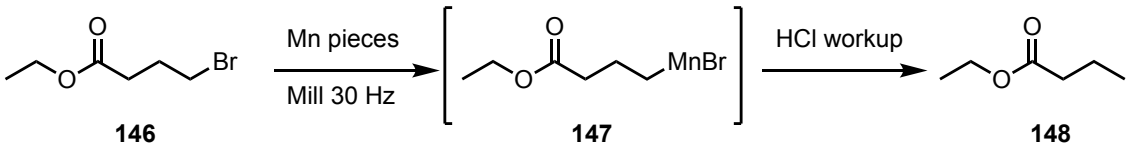
^{19}F NMR (376 MHz, CDCl3) δ -105.41 (dt, *J* = 293.5, 8.0 Hz, 1F), -106.63 (dt, *J* = 293.5, 9.3 Hz, 1F), -128.59 (ddt, *J* = 289.3, 54.1, 8.6 Hz, 1F), -130.31 (dddd, *J* = 289.4, 54.9, 10.0, 7.5 Hz, 1F).

IR 3458, 1694, 1597, 1450, 1278, 1161, 1132, 1097, 1070, 846, 808, 744, 711, 553 cm^{-1}.

HRMS (EI+): [$C_{16}H_{12}F_4O_2$] calc. 312.0773, found 312.0772.

6.5 Mechanochemical activation of metals

6.5.1 Evaluation of mechanochemical organomanganese formation



146 **147** **148**

Ethyl-4-bromobutyrate (0.195 g, 1 mmol), manganese pieces, irregular (relevant quantity) and additive(s) were added to a 14 mL stainless steel jar and a stainless steel ball (10 mm, 4.1 g) added. The mixture was milled at 30 Hz for the appropriate time. The mixture was then washed into a flask with dichloromethane (approx. 50 mL), HCl (1 M, 25 mL) was added and the mixture stirred for ten minutes. Trifluorotoluene (0.041 mL) was added as an internal standard, and a sample from the organic layer was passed through a silica plug, washing with diethyl ether. This sample was subjected to GC analysis to determine the yield of **148** and conversion of **146**.

The GC yield of products and conversion of substrates were determined by using the internal standard method. The response factor (RF) of analytes was determined by analyzing known quantities of internal standard (trifluorotoluene) against known quantities of substrate and product:

$$RF = \frac{Area_{internal\ standard} \times Moles_{analyte}}{Area_{analyte} \times Moles_{internal\ standard}}$$

The quantity of an analyte was then calculated according to the following equation:

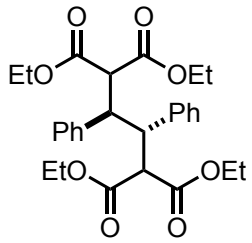
$$Moles_{analyte} = \frac{RF \times Moles_{internal\ standard} \times Area_{analyte}}{Area_{internal\ standard}}$$

6.5.2 General procedure for mechanochemical reactions (GP12)

Manganese pieces, irregular (0.060 g, 1.1 mmol), substrate (1 mmol), ethyl-4-bromobutyrate (0.194 g, 1 mmol, if relevant), THF (0.081 mL, 1 mmol) and lithium chloride (0.043 g, 1 mmol) were added to a 14 mL stainless steel jar and a ball added. The mixture was milled at 30 Hz for 3 hours, and then washed into a flask with dichloromethane (approx. 50 mL). HCl (1 M, 25 mL) was added and the mixture transferred to a separating funnel. The layers were separated and the aqueous phase

further extracted with DCM (3 x 30 mL). The combined organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude mixture was analysed by TLC and ^1H NMR spectroscopy and samples that showed consumption of starting material were purified by flash column chromatography with gradient elution (0 - 25% ethyl acetate in petroleum ether).

Tetraethyl 2,3-diphenylbutane-1,1,4,4-tetracarboxylate, 151



Prepared according to GP12 from ethylbenzylidenemalonate. Colourless crystals (0.182 g, 0.33 mmol, 66%). Relative stereochemistry was determined by single crystal X-Ray diffraction on a sample recrystallized from hot ethanol.

^1H-NMR (400 MHz; $CDCl_3$): δ 7.32-7.24 (m, 10H, Ar-H), 4.12 (dd, *J* = 6.0, 2.2 Hz, 2H, 2(-C**H**$(CO)_2$), 3.98-3.90 (m, 4H, 2(-OC**H**$_2$Me), 3.87-3.81 (m, 4H, 2(-OC**H**$_2$Me), 3.69 (dd, *J* = 6.0, 2.2 Hz, 2H, 2(-C**H**Ph-), 1.13 (t, *J* = 7.1 Hz, 6H, 2($-CH_3$)), 0.94 (t, *J* = 7.1 Hz, 6H, 2($-CH_3$)).

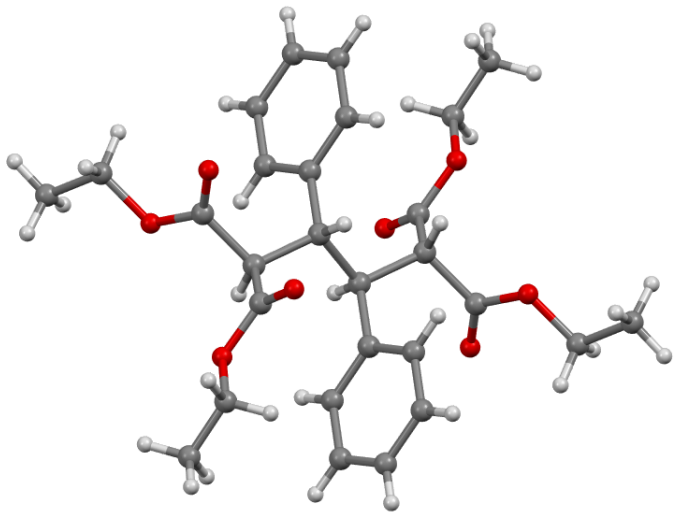
^{13}C {^1H} NMR (101 MHz; $CDCl_3$): δ 168.5 (C=O), 167.8 (C=O), 138.3 (Ar), 130.3 (Ar), 128.2 (Ar), 127.6 (Ar), 61.6 (-O**C**H_2Me), 61.2 (-O**C**H_2Me), 55.9 (-**C**H$(CO)_2$), 48.8 (-**C**HPh-), 14.0 ($-CH_3$), 13.8 ($-CH_3$).

IR 2982, 1744, 1721, 1366, 1314, 1252, 1231, 1169, 1134, 1030, 868, 773, 706, 575, 550 cm^{-1}.

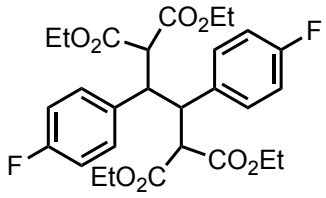
HRMS (ES+): [$C_{28}H_{34}O_8$ + H] calc. 499.2332, found 499.2327.

mp: 89 - 90 °C (ethanol)

single crystal X-Ray diffraction structure:



Tetraethyl2,3-bis(4-fluorophenyl)butane-1,1,4,4-tetracarboxylate, 153



Prepared according to GP12 from diethyl-4-fluorobenzylidenemalonate. Colourless powder (0.100 g, 0.19 mmol, 37%).

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.31-7.28 (m, 4H, Ar-H), 7.00-6.96 (m, 4H, Ar-H), 4.09-4.08 (m, 2H, 2(-C**H**$(CO)_2$), 3.99-3.94 (m, 4H, 2(-OC**H**$_2$Me)), 3.91-3.86 (m, 4H, 2(-OC**H**$_2$Me)), 3.61-3.59 (m, 2H, 2(-C**H**Ar-)), 1.13 (t, *J* = 7.1 Hz, 6H, 2(-CH_3)), 0.98 (t, *J* = 7.1 Hz, 6H, 2(-CH_3)).

^{13}C {^{1}H} NMR (101 MHz; $CDCl_3$): δ 168.3 (C=O), 167.7 (C=O), 162.3 (d, *J* = 248 Hz, Ar-F), 133.8 (d, *J* = 3 Hz, Ar), 131.9 (d, *J* = 8 Hz, Ar), 115.1 (d, *J* = 21 Hz, Ar), 61.7 (-O**C**H_2Me), 61.3 (-O**C**H_2Me), 55.5 (-**C**H$(CO)_2$), 47.9 (-**C**HPh-), 13.95 (-CH_3), 13.82 (-CH_3).

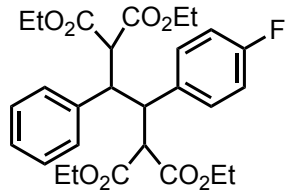
^{19}F NMR (376 MHz; $CDCl_3$): δ -114.7.

IR 2984, 1740, 1506, 1308, 1256, 1219, 1157, 1138, 1094, 1028, 851, 565 cm^{-1}.

HRMS (ES+): [$C_{28}H_{32}O_8F_2$ + H] calc. 535.2143, found 535.2141.

mp: 152 - 154 °C (EtOAc)

Tetraethyl 2-(4-fluorophenyl)-3-phenylbutane-1,1,4,4-tetracarboxylate,166



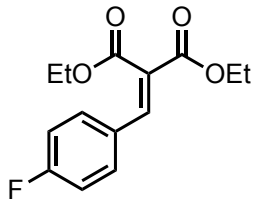
Isolated as a mixture with tetraethyl-2,3-bis(4-fluorophenyl)butane-1,1,4,4-tetracarboxylate **153** as white crystals (0.147 g). Molar ratio determined by ^{19}F NMR spectroscopy as 0.53:1 (**166**:**153**), corresponding to **153** (0.095 g, 0.18 mmol, 36%) and **166** (0.052 g, 0.097 mmol, 38%). Presence of **166** confirmed by HRMS.

^{19}F NMR (376 MHz; $CDCl_3$): δ -115.0.

HRMS (AP+): [$C_{28}H_{33}O_8F$ + H] calc. 517.2238, found 517.2249.

6.5.3 Preparation of starting materials

Diethyl 2-(4-fluorobenzylidene)malonate, 152



Following a modified literature procedure,[20] 4-fluorobenzaldehyde (2.48 g, 20 mmol) and diethyl malonate (3.20 g, 20 mmol) were dissolved in toluene (100 mL). To this were added piperidine (0.296 mL, 3 mmol) and glacial acetic acid (0.172 mL, 3 mmol). The flask was fitted with a Dean-Stark head, heated to reflux and stirred for 24 hours. The reaction mixture was cooled, diluted with diethyl ether (50 mL) and water (50 mL) and transferred to a separating funnel. The layers were separated and the organic layer washed with water (50 mL) and HCl (1 M, 50 mL), dried ($MgSO_4$),

filtered and the solvent removed under reduced pressure. This mixture was initially purified by flash column chromatography with gradient elution (0 - 10% ethyl acetate in petroleum ether). This was then further purified by Kugelrohr distillation (180 °C, 30 mbar) to remove the unreacted diethyl malonate and byproducts. This yielded the product as a red oil (2.238 g, 8.41 mmol, 42%).

^{1}H NMR (500 MHz; $CDCl_3$): δ 7.68 (s, 1H, -ArC**H**-), 7.46 (dd, *J* = 8.5, 5.3 Hz, 2H, Ar-H), 7.07 (t, *J* = 8.6 Hz, 2H, Ar-H), 4.38-4.27 (m, 4H, 2(-OC**H**$_2$Me)), 1.33 (t, *J* = 7.1 Hz, 3H, -Me), 1.30 (t, *J* = 7.1 Hz, 3H, -Me).

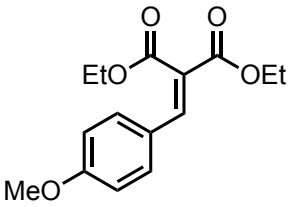
^{13}C {^{1}H} NMR (101 MHz; $CDCl_3$): δ 166.7 (C=O), 164.2 (C=O), 164.0 (d, *J* = 254 Hz, Ar-F), 140.9 (-**C**$(CO)_2$), 131.7 (d, *J* = 9 Hz, Ar), 129.3 (d, *J* = 3 Hz, Ar), 126.3(-Ar**C**H-), 116.2 (d, *J* = 22 Hz, Ar), 61.92 (-O**C**H_2Me), 61.85 (-O**C**H_2Me), 14.3 (-Me), 14.1 (-Me).

^{19}F NMR (471 MHz; $CDCl_3$): δ -108.7.

IR 1721, 1601, 1508, 1258, 1209, 1192, 1161, 1061, 833, 509 cm^{-1}.

HRMS (EI+): [$C_{14}H_{15}O_4F$] calc. 266.0954, found 266.0951.

Diethyl 2-(4-methoxybenzylidene)malonate, 154



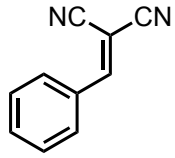
Following a modified literature procedure,[21] diethyl malonate (3.20 g, 20 mmol) and p-anisaldehyde (2.723 g, 20 mmol) were dissolved in ethanol (10 mL). To this were added glacial acetic acid (0.172 mL, 3 mmol) and piperidine (0.296 mL, 3 mmol) and the mixture was heated to reflux and stirred for 2 days. This mixture was purified by Kugelrohr distillation (130 °C, 50 mbar) to remove the unreacted diethyl malonate and byproducts. The product was obtained as a yellow oil (4.905 g, 17.6 mmol, 88%). Data is in agreement with the literature values.[21]

^{1}H NMR (500 MHz; $CDCl_3$): δ 7.67 (s, 1H, (-ArC**H**-), 7.42 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.89 (d, *J* = 8.8 Hz, 2H, Ar-H), 4.35 (q, *J* = 7.1 Hz, 2H, (-OC**H**$_2$Me)), 4.29 (q, *J* = 7.1 Hz, 2H, (-OC**H**$_2$Me)), 3.83 (s, 3H, -Me), 1.32 (t *J* = 7.1 Hz, 6H 2(-Me)).

^{13}C {^{1}H} NMR (126 MHz; $CDCl_3$): δ 167.3 (C=O), 164.6 (C=O), 161.7 (Ar), 141.9 (Ar), 131.7 (Ar), 125.5 (Ar), 123.7 (-**C**$(CO)_2$), 114.4 (-Ar**C**H-), 61.75 (-O**C**H_2Me), 61.57 (-O**C**H_2Me), 55.5 (-OMe), 14.3 (-Me), 14.1 (-Me).

IR 2980, 1717, 1601, 1512, 1254, 1200, 1171, 1061, 1020, 829, 540, 518 cm^{-1}.

2-benzylidenemalononitrile, 162



Following a modified literature procedure[23], benzaldehyde (1.061 g, 10 mmol), malononitrile (0.661 g, 10 mmol) and piperidine (0.099 mL, 1 mmol) were dissolved in ethanol (10 mL). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, dichloromethane (50 mL) and HCl (0.1 M, 50mL) were added and the mixture transferred to a separating funnel. The layers were separated and the aqueous layer further extracted with dichloromethane (2 x 50 mL). The combined organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was then recrystallized from hot $EtOH/H_2O$ to yield the product as yellow crystals (0.941 g, 6.11 mmol, 61%). Data is in agreement with literature values.[23]

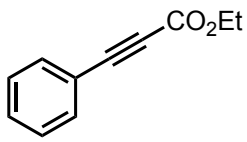
^{1}H NMR (500 MHz; $CDCl_3$): δ 7.91 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.78 (s, 1H, Ar-H), 7.65-7.62 (m, 1H, -ArC**H**-), 7.55 (t, *J* = 7.6 Hz, 2H, Ar-H).

^{13}C {^{1}H} NMR (126 MHz; $CDCl_3$): δ 160.0, 134.8, 131.1, 130.9, 129.8, 113.8, 112.7, 83.1.

IR 2222, 1736, 1670, 1589, 1450, 1217, 959, 754, 677, 615, 519 cm^{-1}.

mp: 80 - 81 °C (ethanol)

Ethyl 3-phenylpropiolate, 164



Following a modified literature procedure;[22] To an oven-dried flask was added potassium carbonate (2.073 g, 15 mmol) and the flask flushed with nitrogen. Ethyl propiolate (0.507 mL, 5 mmol), iodobenzene (0.839 mL, 7.5 mmol) and dry THF (40 mL) were added and stirred. To this mixture was added $Pd(PPh_3)_2Cl_2$ (0.070 g, 0.1 mmol) and CuI (0.018 g, 0.1 mmol) and the flask flushed with nitrogen. The mixture was heated to reflux, stirred for 22 hours, cooled and filtered through cotton wool into a separating funnel. Dichloromethane (50 mL) and water (50 mL) were added, the layers separated and the aqueous layer further extracted with dichloromethane (2 x 50 mL). The combined organic phase was washed (brine), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The product was purified by flash column chromatography with gradient elution (0 - 10% ethyl acetate in petroleum ether) and the product obtained as a yellow oil (0.325 g, 1.87 mmol, 37%). Data is in agreement with literature values.[22]

^{1}H NMR (500 MHz; $CDCl_3$): δ 7.59 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.46-7.43 (m, 1H, Ar-H), 7.37 (t, *J* = 7.6 Hz, 2H, Ar-H), 4.32-4.28 (m, 2H, -OC**H**$_2$Me), 1.36 (t, *J* = 7.1 Hz, 3H, -Me).

^{13}C {^{1}H} NMR (126 MHz; $CDCl_3$): δ 154.2 (C=O), 133.1 (Ar), 130.7 (Ar), 128.7 (Ar), 119.8 (Ar), 86.2 (alkyne), 80.8 (alkyne), 62.3 (-O**C**H_2Me), 14.3 (-Me).

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