

## RESEARCH ARTICLE

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View Journal | View IssueCite this: *Org. Chem. Front.*, 2025, 12, 6273Utilisation of CO<sub>2</sub> in the simultaneous installation of the C–C and C=C bonds of  $\alpha,\beta$ -unsaturated carboxylic acids†Amy Lowry,<sup>a</sup> Rachel E. Lynch,<sup>b</sup> Gerard P. McGlacken<sup>a,c</sup> and Peter A. Byrne<sup>b,c</sup>

Development of methods for the conversion of CO<sub>2</sub> (a major waste product) into value-added chemicals has become an area of great interest. Herein we report the development of a new retrosynthetic double disconnection strategy, translating to a highly efficient synthetic methodology in which both the C=C double bond and the C–C bond of an  $\alpha,\beta$ -unsaturated carboxylic acid can be constructed concurrently, with CO<sub>2</sub> as a chemical feedstock. Central to the success of this methodology are “phosphonium carboxylate ylides”. These unique new entities can undergo novel Wittig-type reactions, forming  $\alpha,\beta$ -unsaturated carboxylic acids with excellent stereoselectivity and perfectly regioselective installation of both the carboxyl group and the C=C bond. The  $\alpha,\beta$ -unsaturated carboxylic acid motif appears widely in the structures of pharmaceutical compounds and precursors thereof. The availability of a broadly applicable approach for synthesising  $\alpha,\beta$ -unsaturated carboxylic acids will thus be highly valuable. Surprisingly, this represents the first general direct Wittig-type methodology for formation of the alkene moiety in  $\alpha,\beta$ -unsaturated carboxylic acids.

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## Introduction

From a waste utilisation perspective, CO<sub>2</sub> is a highly attractive, non-toxic, renewable resource for the construction of valuable target compounds.<sup>1–8</sup> At present, only a small number of chemicals are made industrially using CO<sub>2</sub>,<sup>8,9</sup> and hence there exists an extraordinary opportunity to expand the utilisation of CO<sub>2</sub> as a feedstock in chemical synthesis as the efficiency and scalability of carbon capture strategies increase.<sup>10–20</sup> Motivated by this, we have developed a novel means of utilisation of CO<sub>2</sub> for the synthesis of a particularly important class of carboxylic acids in the context of pharmaceutical production –  $\alpha,\beta$ -unsaturated carboxylic acids.

The  $\alpha,\beta$ -unsaturated carboxylic acid structural motif and derivatives thereof appear with astonishing regularity in the structures of pharmaceutical compounds and synthetic intermediates leading to these compounds.<sup>21–29</sup> For example, 38 of the new drugs approved for clinical use since 2015 contain an

$\alpha,\beta$ -unsaturated carboxylic acid or derivative thereof in their final structure or in a synthetic intermediate used to make them.<sup>24,27,29–32</sup> This motif also appears in the structures of important commodity chemicals such as acrylic acid.<sup>33</sup>  $\alpha,\beta$ -Unsaturated carboxylic acids are frequently accessed by various indirect methods<sup>34–38</sup> which may involve multiple synthetic steps either for the  $\alpha,\beta$ -carboxylic acid syntheses themselves or for preparation of the starting materials required, and consequently involve use of a multiplicity of reagents and solvents. Taking into account the entirety of the synthetic sequence (rather than just the step in which the  $\alpha,\beta$ -unsaturated carboxylic acid is produced), more direct syntheses of  $\alpha,\beta$ -unsaturated carboxylic acids (and derivatives thereof) become possible if CO<sub>2</sub> can be incorporated into the target compound(s). However, the pre-eminent existing strategies for achieving such CO<sub>2</sub> incorporations all rely on the retrosynthetic approach shown in Scheme 1a – *i.e.*, alkene or alkyne carboxylation reactions involving formation of the C <sub>$\alpha$</sub> –CO<sub>2</sub> bond<sup>39–43</sup> (see Scheme 2a for an example of a recent leading strategy that uses CuCl, an additional ligand, MeI, B<sub>2</sub>(pin)<sub>2</sub>, LiO<sup>t</sup>Bu at elevated temperatures).<sup>39</sup>

We envisaged that a particularly direct means of formation of  $\alpha,\beta$ -unsaturated carboxylic acids might be possible if a synthetic approach based around the retrosynthetic double disconnection shown in Scheme 1b could be realised; this would entail formation of both the C <sub>$\alpha$</sub> =C <sub>$\beta$</sub>  double bond and the C <sub>$\alpha$</sub> –CO<sub>2</sub> bond in a single, one-pot procedure. Such a strategy

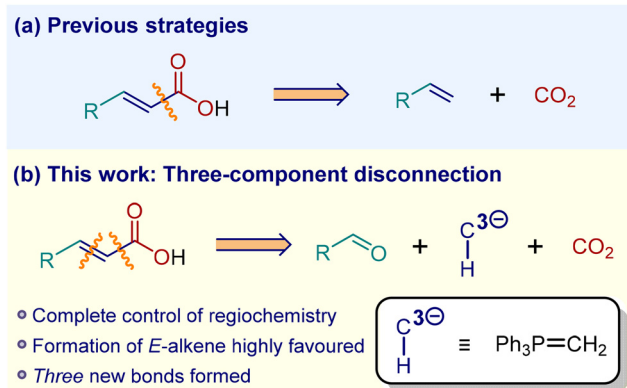
<sup>a</sup>School of Chemistry & Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland

<sup>b</sup>Centre for Synthesis & Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland. E-mail: peter.byrne@ucd.ie

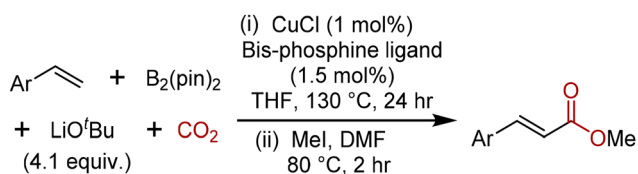
<sup>c</sup>SSPC, the Research Ireland Centre for Pharmaceuticals, Ireland

† Electronic supplementary information (ESI) available: Details of experimental methods, characterisation data, copies of NMR spectra. See DOI: <https://doi.org/10.1039/d5qo00770d>





**Scheme 1** Retrosynthetic approaches to  $\alpha,\beta$ -unsaturated carboxylic acids. (a) Existing methodologies:  $C_\alpha$ - $CO_2$  bond formation (alkene or alkyne carboxylation); (b) this work: formation of the  $C_\alpha=C_\beta$  bond and the  $C_\alpha$ - $CO_2$  bond in a single process.

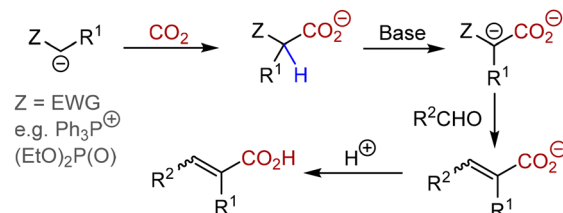


**Scheme 2** Example of a leading method for synthesis of  $\alpha,\beta$ -unsaturated carboxylic acids involving Cu-catalysed carboxylation of terminal alkenes.<sup>39</sup>

would involve concurrent formation of *three* new carbon-carbon bonds, enabling rapid increases in molecular complexity to be achieved through a single process (with  $CO_2$  utilisation incorporated). To achieve this goal, we envisaged utilisation of a nucleophilic species (*e.g.*, a phosphonium ylide or phosphono carbanion) that is capable of reacting with  $CO_2$  to form an adduct that can thereafter be deprotonated to produce an anionic species that can undergo an olefination reaction (see Scheme 3a) – *e.g.*, a Wittig,<sup>44–53</sup> Wadsworth–Emmons,<sup>54,55</sup> Julia,<sup>56,57</sup> or other related olefination.<sup>58–61</sup> This would enable installation of both the  $C=C$  double bond and the carboxyl moiety (from  $CO_2$ ) of an  $\alpha,\beta$ -unsaturated carboxylic acid in one go (*i.e.*, in a single process), thus realising the goal of the retrosynthesis shown in Scheme 1b, with the nucleophilic species mentioned above fulfilling the role of the carbon trianion synthon ( $H-C^{3-}$ ) shown therein. Furthermore, such an approach would have the advantage of providing a high degree of control over the position in which the carboxyl moiety is installed and over the placement (regiochemistry) and stereochemistry of the  $C=C$  double bond, in contrast to existing alkene and alkyne carboxylation methodologies. In addition, it would employ carbonyl compounds as starting materials, which are naturally abundant<sup>62</sup> and can be sustainably derived from biomass.<sup>63,64</sup>

However, although this approach appears to afford the opportunity for straightforward access to  $\alpha,\beta$ -unsaturated car-

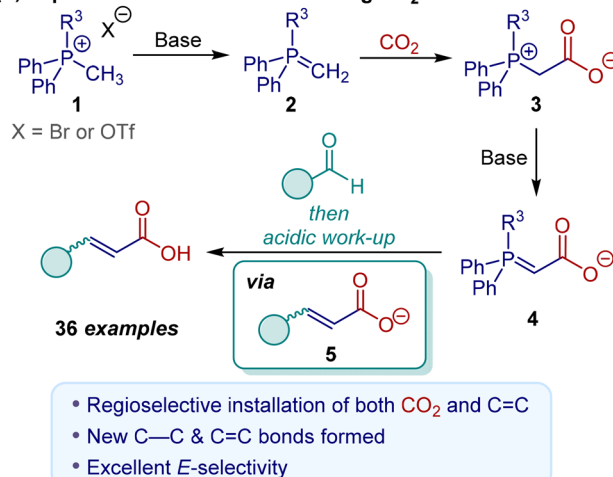
**(a) Target strategy: Activation of  $CO_2$ , adduct deprotonation, and olefination**



Complete control over....

- Position of carboxyl
- Position and stereochemistry of alkene

**(b) Implementation in this work: Wittig  $CO_2$  utilisation<sup>a</sup>**



**Scheme 3** Targeted synthetic strategy:  $CO_2$  utilisation in formation of  $C_\alpha$ - $CO_2$  and  $C=C$  bonds in one process.<sup>a</sup>  $R^3 = Ph$  or  $Me$ .

boxylic acids, thus far, this very direct means of formation of the  $C=C$  and  $C_\alpha$ - $CO_2$  bonds of  $\alpha,\beta$ -unsaturated carboxylic acids has not been exploited, despite the fact that carbanion equivalents of the general type represented in Scheme 3a can be generated from carboxylic acid precursors (which in some cases can be synthesised using  $CO_2$  in a separate step)<sup>65,66</sup> and have the capacity to undergo olefination reactions.<sup>65–69</sup> Furthermore, our attempts as part of this project to effect one-pot syntheses of  $\alpha,\beta$ -unsaturated carboxylic acids *via* a Wadsworth–Emmons-type  $CO_2$  utilisation approach (using phosphono carbanions) proved unsuccessful. However, we did find that a Wittig-type  $CO_2$  utilisation method could be employed to enable efficient, one-pot construction of  $\alpha,\beta$ -unsaturated carboxylic acids (Scheme 3b) with no requirement to isolate a carboxylic acid derivative of the ylide- $CO_2$  adduct.

Central to the new methodology are unique new species that we refer to as “phosphonium carboxylate ylides” (4). These entities are formed *in situ* in two steps – (i) reaction of a non-stabilised phosphonium ylide with  $CO_2$  to form a zwitterionic intermediate (compound 3 in Scheme 3), and (ii) deprotonation of the zwitterionic ylide- $CO_2$  adduct. While the capacity of phosphonium ylides (2) to react with  $CO_2$  is known,<sup>70–74</sup> only a limited number of examples exploiting the



potential for application of this in CO<sub>2</sub> utilisation strategies have been reported. Deprotonation of the zwitterionic ylide-CO<sub>2</sub> adducts affords reactive entities that open up the potential for widespread exploitation of ylide-CO<sub>2</sub> reactions in CO<sub>2</sub> utilisation applications, *i.e.*, for incorporation of CO<sub>2</sub> into the structures of high value products. As will be shown below, we found that phosphonium carboxylate ylides undergo Wittig reactions with carbonyl compounds, thus affording a very direct means of access to  $\alpha,\beta$ -unsaturated carboxylic acids using CO<sub>2</sub> as a starting material. Astonishingly, despite the ubiquity of the Wittig reaction in C=C bond construction,<sup>44–53</sup> this represents the first general method for direct formation of  $\alpha,\beta$ -unsaturated carboxylic acids using Wittig reactions.<sup>75</sup>

## Results and discussion

In this project, we have found that if the reaction of phosphonium ylide with CO<sub>2</sub> is carried out in the presence of excess base, the initial zwitterionic adduct formed (formation of **3** from ylide **2** in Scheme 3b) is immediately deprotonated to form a previously unreported entity (phosphonium carboxylate ylide **4**) that is comparatively resistant to decarboxylation.<sup>76,77</sup> This can be used *in situ* to effect Wittig-type reactions with a wide variety of structurally diverse aldehydes to produce, initially,  $\alpha,\beta$ -unsaturated carboxylate salts (**5**; see Scheme 3b). These can subsequently be protonated to furnish the corresponding carboxylic acids (see further details below). The  $\alpha,\beta$ -unsaturated carboxylate salts formed in these reactions (prior to treatment with acid) can be isolated (see details of this in the ESI†).‡ The establishment of these entities as the initial products of these reactions supports the operation of the mechanism shown in Scheme 3b.

The ylide-CO<sub>2</sub> combination step occurs readily at room temperature over 1–2 hours,§ requiring CO<sub>2</sub> pressure at only atmospheric pressure levels, while the subsequent Wittig-type reaction requires heating to between 80 and 105 °C for 24–48 hours, depending on the electrophilicity of the carbonyl group involved.‡ The process occurs efficiently in both toluene and THF,‡ but toluene is preferable for reactions of less electrophilic aldehydes since it allows higher reaction temperatures to be employed (see details below).

Although the acidity of the  $\alpha$ -proton of zwitterionic species **3** makes it likely that the second deprotonation step (*i.e.*, formation of **4** from **3**) requires only a relatively weak base in principle, in practice it is necessary that the pK<sub>a</sub> of the base employed is higher than the pK<sub>aH</sub> of the starting ylide (*e.g.*, **2a** – see structure in Fig. 1 above), as otherwise the starting ylide may undergo protonation (forming phosphonium salt, *e.g.*, **1a**) in competition with CO<sub>2</sub> activation. Thus, a second equivalent of base of pK<sub>a</sub> higher than the pK<sub>aH</sub> of the starting ylide is

required. We investigated the efficacy of various bases in Wittig CO<sub>2</sub> utilisation reactions, and found that use of KHMDS led to the highest yields of  $\alpha,\beta$ -unsaturated carboxylic acid products.‡ In practice, to achieve the highest possible yields, we observed that it was necessary to employ 2.9 to 3.5 equivalents of KHMDS in total to effect the two deprotonation steps, in part due to batch-to-batch variability in commercial solutions of KHMDS or solutions we generated ourselves using solid KHMDS.<sup>78‡</sup> We also observed that the identity of the acid used in the work-up to protonate the initial  $\alpha,\beta$ -unsaturated carboxylate salt products has a significant bearing on the outcomes of these reactions, with use of MsOH and (+)-CSA leading to the highest yields.<sup>79</sup>

With effective reaction conditions in hand from our optimisation studies, we set about employing the methodology for the synthesis of a range of cinnamic acids and analogues thereof using a variety of different aromatic aldehydes (see Fig. 1). The *E/Z* ratios of the products were determined using the integrations of characteristic signals of the *E*- and *Z*-isomers in the <sup>1</sup>H NMR spectra of the products, and are indicated in brackets, where applicable, for products in Fig. 1 and other figures below. In several instances, only signals of the *E*-isomer could be detected in the <sup>1</sup>H NMR spectrum of the product. For these, we can conclude that the *Z*-isomer constitutes no more than 2% of the product.

In Wittig CO<sub>2</sub> utilisation reactions of ylide **2a** (generated by the reaction of **1a** + KHMDS; see Fig. 1) with electron withdrawing group-substituted benzaldehydes at 80 °C, yields of 67–97% of cinnamic acids **6–18** were obtained.¶ The benzaldehydes in this selection include *para*-, *meta*- and *ortho*-substituted examples, and functional groups such as aryl halides, aryl nitriles, esters, ethers, and nitro groups are shown to be tolerant to the reaction conditions. It is noteworthy that were the carboxylic acids synthesised in this project to be accessed using ester-stabilized ylides followed by ester hydrolysis, the nitrile or ester-substituents on products **8** or **13** would be likely to hydrolyse. Wittig CO<sub>2</sub> utilisation reactions of ylide **2a** with benzaldehyde itself (giving product **19**), with benzaldehydes bearing weak electron donating substituents (resulting in formation of products **20–23**, **28** and **29**), or with benzaldehydes bearing alkoxy or phenoxy substituents (giving products **24–27**) required higher temperatures and/or longer times for the Wittig reaction part of the process to result in good to excellent yields (68–93%).||,\*\* Higher temperatures (100 °C) and longer reaction times were also required to produce good

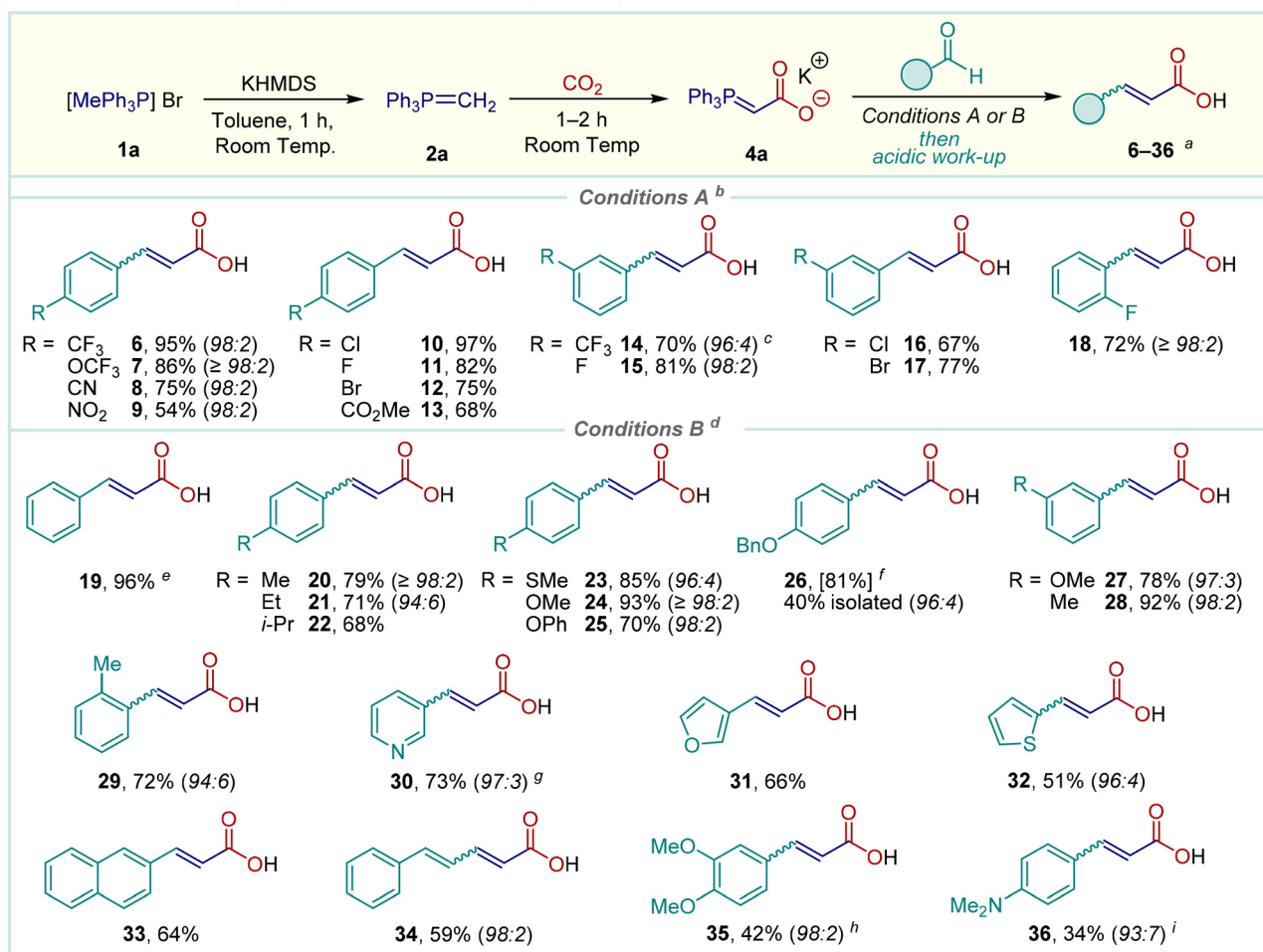
¶The *E*-isomer of each of *p*-cyanocinnamic acid (product **8**) and *p*-nitrocinnamic acid (product **9**) was observed to undergo dimerisation (forming 4-membered carbocyclic ring-containing derivatives of “ $\beta$ -truxinic acid”) upon exposure to light. By taking great care to protect the reactions and purifications involving these compounds from light, it was possible to isolate products **8** and **9** in yields of 75% and 54%, respectively. See ESI Section 8† – Substrate scope of  $\alpha,\beta$ -unsaturated carboxylic acids, (3-(4-nitrophenyl)acrylic acid and 4-nitro- $\beta$ -truxinic acid dimer).

||The importance of temperature in these reactions is illustrated by reactions of *m*-tolualdehyde (to give *m*-methylcinnamic acid, product **28**): At 80 °C, this reaction gave **28** in a yield of only 29% after 70 hours of stirring, while if the reaction

‡See ESI Section 6.† Optimisation of reaction conditions & mechanistic experiments.

§See ESI Section 4.† General set-up for CO<sub>2</sub> addition during Wittig CO<sub>2</sub> utilisation reactions.





**Fig. 1**  $\alpha,\beta$ -Unsaturated carboxylic acids synthesized using methyltriphenylphosphonium bromide (**1a**).<sup>a</sup> Isolated yields after chromatography are shown. The *E* : *Z* ratios of alkenes are shown in parentheses, where appropriate. These were determined using the relative integrations of characteristic signals of the isomers in the <sup>1</sup>H NMR spectra of the products. In the instances that no ratio is shown, only signals of the *E*-isomer could be detected in the <sup>1</sup>H NMR spectrum of the product. <sup>b</sup> Conditions A: Wittig step: 20–24 hours, at 80 °C. <sup>c</sup> Chromatography-free isolation (acid/base workup only). <sup>d</sup> Conditions B: Wittig step: 48–50 hours, 100 °C. <sup>e</sup> Wittig step: 48 hours, 80 °C. <sup>f</sup> <sup>1</sup>H NMR spectral yield shown in square brackets (established by reference to integrations of signals of internal standard 1,3,5-trimethoxybenzene); difficulties during purification led to lower yields upon isolation of the product. <sup>g</sup> Wittig step: 45 hours, 80 °C. <sup>h</sup> Wittig step: 60 hours, 100 °C. <sup>i</sup> Wittig step: 68 hours, 110 °C.

yields of  $\alpha,\beta$ -unsaturated carboxylic acids **30–32** in Wittig CO<sub>2</sub> utilisation reactions of heteroaryl aldehydes and in the corresponding reactions of 2-naphthaldehyde (giving product **33**) and *E*-cinnamaldehyde (giving product **34**).

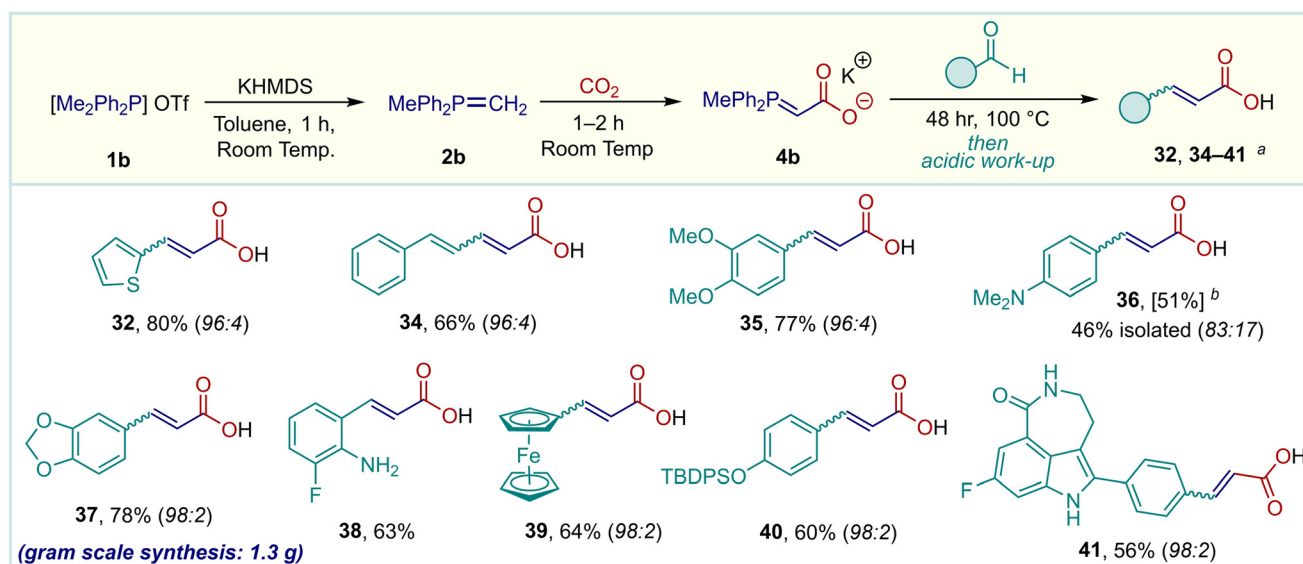
For reactions of very electron-rich benzaldehydes (bearing 3,4-dimethoxy or *p*-dimethylamino substituents, leading to products **35** and **36**, respectively) relatively low yields of 42%

(of **35**) and 34% (of **36**), respectively, were obtained. Since these yields were likely to be due to the relatively low electrophilicity of the carbonyl groups of the aldehydes involved, we reasoned that by employing phosphonium ylides (and hence carboxylate ylides) of higher nucleophilicity, higher yields might be achievable in these challenging reactions. Previous literature reports on Wittig reactions have demonstrated that modifying Ph<sub>3</sub>P-derived ylides by replacing one *P*-phenyl group with a *P*-alkyl group (while maintaining the other features of the ylide in question) results in ylides of significantly higher nucleophilicity.<sup>45,50,73,80</sup> Prompted by these observations, syntheses of  $\alpha,\beta$ -unsaturated carboxylic acids **32** and **34–36** that had proved challenging using Ph<sub>3</sub>P-derived phosphonium salt **1a** as starting material (to produce ylide **2a**) were attempted using MePh<sub>2</sub>P-derived phosphonium salt **1b** instead, in the hope of exploiting the greater nucleophilicity of ylide **2b** and its derived carboxylate ylide, **4b** (see Fig. 2 for

temperature was increased to 100 °C (for 48 hours), a yield of 92% of **26** was obtained, as shown in Fig. 1.

\*\*A <sup>1</sup>H NMR spectral yield of 81% was observed for the reaction producing compound **26**, showing that the synthetic method enables efficient formation of this product. However, significant difficulties arose during purification of compound **26** by column chromatography (including in instances in which it was synthesised using a second method) that resulted in a relatively low isolated yield for this compound. Similar difficulties also arose in the chromatographic purification of compound **36**. For further details, see Section 8 of the ESI† – Substrate scope of  $\alpha,\beta$ -unsaturated carboxylic acids.

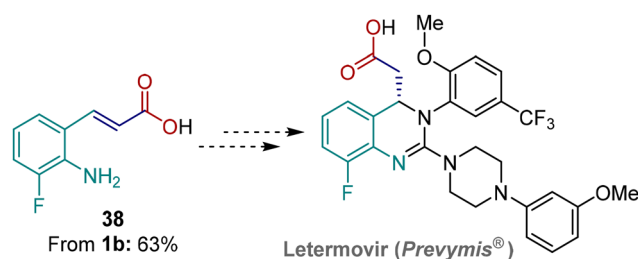




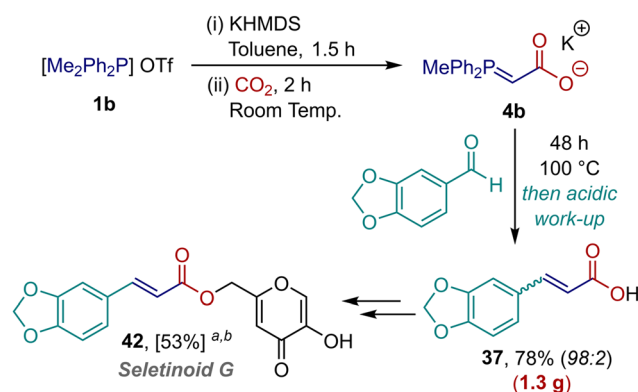
**Fig. 2**  $\alpha,\beta$ -Unsaturated carboxylic acids synthesized using dimethyldiphenylphosphonium triflate (**1b**).<sup>a</sup> Isolated yields after chromatography are shown. The  $E:Z$  ratios of alkenes are shown in parentheses, where appropriate. These were determined using the relative integrations of characteristic signals of the isomers in the  $^1\text{H}$  NMR spectra of the products. In the instances that no ratio is shown, only signals of the  $E$ -isomer could be detected in the  $^1\text{H}$  NMR spectrum of the product. <sup>b</sup> NMR spectral yield shown in square brackets (established by reference to integrations of signals of internal standard 1,3,5-trimethoxybenzene); difficulties during purification led to lower yields upon isolation of the product.

structures). Gratifyingly, we found that use of **1b** as starting material enabled us to increase the yields of products **32** and **34–36** (**32**, from 51% to 80%; **34**, from 59% to 66%; **35**, from 42% to 77%; **36**, from 34% to 51% (46% isolated));\*\* see Fig. 2). With a means in hand of improving yields in reactions involving aldehydes of relatively low electrophilicity, we then undertook Wittig  $\text{CO}_2$  utilisation reactions of a variety of other relatively unreactive aromatic aldehydes (bearing electron donating substituents on the aryl group) using **1b** as the starting phosphonium salt. This enabled us to access  $\alpha,\beta$ -unsaturated carboxylic acids **37–41** (see Fig. 2) in isolated yields of 78%, 63%, 64%, 60%, and 56%, respectively. Use of ylides with  $\alpha$ -substitution (e.g.,  $\text{Ph}_3\text{P}=\text{CHMe}$ ) in Wittig  $\text{CO}_2$  utilisation reactions does lead to formation of  $\alpha,\beta$ -unsaturated carboxylic acid products, but only in relatively low yields. We surmise that this is a consequence of steric hindrance in the derived phosphonium carboxylate ylide, as Wittig reactions of analogous  $\alpha,\alpha$ -disubstituted ester-stabilised ylides are notoriously low yielding.<sup>45</sup> Work is ongoing in our research group to develop Wittig  $\text{CO}_2$  utilisation processes to enable access to  $\alpha,\beta$ -unsaturated carboxylic acids containing trisubstituted alkenes.

Several of the products synthesised in this project are important precursors employed in the industrial synthetic procedures used to access pharmaceutical compounds. For example, compound **38** is a precursor for letermovir (see Fig. 2 and Scheme 4),<sup>31,81</sup> a drug for treatment of T-cell lymphoma, while compounds **30**, **31**, **35** and **37** (see Fig. 1 and 2) are, respectively, precursors to chidamide,<sup>82</sup> nalfurafine,<sup>83</sup> istradefylline,<sup>84</sup> and Seletinoid G (**42**; Scheme 5). Compound **37** was



**Scheme 4** Example of an  $\alpha,\beta$ -unsaturated carboxylic acid-containing precursor to a pharmaceutical agent (Letermovir) synthesized in this work.



**Scheme 5** Gram-scale synthesis of piperonyl acrylic acid (**37**) and use to produce Seletinoid G (**42**).<sup>a</sup> See Section 8 of the SI for details of the synthetic process used for the transformation of **37** to **42**. <sup>b</sup> $^1\text{H}$  NMR spectral conversion.



synthesised on gram scale and was subsequently used to form Seletinoid G (**42**) in an NMR spectral yield of 53% (Scheme 5).<sup>85,86</sup> In addition, polyfunctional compound **41** (Fig. 2) is an analogue of anti-cancer compound rucaparib.<sup>87</sup> Thus, the methodology reported herein provides a means of utilising CO<sub>2</sub> for the synthesis of pharmaceutical compounds that can be derived from  $\alpha,\beta$ -unsaturated carboxylic acids, and has great potential utility for access to pharmaceutical compounds and their precursors on scale.

The Wittig CO<sub>2</sub> utilisation reactions of **4a** (Fig. 1) and **4b** (Fig. 2) are all completely regioselective and result in exclusive or almost exclusive formation of *E*- $\alpha,\beta$ -unsaturated carboxylic acids. Since Wittig reactions of stabilised phosphonium ylides generally exhibit very high *E*-selectivity (in particular Ph<sub>3</sub>P-derived stabilised ylides),<sup>45,49,50</sup> it is likely that *E*-alkene formation is also kinetically favoured in the Wittig CO<sub>2</sub> utilisation reactions described above. High *E*-selectivity in reactions of this type is consistent with the rationale proposed by Aggarwal, Harvey and co-workers for selectivity in Wittig reactions of stabilised ylides,<sup>49</sup> with stereoselectivity being dictated in formation of the transition state of the [2 + 2] cycloaddition leading to the oxaphosphetane intermediate. In this instance, kinetically favoured formation of the *trans*-oxaphosphetane

(*via* the transition state represented in Fig. 3a) should lead to preferential formation of *E*-alkene. However, we did also observe isomerisation of a *Z*-cinnamic acid (*Z*-**27**) under our reaction conditions when it was deliberately added into the reaction of ylide **2a** + CO<sub>2</sub> + *p*-(trifluoromethyl)benzaldehyde (Scheme 6). Thus, augmentation of the amount of *E*-isomer present (at the expense of the *Z*-alkene) may also contribute to the observed high *E*-selectivity of Wittig CO<sub>2</sub> utilisation reactions.

## Conclusion

We have designed a new retrosynthetic strategy which led to the development of an efficient and straightforward route to  $\alpha,\beta$ -unsaturated carboxylic acids. A novel Wittig-type reaction involving CO<sub>2</sub> activation by phosphonium ylides was utilised to generate a wide scope of  $\alpha,\beta$ -unsaturated carboxylic acids, in good yields and high levels of *E*-selectivity. This method allows the installation of both the carboxyl group and the C=C bond of an  $\alpha,\beta$ -unsaturated carboxylic acid to be realised with perfect regioselectivity, thereby addressing a problem that has proved challenging in many existing alkene and alkyne carboxylation methods. This approach thus enables utilisation of CO<sub>2</sub> while exploiting the unique advantages of the Wittig reaction, and for the first time facilitates the creation of *three* new carbon-carbon bonds (the C=C  $\sigma$ - and  $\pi$ -bonds and the C <sub>$\alpha$</sub> -CO<sub>2</sub> bond) in a single, one-pot process (see Scheme 1b above). The methodology was shown to be applicable in the synthesis of pharmaceutically-relevant compounds and for challenging substrates, while improved yields can be achieved through use of more reactive alkyldiphenylphosphine-derived carboxylate ylides.

## Author contributions

Conceptualisation, P. A. B.; methodology, P. A. B. and G. P. M.; investigation, A. L., R. E. L., and P. A. B.; formal analysis, A. L., R. E. L., and P. A. B.; writing – original draft, P. A. B. and A. L.; writing – review & editing, P. A. B., G. P. M., A. L. and R. E. L.; funding acquisition, P. A. B., G. P. M., A. L. and R. E. L.; resources, P. A. B. and G. P. M.; supervision, P. A. B. and G. P. M.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The data supporting this article (synthetic details, experimental methods, and characterisation data (including copies of NMR spectra)) have been included as part of the ESI.†

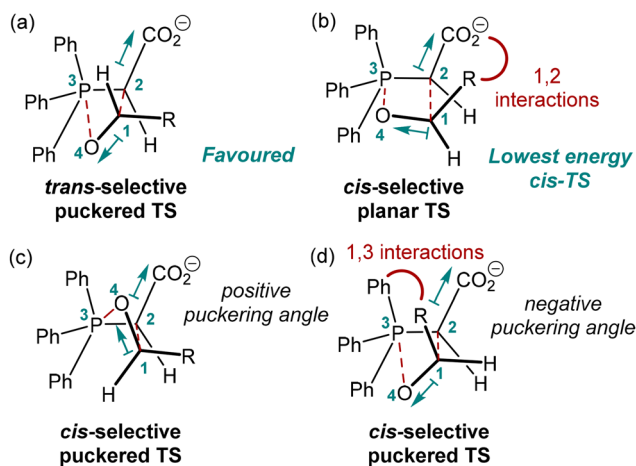
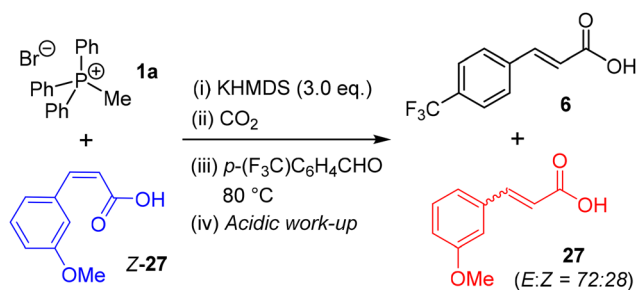


Fig. 3 Possible transition states (TSs) for the Wittig reaction of phosphonium carboxylate ylide **4a** with an aldehyde, RCHO.<sup>49</sup>



Scheme 6 Experiment demonstrating isomerisation of *Z*-**27** when subjected to our standard reaction conditions and work-up procedure.



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