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Purification of α,β-Unsaturated Carboxylic Acids as Their Potassium Carboxylate Salts Using Dry Column Vacuum Chromatography

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ABSTRACT

Carboxylic acids are ubiquitous functional groups and are used widely in the bulk chemistry and fine pharmaceutical industries. During the development of novel methodology for the synthesis of α,β-unsaturated carboxylic acids, it was found that established methods for the purification of the product carboxylic acids led to unsatisfactory outcomes. However, chromatographic purification of the products of these reactions as their potassium carboxylate salts proved highly successful. Unlike their parent carboxylic acids, the carboxylate salts could be separated readily from the other constituents of the reaction mixture using dry column vacuum chromatography (DCVC). The yields of the carboxylic acid products obtained by subsequent protonation of the carboxylate salts were found to depend strongly on the identity of the acid used to effect the protonation, with methanesulfonic acid and (+)-camphorsulfonic acid resulting in the highest recoveries of pure products. The combined DCVC and acidification protocols developed were shown to be effective for the purification of numerous functionalised α,β-unsaturated carboxylic acids.

1 | Introduction

Carboxylic acids are an important class of chemicals, spanning applications from use as bulk starting materials to advanced medicines. For example, salicylic acid is an active ingredient in pharmaceuticals [1] and acrylic acid, an α,β-unsaturated carboxylic acid, is a large-scale commodity chemical [2]. Acrylic acid and its ester derivatives are manufactured on a multimillion-tonne level [2, 3], and these entities are essential building blocks in the production of polyacrylates, which are used in a broad array of applications [4–6]. There exist many ways in which one can synthesise the carboxyl motif, and there are various options for the purification of carboxylic acids. Column chromatography is used extensively to purify carboxylic acids in academic research applications [7–10]. Due to the acidity of carboxylic acids, suitably designed aqueous work-ups can also afford pure carboxylic acids [11, 12]. Furthermore, many carboxylic acids are solids and can therefore be purified by recrystallisation or trituration [13–17].

Recent work in our research group has focused on the development of a novel method for the synthesis of α,β-unsaturated carboxylic acids through Wittig-type reactions involving CO_2 incorporation into the alkene product as part of the process (see further details below). α,β-Unsaturated carboxylic acids are a particularly important class of carboxylic acids—for example, they are ubiquitous in natural products and pharmaceuticals (see examples in Figure 1), and indeed, of the new pharmaceuticals approved since 2015 (up to 2022, the most recent year for which data is available), 38 contain an α,β-unsaturated carboxylic acid or ester derivative in their final structure (see examples in Figure 1) [18, 19] or in a synthetic intermediate leading to these compounds, constituting 14% of all newly approved pharmaceuticals from this period [1, 18–25]. During our

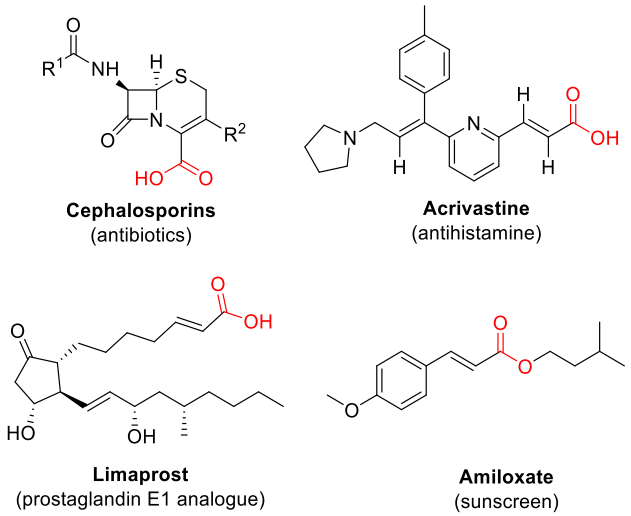


FIGURE 1 | Examples of biologically and medicinally important α,β-unsaturated carboxylic acids and enoates.

development of this synthetic methodology, we found that known methods for the purification of carboxylic acids were either ineffective (i.e., failed to yield pure product) or resulted in low yields of our desired α,β-unsaturated carboxylic acid products. Consequently, borne out of necessity, we were obliged to develop a new means of the purification of α,β-unsaturated carboxylic acids that enabled the isolation of these compounds both in high yield and high purity. Since purification of carboxylic acids can frequently prove to be troublesome, the purification procedure developed during this project is likely to be of general utility in a broader sense in any applications in which carboxylic acid purification is necessary.

2 | Results and Discussion

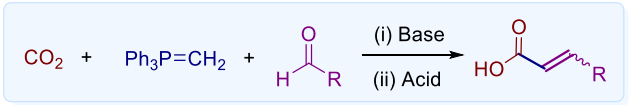
In our recently reported method for the direct synthesis of α,β-unsaturated carboxylic acids, both the C═C double bond and the C—C bond are formed in a one pot process (Scheme 1) [26]. The method involves utilisation of CO_2 as a one-carbon building block, undergoing fixation by a phosphonium ylide, allowing for a Wittig reaction between the in situ generated phosphonium 'carboxylate ylide' and a variety of aldehydes.

At the end of each of our Wittig-type reactions, excluding solvent, the reaction mixture contained the α,β-unsaturated carboxylic acid product, the phosphine oxide by-product of the reaction, residual unreacted aldehyde (in some cases), residual unreacted phosphonium salt starting material (phosphonium ylide precursor; in some cases), the conjugate acid of the base used to generate the ylide (hexamethyldisilamine, derived from KHMDS base), and a potassium salt (KBr or KOTf) derived from the counterions of the base (K^+) and the phosphonium salt (Br^- from [$MePh_3P$]Br, TfO^- from [Me_2Ph_2P]OTf) (see Scheme 2). In addition, hydrolysis and oxidation of the non-stabilised phosphonium ylides that are generated as key reactive entities in these Wittig reactions can also lead to formation of phosphine oxides as side-products [27, 28]. For reactions of Ph_3P-derived non-stabilised ylides, ylide oxidation leads to formation of Ph_3PO (i.e., the by-product that would be formed in the event of the occurrence of the desired Wittig reaction), while ylide hydrolysis leads to the formation of alkyldiphenylphosphine oxide as a side-product. A final potential constituent that can in principle be found in the final reaction mixture is the alkene product of a 'standard' Wittig reaction (i.e., the Wittig reaction that would occur between the ylide and aldehyde concerned if CO_2 were not introduced into the reaction mixture).

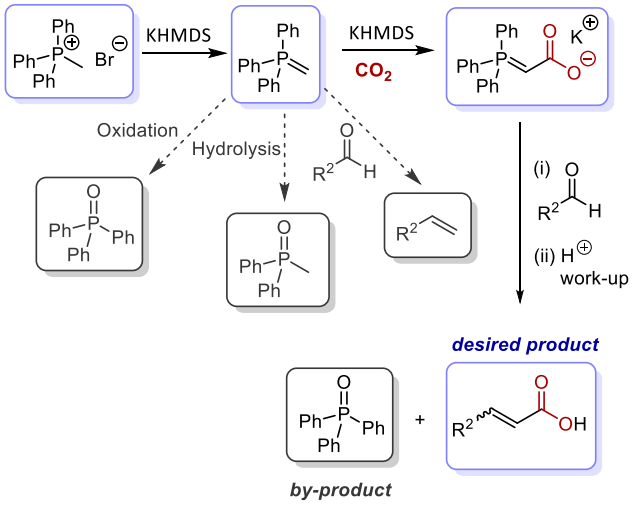
Although at the outset of our work numerous options already existed that should, in principle, enable isolation of α,β-unsaturated carboxylic acids from such reaction mixtures [7–17], in practice, we found that when we applied these methods, either the isolated yields of pure products were compromised (for reactions that we had established through NMR spectral yield studies were operating with essentially quantitative product formation), or else the purification methods were not effective in ensuring the complete removal of the undesired materials from our products. In particular, the phosphine oxide by-product of the reactions proved to be especially persistent and difficult to separate from our carboxylic acid products.

In order to find a suitable method for the separation of our carboxylic acid products from phosphine oxide by-products, we conducted a series of purification tests using a 1:1 mixture of cinnamic acid and Ph_3PO (to emulate the reaction mixture at the end of the Wittig CO_2 utilisation reaction). We did not investigate the efficacy of our previously reported phosphine oxide removal technique based on the treatment of the phosphine oxide-containing material with oxalyl chloride (followed by filtration) [29] due to the propensity of carboxylic acids to form acyl chlorides under these conditions.

Several methods have been reported in the chemical literature that involve the removal of Ph_3PO from crude products of reactions by precipitation using metal halide salts —namely $MgCl_2$



SCHEME 1 | Wittig CO_2 utilisation methodology for the synthesis of α,β-unsaturated carboxylic acids.



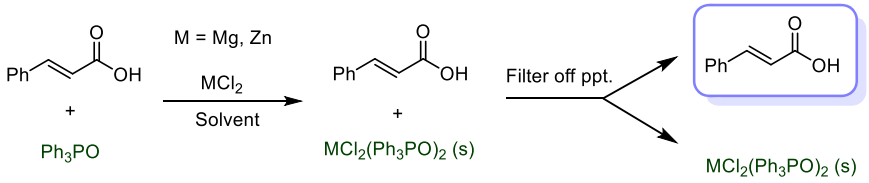
SCHEME 2 | Outline of potential products from the Wittig CO_2 utilisation reactions of methyltriphenylphosphonium bromide.

[30, 31], $ZnCl_2$ [32], or $CaBr_2$ [33]. To test these purification methods for our purposes, 1:1 mixtures of cinnamic acid and Ph_3PO were mixed across several experiments with different numbers of equivalents of metal halide salts in different solvents and stirred for a certain period (see details for each experiment in Table 1) to allow formation and precipitation of the desired insoluble Ph_3PO-metal halide complex. The resulting mixtures were then filtered to remove the precipitated Ph_3PO-metal halide complex, and the filtered material was then washed with more of the solvent used for the experiment to ensure maximal recovery of cinnamic acid. The amounts of cinnamic acid recovered and of Ph_3PO remaining at the end of each of these experiments (assessed by comparison of the integrations of the characteristic NMR signals of the compounds in question against the integrations of the signals of 1,3,5-trimethoxybenzene as an internal standard in the ^1H NMR spectrum of the filtered material after solvent removal) are shown in Table 1. While good cinnamic acid recovery was achieved in each of the experiments described in Table 1 entries 1–5, in all cases a significant quantity of phosphine oxide remained mixed in with the cinnamic acid. It was possible to exclude most of the phosphine oxide by using toluene as the solvent for the $ZnCl_2$ treatment method (Table 1, entry 6), but this came at the expense of cinnamic acid recovery.

An alternative approach to the separation of carboxylic acid from phosphine oxide that was investigated involved the utilisation of a biphasic organic/aqueous work-up under basic conditions. Under these conditions, the carboxylic acid would be deprotonated, hence existing as a carboxylate salt, and thus would exist predominantly in the aqueous phase, while the phosphine oxide remained in the organic phase. Since the initial products of our Wittig-type reactions were carboxylate salts, we endeavoured in our first experiments to emulate the reaction mixtures as they would exist at the end of the reactions by treating a 1:1 mixture of cinnamic acid and Ph_3PO in anhydrous toluene with KHMDS to generate an insoluble potassium cinnamate salt. Filtration of the salt followed by acidification led to incomplete recovery of the cinnamic acid (*ca.* 67%), with a small amount (6%–10%) of Ph_3PO contaminant remaining [34]. Another closely related approach involved the treatment of solutions of cinnamic acid and phosphine oxides (in a 1:1 ratio) in organic solvents with aqueous $NaHCO_3$ or K_2CO_3 solutions to generate biphasic mixtures in which the carboxylate salt is in the aqueous phase and the phosphine oxide is in the organic phase, and hence the two compounds should be readily separable from each other. In contrast to the related method discussed above in this paragraph, this approach did result in good recoveries of the cinnamic acid after acidification and extraction of the aqueous phase (see Table 2). However, although this approach did result in exclusion of most of the phosphine oxide by-product from the aqueous phase in all examples tried, nonetheless, small amounts of phosphine oxide contaminant did remain in the recovered cinnamic acid. Application of the $NaHCO_3$-based work-up procedure to the crude product formed in the synthesis of *p*-(trifluoromethyl)cinnamic acid using our Wittig-type methodology did enable good recovery of the carboxylic acid product (*ca.* 96%), but as above, it was contaminated with a small quantity of phosphine oxide. One cinnamic acid synthesised using our Wittig-type methodology (*m*-(trifluoromethyl)cinnamic acid) was successfully isolated (pure) in a yield of 70% using a basic aqueous work-up (using aqueous NaOH solution) followed by acidification of the isolated aqueous phase(s) [26].

With the exception of the last example mentioned above, the approaches described above each resulted in samples of carboxylic acid that were contaminated to some extent with phosphine oxide. While pure samples of the carboxylic acids could be obtained by subjecting the contaminated samples to recrystallisation, this resulted in a significant loss of yield [34]. Hence, to obtain phosphine oxide-free samples of our desired carboxylic acids in high yields, it became clear that having a method for chromatographic purification of the products of our reactions would be highly advantageous.

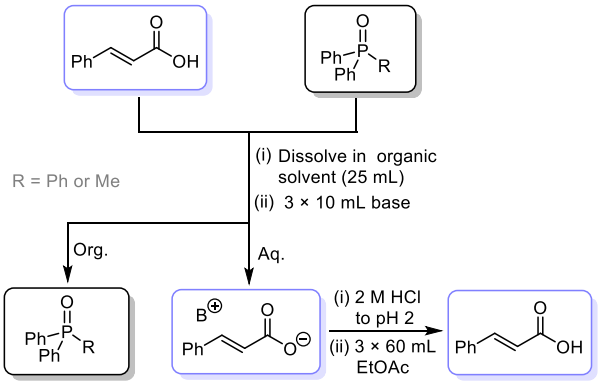
TABLE 1 | Results of experiments investigating separation of cinnamic acid and Ph_3PO using precipitation and filtration of a phosphine oxide-metal halide complex.



# [a]	Metal salt	Equiv. of metal salt	Solvent	Temp., °C	Stirring time, h	Product recovery, % [b]	Ph_3PO remaining, % [b]
1	$MgCl_2$	1	Toluene	60	2	84	50
2	$MgCl_2$	2	Toluene	60	2	89	51
3	$ZnCl_2$	2	EtOAc	22	18	92	10
4	$ZnCl_2$	3	EtOAc	22	18	94	19
5	$ZnCl_2$	2	EtOH	22	18	99	22
6	$ZnCl_2$	2	Toluene	22	18	73	2

[a]1:1 molar ratio of cinnamic acid and Ph_3PO used. Cannula filtration used for the filtration procedure. Concentration of cinnamic acid in $MgCl_2$ tests was 0.50 mol L^{-1}; concentration of cinnamic acid in $ZnCl_2$ tests was 0.37 mol L^{-1}.
[b]Percentages determined from integrations of signals in the ^1H NMR spectrum with 1,3,5-trimethoxybenzene as internal standard. This was added to the whole sample after filtration and concentration of the mixture, followed by dissolving the whole sample in DMSO-d_6.

TABLE 2 | Removal of phosphine oxide by-products from cinnamic acid by acid/base work-up.



#[a]	R	Base	Solvent	% Recovery	
				Cinnamic acid	RPh_2PO
1	Ph	Sat. $NaHCO_3$	Et_2O	95	99
2	Ph	Sat. K_2CO_3	Et_2O	87	94
3	Me	Sat. $NaHCO_3$	Et_2O	— [b]	— [b]
4	Me	Sat. $NaHCO_3$	CH_2Cl_2	87	89

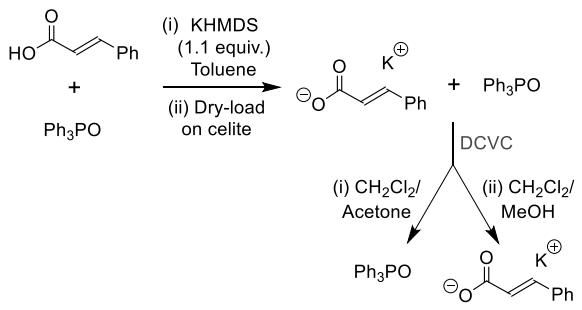
[a]1:1 ratio of cinnamic acid and phosphine oxide used.
[b]Full separation of the phosphine oxide and cinnamic acid was not achieved due to the phosphine oxide being partially soluble in Et_2O.

However, we found that the separation of α,β-unsaturated carboxylic acids from Ph_3PO by column chromatography was very challenging, as these compounds typically showed very similar elution characteristics under all conditions investigated, resulting in substantial co-elution of the compounds from columns, and hence low yields of the desired α,β-unsaturated carboxylic acid products. Thus, we were prompted to try an alternative chromatographic separation approach involving carboxylic acids in their carboxylate form (i.e., as the conjugate base of the acid) in order to engender greater differences between the elution characteristics of the two species. Furthermore, rather than focusing on standard flash column chromatography, we decided instead to pursue a chromatographic separation approach based around the method of dry column vacuum chromatography (DCVC) optimised and popularised by Pedersen and Rosenbohm [35, 36]. However, as will be shown below, use of DCVC to achieve separation of carboxylate salt from Ph_3PO is not essential; this can also be achieved readily using standard flash column chromatography.

DCVC involves the use of finer-grained silica than is typically used for flash column chromatography, and the silica bed is pressed/compacted prior to solvent addition [35, 36]. As per the procedure described by Pedersen and Rosenbohm [35–37], we typically employed a sintered glass funnel of 3 or 4 cm internal diameter and 10 cm height (above the sintered glass frit), with the silica bed packed to a height of 5 cm above the frit, although wider columns can be employed for purification of larger amounts of material. When using DCVC, samples to be purified are dry-loaded (using Celite) onto the silica column. Fractions of elution solvent are then added to the space above the silica column, and the solvent is pulled through the column under a relatively low vacuum (e.g., using a variable pressure diaphragm pump), eluting into a separating funnel (the outlet of which is closed). This can be emptied into a test tube after disengaging the vacuum after each fraction is eluted. Thus, in contrast to standard column chromatography, the silica bed is deliberately caused to run dry after each fraction. We typically employed solvent fractions of approximately 20 mL volume. As per the procedure of Pedersen and Rosenbohm [35, 36], a solvent gradient was employed over successive elution fractions (see further details below). The DCVC method is attractive because it can often be executed quickly, requires less silica and solvent use than standard flash column chromatography, and is much better suited to scale-up than standard flash column chromatography [35].

To test the effectiveness of the DCVC approach for the separation of α,β-unsaturated carboxylic acids from Ph_3PO, we again conducted tests using 1:1 mixtures of cinnamic acid and Ph_3PO. In each experiment, such a mixture was dissolved in toluene and then treated with KHMDS to generate potassium cinnamate salt (mixed with an equimolar amount of Ph_3PO and hexamethyldisilamine ($(Me_3Si)_2NH$). The resulting mixture was then dry-loaded on to celite for loading onto the top of a DCVC column. Our TLC tests indicated that mixtures of CH_2Cl_2 and MeOH could effect the elution of potassium cinnamate. When gradient elution of a 1:1 mixture of potassium cinnamate and Ph_3PO was carried out using CH_2Cl_2 and MeOH (i.e., starting with 100% CH_2Cl_2 in fraction 1, moving to 95:5 CH_2Cl_2/MeOH for fraction 2, and increasing the percentage of MeOH in each successive fraction by 5%), recovery of pure potassium cinnamate occurred quite effectively (76% of pure compound recovered; Table 3 entry 1). The potassium cinnamate that was not isolated in pure form had co-eluted with Ph_3PO. A slightly increased recovery of potassium cinnamate of 79% was achieved using CH_2Cl_2/MeOH solvent mixtures if the percentage of MeOH was increased by only 2.5% in each successive fraction instead of 5% (Table 3 entry 2), but again, substantial co-elution of potassium cinnamate and Ph_3PO occurred. Through testing of a variety of other elution solvent mixtures (TLC tests), we

TABLE 3 | Removal of Ph_3PO from cinnamic acid by DCVC.



#[a]	Solvent mixture	Solvent gradient[b]	% Recovery[c]
1	CH_2Cl_2/MeOH	5%	76
2	CH_2Cl_2/MeOH	2.5%	79
3	CH_2Cl_2/Me_2CO followed by CH_2Cl_2/MeOH	5% (CH_2Cl_2/Me_2CO) followed by 5% (CH_2Cl_2/MeOH)	99

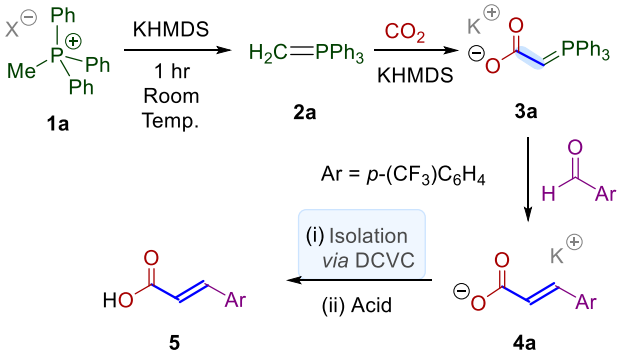
[a]1:1 ratio of cinnamic acid and Ph_3PO used.
[b]A 5% solvent gradient refers to increasing the percentage of the more polar solvent (acetone or methanol) by 5% for each fraction of solvent eluent prepared.
[c]Recovery of cinnamic acid.

observed that mixtures of CH_2Cl_2 and acetone resulted in the elution of Ph_3PO but did not cause any movement of potassium cinnamate from the baseline of a silica TLC plate.

Thus, subjecting a 1:1 mixture of potassium cinnamate and Ph_3PO to DCVC using CH_2Cl_2/acetone (increasing the percentage of acetone by 5% in each successive fraction) caused selective and complete elution of Ph_3PO. Once elution of the Ph_3PO was complete, the solvent could immediately be changed to CH_2Cl_2/MeOH (changing solvent systems in DCVC is trivial since the column is eluted to dryness after each fraction) to effect elution of the potassium cinnamate, and hence the latter could be isolated in pure form and with essentially complete recovery (Table 3 entry 3). Since our optimised purification process furnished potassium carboxylate salt, it remained for us to verify that these salts could be protonated readily to yield the parent carboxylic acids without loss of material. Although superficially this process appears to be trivial, in practice, we observed that there is a very large variability in the yield of α,β-unsaturated carboxylic acid, which depends strongly on the acid employed to protonate the potassium carboxylate salt.

To determine the optimal acid to use for carboxylate salt protonation, the Wittig CO_2 utilisation reaction (to produce *p*-(trifluoromethyl)cinnamic acid) shown in the scheme associated with Table 4 was used as our test reaction. In these experiments, different acids were used to acidify the reaction mixture, and the effectiveness of the acidification process for the production of cinnamic acid **5** from the initial potassium cinnamate salt product was determined through the establishment of the ^{1}H NMR spectral yield of the reaction. The ^{1}H NMR spectral yields of **5** determined from these experiments are shown in Table 4**.** The highest yield in our initial investigations using THF as the solvent was obtained in the experiment in which (+)camphorsulfonic acid was used to effect the acidification, giving an NMR spectal yield of 87% (Table 4, entry 6). When the reaction was subsequently

TABLE 4 | Selected optimisation data for the Wittig CO_2 utilisation reaction for the synthesis of 4-(trifluoromethyl)cinnamic acid.



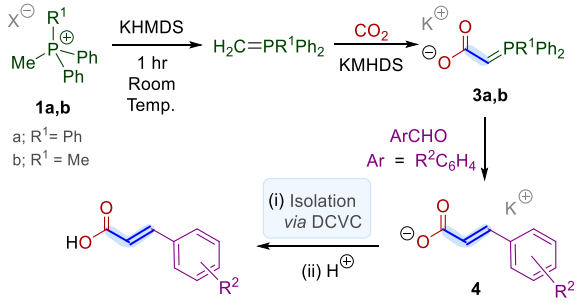
#[a]	Acid	Added solvent	Conc., mol L^{-1}[b]	*T*, °C[c]	% Yield
1	HCl	THF	0.1	50	51
2	HCl/ MeOH	THF	0.1	50	63
3	AcOH	THF	0.1	50	60
4	TfOH	THF	0.1	50	70
5	*p*-TsOH	THF	0.1	50	73
6	(+)-CSA	THF	0.1	50	87
7	(+)-CSA	Toluene	0.1	50	73[d]
8	(+)-CSA	Toluene	0.1	80	77[d]
9	(+)-CSA	Toluene	0.1	80	95[d,e]
10	(+)-CSA	Toluene	0.2	80	83[e,f]

[a]The constituents added for each reaction were: [$MePh_3P$]Br (1.0 equiv.), KHMDS (commercial solution in toluene; 3 equiv. unless otherwise indicated), CO_2 (atmospheric pressure), 4-(trifluoromethyl)benzaldehyde (1.0–1.1 equiv.), and additional solvent (THF or toluene; see Added Solvent' column for each entry). The duration of the Wittig reaction step was 22 h unless otherwise indicated. Unless otherwise indicated, yields were determined after acidic work-up, using ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.
[b]Concentration with respect to phosphonium ylide.
[c]Heating bath temperature for Wittig reaction step.
[d]20 h duration for the Wittig reaction step. Isolated yield determined after chromatography and acidic work-up.
[e]3.5 equiv. of KHMDS used. Isolated yield determined after chromatography and acidic work-up.
[f]8 h duration for the Wittig reaction step.

carried out using optimised reaction conditions (3.5 equivalents of KHMDS, with the Wittig step of the reaction being carried out in toluene at 80°C, and with a reaction time of 20 h), an isolated yield of 95% was obtained (Table 4, entry 9) [38]. Despite the effectiveness of (+)-CSA for the acidification of the product, it was observed that if an excess of (+)-CSA aqueous solution was used during the work-up, small amounts of (+)-CSA were present in the product due to it being an organic-soluble acid. Using only 1 equivalent of (+)-CSA circumvented this problem. Another alternative to this was to try a similar but more atom economical acid, methanesulfonic acid, which was found to give a comparable yield of the same product (92%) [39], with all other factors being otherwise identical.

With an optimised post-Wittig reaction purification process in hand, we set about applying our DCVC-based method for the

TABLE 5 | α,β-Unsaturated carboxylic acids (**5–29**) isolated as potassium carboxylate salts by DCVC (except where otherwise noted) followed by acidification.

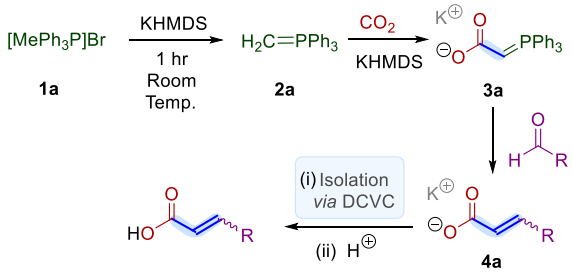


Entry	R^1	R^2	% of *E*-Isomer[a]	Yield, %[b]
1	Ph	H	>98[c]	96[d]
2	Ph	4-CF_3	98	95
3	Ph	4-Cl	>98[c]	97
4	Ph	4-Br	>98[c]	75
5	Ph	4-F	>98[c]	82
6	Ph	3-Cl	>98[c]	67
7	Ph	3-Br	>98[c]	77
8	Ph	3-F	98	81
9	Ph	2-F	>98	72
10	Ph	4-CN	98	75
11	Ph	4-NO_2	98	54
12	Ph	4-OCF_3	>98	86
13	Ph	4-Me	98	79[e]
14	Me	4-OMe	>98	93[e]
15	Ph	4-Et	94	71[e]
16	Ph	4-*i*-Pr	>98[c]	68[e]
17	Ph	4-SMe	96	85[d]
18	Ph	4-NMe_2	93	34[f]
19	Ph	4-OBn	96	40[e]
20	Ph	3-Me	98	92[e]
21	Ph	3-OMe	97	78[e]
22	Me	3,4-dimethoxy	96	77[e]
23	Ph	CO_2Me	>98[c]	68[g]
24	Ph	4-PhO	98	70[g]
25	Ph	2-Me	94	72[g]

[a]The relative amounts of *E*- and *Z*-isomers were determined using the relative integrations of characteristic signals of the isomers in the ^{1}H NMR spectra of the products.
[b]Wittig step: 24 h at 80°C unless otherwise indicated.
[c]Only *E*-isomer could be detected by ^{1}H NMR spectroscopy.
[d]Wittig step: 48 h at 80°C.
[e]Wittig step: 48 h at 100°C.
[f]Wittig step: 68 h at 110°C.
[g]Purified by column chromatography.

isolation of the initial α,β-unsaturated carboxylate salt products of our reactions. Upon completion of each reaction, the reaction solvent was removed under vacuum, and the residual material was dry-loaded (using celite) onto a DCVC column and then

TABLE 6 | Heteroaryl- and vinyl-substituted α,β-unsaturated carboxylic acids (**30–34**) isolated as potassium carboxylate salts by DCVC followed by acidification.



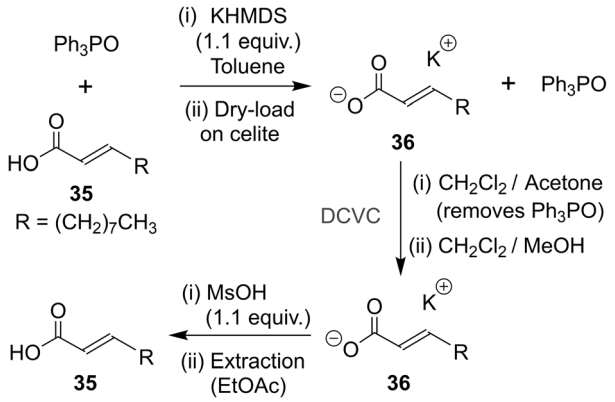
Entry	R	% of *E*-Isomer[a]	Yield, %[b]
1	Pyridin-3-yl	97	73[c]
2	Furan-3-yl	>98[d]	66
3	Thiophen-2-yl	96	51
4	Naphthalen-2-yl	>98[d]	64
5	Cinnamyl	98	59

[a]The relative amounts of *E*- and *Z*-isomers were determined using the relative integrations of characteristic signals of the isomers in the ^{1}H NMR spectra of the products.
[b]Wittig step: 48 h at 100°C unless otherwise indicated.
[c]Wittig step: 24 h at 80°C.
[d]Only *E*-isomer could be detected by ^{1}H NMR spectroscopy.

subjected to our DCVC protocol. We then applied our acidification protocol to the purified carboxylate salts to furnish the derived α,β-unsaturated carboxylic acids. The scope of products isolated in this manner is shown in Tables 5 and 6, and includes cinnamic acids with different substituents on the phenyl ring (including alkyl- (Table 5 entries 2, 13, 15, 16 and 20), halo- (Table 5 entries 3–9), cyano- (entry 10), nitro- (entry 11), ether- (entries 12, 14, 19, 21 and 22), thioether- (entry 17), and amino- (entry 18) substituents) and further α,β-unsaturated carboxylic acids with heteroaryl or vinyl groups appended to the *β*-position (see Table 6 below).

To demonstrate that the approach of chromatographic purification of carboxylic acid products as their carboxylate salts is applicable using chromatographic techniques other than DCVC, we employed flash column chromatography instead of DCVC for purification of the products formed in the experiments described in entries 23, 24, and 25 of Table 5.

The CO_2 utilisation methodology employed for the synthesis of α,β-unsaturated carboxylic acids [26] has only recently been extended to incorporate products derived from aliphatic aldehydes [40]. To investigate whether the purification methodology reported herein can be applied effectively to α,β-unsaturated carboxylic acids with aliphatic substituents at the *β*-position, we attempted to isolate α,β-unsaturated carboxylic acid **35** from a 1:1 mixture of this compound with Ph_3PO (Scheme 3). Acid **35** was converted to the derived potassium carboxylate salt (**36**) by treatment of the mixture with KHMDS, and the mixture was then subjected to DCVC to enable isolation of **36** (Scheme 3). Acidification of this by treatment with MsOH led to isolation of **35** in a recovery of 99%, albeit with an impurity of identical elution characteristics present that originated from the commercial starting material. This demonstrates that the methodology is also



SCHEME 3 | Isolation of α,β-unsaturated carboxylic acid **35** (with aliphatic *β*-substituent) from a mixture of **35** + Ph_3PO, involving chromatographic separation of carboxylate salt **36** from Ph_3PO.

applicable for α,β-unsaturated carboxylic acids derived from aliphatic aldehydes.

The results described above show that purification of a range of differently substituted α,β-unsaturated carboxylic acids can be achieved through the novel approach of chromatographic purification of the potassium carboxylate salt (i.e., the potassium salt of the conjugate base) followed by acidification. While we have not attempted to minimise our solvent or silica usage in the DCVC-based purifications described herein, we nonetheless found that the amount of solvent required to conduct a DCVC procedure was significantly lower than what was required to conduct a comparable purification by flash column chromatography (e.g., *ca*. 520 mL solvent usage for DCVC versus *ca*. 640 mL for column chromatography). Furthermore, use of the DCVC technique affords the potential to minimise solvent usage further—for example, isolation of the carboxylate salts discussed herein could be achieved with significantly less solvent by starting the Ph_3PO elution using a 90:10 mixture of CH_2Cl_2/acetone rather than neat CH_2Cl_2, and then starting the carboxylate salt elution using a 85:15 or 80:20 mixture of CH_2Cl_2/MeOH (again rather than neat CH_2Cl_2). In addition, we found that the amount of silica required for a DCVC purification was approximately 10% less than the amount required for purification by column chromatography for our purposes.

3 | Conclusions

To the best of our knowledge, there have been no previous publications on the chromatographic purification of carboxylic acids as their carboxylate salts. In the research work described above, we have shown that effective isolation of carboxylic acids as their carboxylate salts can be achieved chromatographically, providing a highly valuable new means of purifying carboxylic acids. This method is likely to be particularly useful in applications in which chromatographic purification is necessary, and the carboxylic acids show similar elution characteristics to other materials in the crude product mixture. In such instances, one can take advantage of the deprotonation of the carboxylic acid to generate a carboxylate salt. This salt is highly likely to exhibit different elution characteristics to the other materials in the crude product mixture and hence can be separated from them using chromatographic methods.

In the present project, we found that, although various purification methods were available that can, in principle, enable the isolation of carboxylic acids from crude product mixtures obtained from Wittig-type reactions, in practice, these methods either resulted in sub-optimal recoveries of pure carboxylic acid product or gave contaminated product. Hence, to enable isolation of the carboxylic acid products with high isolated yields and high purity, chromatographic purification was necessary. However, the α,β-unsaturated carboxylic acids of interest showed very similar elution characteristics to the Ph_3PO side-product. The chromatographic separation of these compounds from each other was highly challenging. By exploiting the fact that the potassium carboxylate salt conjugate bases of our desired carboxylic acid products could be separated chromatographically from the Ph_3PO by-product (and other materials present in the crude product) using a DCVC-based method (or indeed flash column chromatography; *vide supra*), it was possible to obtain the desired carboxylic acid products in high yields and purities.

4 | Experimental

For general experimental details, see Section 1 of the SI. The following representative procedure was applied for the synthesis of all α,β-unsaturated carboxylic acid products listed in Tables 5 and 6. For full details and for details on the other experiments discussed in this article, refer to the SI.

Phosphonium salt starting material (1.0 equiv.) was added to a Schlenk flask under an atmosphere of nitrogen (after which the flask was fitted with a second stopcock—see SI for details). To this was added KHMDS (3 – 4 equiv.) as a commercially available solution in toluene. The reaction was left to stir under a static nitrogen atmosphere for 1 h at room temperature, giving a coloured solution of the ylide. CO_2 vapour evolved from a chip of dry ice was then allowed to flow over the reaction mixture for 1 h, giving a white or pale yellow cloudy reaction mixture (see Supporting Information Section 2 for a detailed description on how the CO_2 was administered). After this, the nitrogen gas supply to the reaction flask was restored, and then the appropriate aldehyde (1 equiv.) was added by syringe to the Schlenk flask under an atmosphere of nitrogen. Once the carbonyl compound was added, the reaction mixture was heated using an oil bath (set to 80°C–100°C). After aldehyde addition, the reaction mixture was left to stir for 24 – 48 h. For details on the reaction temperatures and durations used in specific syntheses, see Section 5 of the SI.

After completion of the reaction, celite was added to the reaction mixture, and the solvent was removed under vacuum to load the crude product (containing the product as its potassium carboxylate salt) on to the celite. The potassium carboxylate salt was isolated by DCVC [35] using silica of 60 Å pore size and 20–45 μm particle size (height of silica bed = 5 cm, diameter = 3 cm or 4 cm). The celite containing the components of the crude product was dry-loaded on to the silica DCVC column. Gradient elution was performed using, first, CH_2Cl_2/acetone mixtures (starting with CH_2Cl_2 and increasing the proportion of acetone by 5% for each fraction) to elute the phosphine oxide, and then using CH_2Cl_2/MeOH mixtures (starting with CH_2Cl_2 and

increasing the proportion of MeOH by 5% for each fraction) to elute the potassium carboxylate salt. Once the collection and combination of the fractions containing potassium carboxylate salt had been completed, the solvent was removed under vacuum, and the carboxylate salt was then acidified to pH 2 using 1 equiv. of aqueous acid ((+)-CSA or methanesulfonic acid) along with deionised water (10 mL). The resulting acidic solution was extracted three times with ethyl acetate (30 mL per extraction). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under vacuum to give the isolated α,β-unsaturated carboxylic acid.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. The authors have cited additional references within the Supporting Information [41–86] in the Supporting Information statement.