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Synthesis of tri-substituted, aliphatic and ^{13}C-labelled α,β-unsaturated carboxylic acids *via* Wittig CO_2 utilisation reactions

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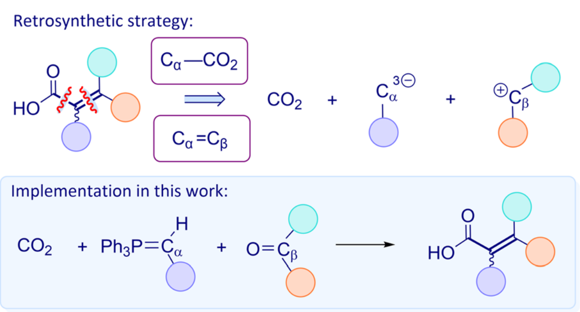
Phosphonium carboxylate ylides are formed through CO_2 activation by phosphonium ylides. These can undergo Wittig reactions with carbonyl compounds, thereby enabling formation of both the C—CO_2 bond and the two bonds of the C═C double bond of an α,β-unsaturated carboxylic acid in a one-pot transformation. In this work, we have developed methodology to enable the synthesis of very useful trisubstituted alkene-containing products. Secondly, the protocol allows for the use of base-sensitive aliphatic aldehydes, avoiding the occurrence of aldol self-condensation. Thirdly, we show that this methodology enables production of a labelled α,β-unsaturated carboxylic acid using ^{13}C-labelled CO_2.

Introduction

Utilisation of waste products as chemical feedstocks for the production of valuable chemical products has become a point of significant focus in recent years.[1–3] CO_2 is arguably the most important waste product of the modern industrialised world, and hence development of methods for utilisation of CO_2 is of particular significance. Indeed, due to its ready availability, renewability, low cost, and non-toxicity, CO_2 is a highly attractive one-carbon building block for the construction of valuable target compounds.[4–7] Although much research has been conducted into chemical transformations of CO_2,[8–18] only a small number of chemicals are made industrially using CO_2.[6,19,20] Development of approaches for utilisation of CO_2 in the synthesis of high value entities of industrial importance, such as synthetic buildings blocks and Active Pharmaceutical Ingredients (APIs), is thus of paramount importance.

Recently, we reported on a novel CO_2 utilisation methodology in which three new carbon–carbon bonds could be formed in one process, enabling formation of both the C_α–CO_2 single bond and the C_α═C_β double bond of α,β-unsaturated carboxylic acids using aromatic or vinylic aldehydes, CO_2 and phosphonium ylides as the starting materials.[21] This approach originates from a novel retrosynthetic strategy involving an unprecedented three bond disconnection (see Scheme 1). The first C–C bond is formed by nucleophilic addition of a phosphonium ylide (**2**) to CO_2. In the presence of base, the resulting ylide-CO_2 adduct (**3**) is deprotonated to give phosphonium carboxylate ylide **4**, which can undergo Wittig reactions with aldehydes to form the two bonds in the C_α═C_β double bond. This methodology enables a very direct means of access to α,β-unsaturated carboxylic acids to be realised, utilising CO_2. The α,β-unsaturated carboxylic acid motif is prevalent in the structures of pharmaceutical compounds and their synthetic precursors[22,23] and also appears in the structures of important commodity chemicals such as acrylic acid (manufactured on a multimillion ton level).[24,25] The availability of the new methodology represented in Scheme 2 for direct access to compounds containing the α,β-unsaturated carboxylic acid motif through combination of relatively simple starting materials is thus highly significant.

In our previously reported method for the construction of disubstituted α,β-unsaturated carboxylic acids from phosphonium salts **1a** and **1b** (*via* derived carboxylate ylides **4a** and **4b** (formed using CO_2); see Scheme 2), a wide substrate scope



Scheme 1 Novel retrosynthetic strategy demonstrating a three-bond disconnection for α,β-unsaturated carboxylic acids.

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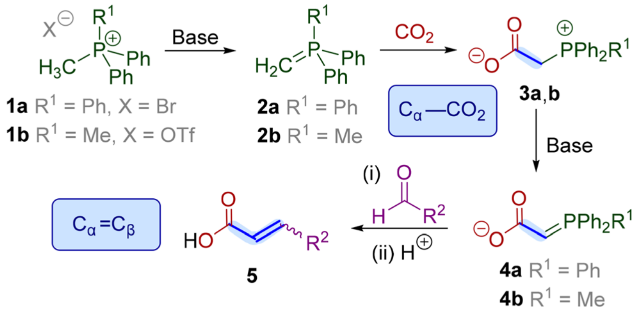


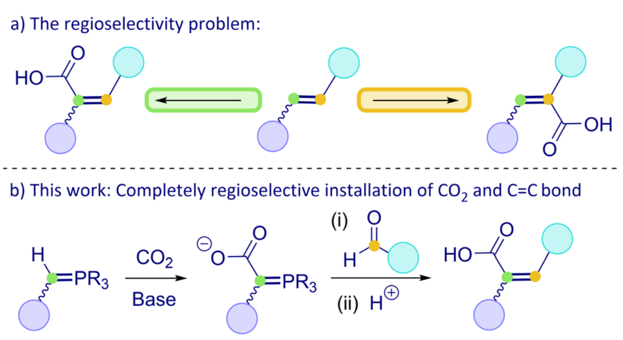
Scheme 2 Formation of three new carbon–carbon bonds *via* a novel CO_2 utilisation methodology mediated by phosphonium ylides.

was demonstrated by synthesising a library of 37 disubstituted α,β-unsaturated carboxylic acids from aromatic and vinylic aldehydes.[21] We wished to further develop this methodology to include the synthesis of α,β-unsaturated carboxylic acids containing trisubstituted C═C entities and to investigate the applicability of the methodology in reactions with aliphatic aldehydes, each of which posed its own unique new challenges that had not required consideration in the development of our previously reported methodology (see further details below).

Results and discussion

Synthesis of trisubstituted alkenes

There exist many examples of regioselective carboxylation of terminal alkenes and alkynes for the synthesis of disubstituted α,β-unsaturated carboxylic acids.[18,26–33] If one considers the installation of a carboxylic acid group as a substituent on an internal alkene, however, there are obvious regioselectivity concerns, with there being the possibility of carboxylation at either of the alkene carbons, as outlined in Scheme 3a. We envisaged that expansion of our methodology to include trisubstituted α,β-unsaturated carboxylic acids could allow for completely regioselective installation of not only the carboxyl group (originating from CO_2) but also the C_α═C_β double bond (which is already installed in the unsaturated starting material in alkene and alkyne carboxylation methods).[18,26–33]



Scheme 3 Regiochemical considerations in the synthesis of trisubstituted α,β-unsaturated carboxylic acids.

Access to α-substituted α,β-unsaturated carboxylic acids can in principle be facilitated through use of α-substituted phosphonium carboxylate ylides such as **4c** and **4d** (derived from phosphonium salts **1c** and **1d**; see Fig. 1), while reactions of carboxylate ylides such as **4b** (derived from phosphonium salt **1b**) with ketones should enable access to β-substituted α,β-unsaturated carboxylic acids. In practice, when we attempted our previously reported[21] Wittig CO_2 utilisation methodology using phosphonium carboxylate ylide **4c** (formed from phosphonium salt **1c** *via* ylide **2c** and ylide-CO_2 adduct **3c**) with several representative aromatic aldehydes, we found that compounds **6–9** were indeed accessible. However, only moderate yields were obtained for reactions of electron-deficient aldehydes (37% for **6**, 46% for **7**, and 55% for **8**), and a poor yield of 18% was obtained for the reaction of relatively electron-rich *p*-methoxybenzaldehyde to produce **9**. Thus, unfortunately, our original methodology was rendered unviable for these useful targets and we set out to design a more active ylide. Since exchanging a *P*-phenyl substituent on the phosphonium ylide for a *P*-alkyl substituent is known to enhance the nucleophilicity of the ylidic carbon,[21,34,35] we imagined that carboxylate ylide **4d** (generated *in situ* from **1d**; see Fig. 1) might allow higher yields of trisubstituted α,β-unsaturated carboxylic acids such as **6–9** to be achieved. Utilisation of a carboxylate ylide of enhanced nucleophilicity proved to be successful, enabling very substantial improvements in the yields of compounds **6–9** (Fig. 1), with yields of 82% for **6**, 68% for **7**, 69% for **8**, and 64% for **9**. The reactions investigated of carboxylate ylides **4c** and **4d** (derived from phosphonium salts **1c** and **1d**) all exhibited very high or even exclusive selectivity for *E*-configured C═C bonds in each of the α,β-unsaturated carboxylic acid products (see *E*/*Z* ratios in Fig. 1). This methodology thus affords completely regioselective and highly stereoselective access to trisubstituted alkene-containing α,β-unsaturated carboxylic acids, thereby exploiting the major advantages conferred by the Wittig reaction while also incorporating CO_2 into the products.

The very high *E*-selectivity in these reactions is consistent with the rationale proposed by Aggarwal, Harvey and coworkers for selectivity in Wittig reactions of α-substituted ester-stabilised ylides.[36–41] We propose that in the transition state leading to the oxaphosphetane intermediate, puckering of the forming four-membered ring occurs because it results in a favourable antiparallel arrangement of the dipoles along the aldehyde C–O bond and ylide C–CO_2 bond (see Fig. 2a). In this conformation, minimisation of steric interactions (between the substituents on C-1 and C-2 and between those on C-1 and P) leads to formation of the *trans*-oxaphosphetane and hence *E*-alkene being strongly favoured, particularly for reactions of Ph_3P-derived ylide **4c**. Potential *cis*-selective transition states are destabilised by the occurrence of 1,2 or 1,3 steric interactions (Fig. 2b and d) or unfavourable dipole–dipole interactions (Fig. 2c). As a caveat to this rationale, which is predicated on the stereochemistry of the alkene C═C bond being set during the Wittig reaction, we note that we did observe previously that isomerisation of a *Z*-cinnamic acid

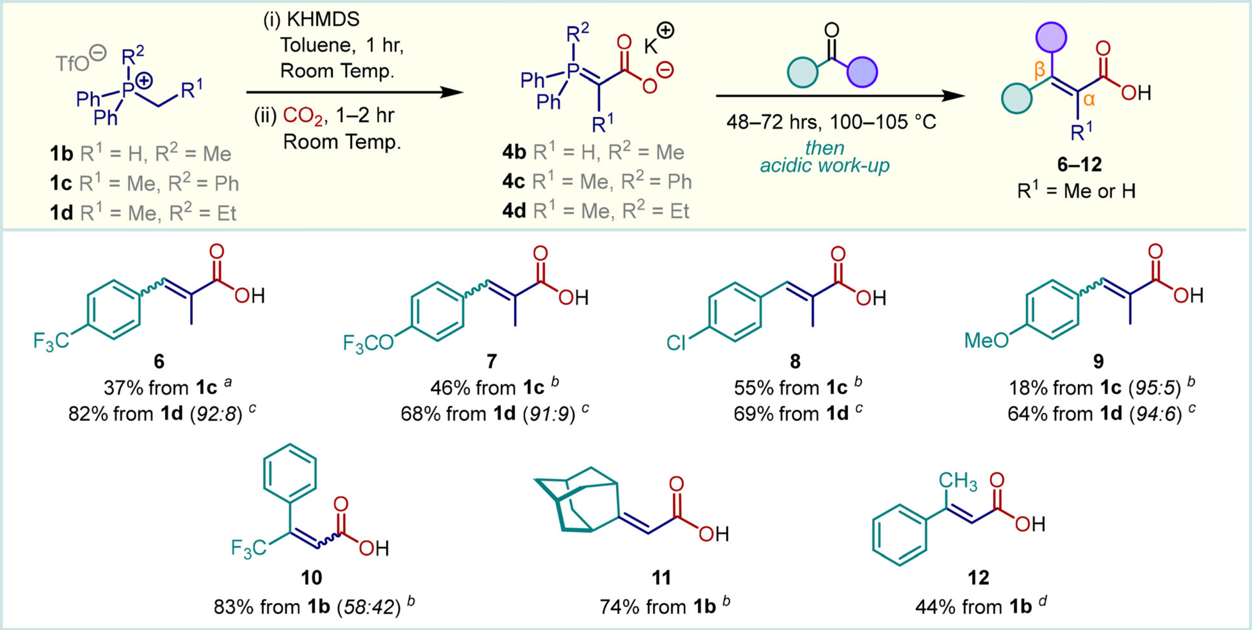


Fig. 1 α,β-Unsaturated carboxylic acids containing trisubstituted alkenes synthesised using phosphonium salts **1c** and **1d**. Isolated yields after chromatography are shown. Alkene *E* : *Z* ratios are shown in parentheses, where appropriate. Reactions were generally conducted on 1 mmol scale. [a] Wittig step: 24 hours, 100 °C. [b] Wittig step: 48 hours, 100 °C. [c] Wittig step: 72 hours, 100 °C. [d] Wittig step: 5 days 105 °C.

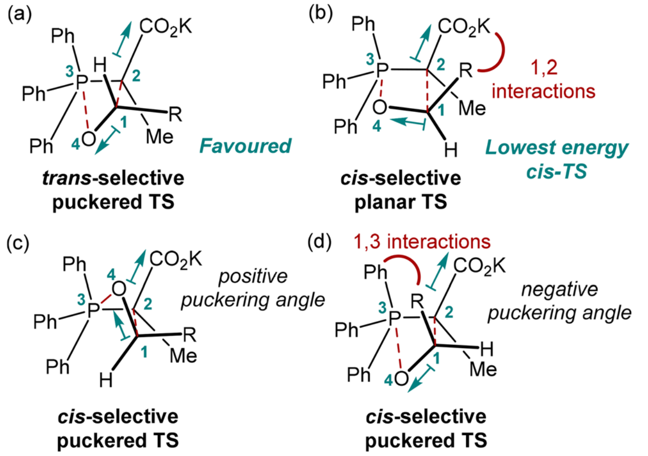


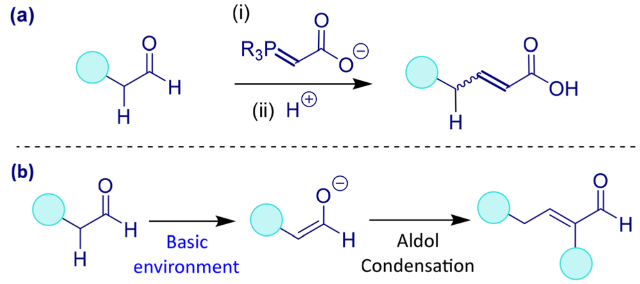
Fig. 2 Possible transition states (TSs) for the Wittig reaction of α-methyl substituted phosphonium carboxylate ylide **4c** with an aldehyde, RCHO.[36]

does occur under the conditions of our Wittig CO_2 reactions.[21] Consequently, we must acknowledge that isomerisation of the *Z*-isomers of our products may have occurred in the reactions discussed above, thereby potentially contributing to the observed high *E*-selectivity.

We also wished to investigate whether the methodology would be effective for formation of β-substituted α,β-unsaturated carboxylic acids (with trisubstituted alkene moieties) by using ketones as the starting materials. Reactions of phosphonium carboxylate ylide **4b** (derived from **1b**, $[Me_2Ph_2P]OTf$), with representative ketones were indeed found to give trisubstituted α,β-unsaturated carboxylic acids **10** and **11** in high yields (see Fig. 1). The Wittig reaction of phosphonium carboxylate ylide **4b** with acetophenone afforded product **12** in only a moderate yield of 44%, even after pushing the reaction time to 5 days. Interestingly, this reaction gave the *E*-isomer of product **12** exclusively.

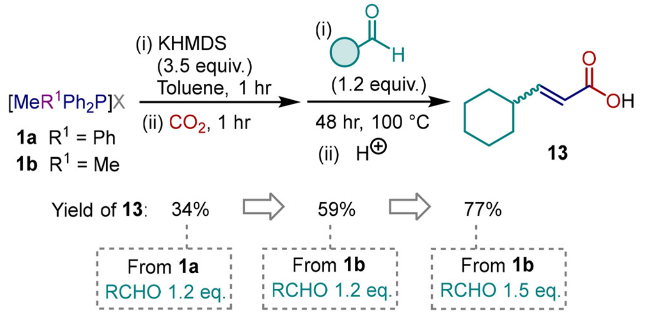
Extension of methodology to aliphatic aldehydes

In addition, we wished to test our Wittig CO_2 utilisation methodology further by investigating its applicability in reactions with aliphatic aldehydes (Scheme 4a). As indicated above, our previously reported methodology involved only aromatic or vinylic aldehydes,[21] which do not bear acidic protons at the α-position. The α-proton(s) of aliphatic aldehydes are susceptible to deprotonation by strong bases, and hence there is a high likelihood that aldol self-condensation reactions could occur under the basic



Scheme 4 (a) Wittig CO_2 utilisation reaction of an aliphatic aldehyde. (b) Aldol self-condensation of an aliphatic aldehyde under basic conditions.

conditions typically employed in our Wittig CO_2 utilisation reactions (Scheme 4b).[42] To investigate whether conditions could be found under which Wittig CO_2 utilisation reactions could be accomplished in preference to aldol self-condensation reactions, a series of optimisation experiments were undertaken using cyclohexanecarboxaldehyde as the test substrate (Scheme 5).[43] When the reaction was performed starting from phosphonium salt **1a** (*via* ylide **2a** and hence carboxylate ylide **4a**), a low yield of 34% of compound **13** was obtained (Scheme 5). Changing the starting phosphonium salt from **1a** to **1b** saw an increase in the yield of **13** (34% to 59%; Scheme 5), demonstrating a similar trend to the increase in yields obtained in other reactions discussed above when a *P*-phenyl substituent was exchanged for a *P*-methyl (compare yields for products derived from **1c** and **1d** in Fig. 1). Increasing the amount of the aldehyde added from 1.2 equivalents to 1.5 equivalents, we were able to obtain a good yield of the α,β-unsaturated carboxylic acid product (**13**, 77%; Scheme 5). The Wittig step of this reaction was carried out at 100 °C over 48 hours, starting from phosphonium salt **1b** (and proceeding *via* ylide **2b** and phosphonium carboxylate ylide **4b**). Several other products derived from aliphatic aldehydes, **13–17**, were generated using these reaction conditions (starting from phosphonium salt **1b**) in moderate to good yields of (54–73%; see Fig. 3). Similar to the Wittig CO_2 utilisation reactions discussed above and those reported in our previous publication,[21] the reactions of phosphonium carboxylate ylide **4b** with aliphatic aldehydes also result in preferential formation of *E*-α,β-unsaturated carboxylic acids (see *E*/*Z* ratios in Fig. 3). The high *E*-stereoselectivity exhibited in these reactions is consistent with the selectivity exhibited by reactions of $MePh_2P$-derived ester-stabilised ylides,[37,40,41] which, while highly *E*-selective, are expected to result in formation of *Z*-alkene in small but significant amounts, in contrast to reactions of Ph_3P-derived ester-stabilised ylides, which are almost exclusively *E*-selective.



Scheme 5 Development of conditions for Wittig CO_2 utilisation reactions of aliphatic aldehyde and phosphonium salts **1a** or **1b**.

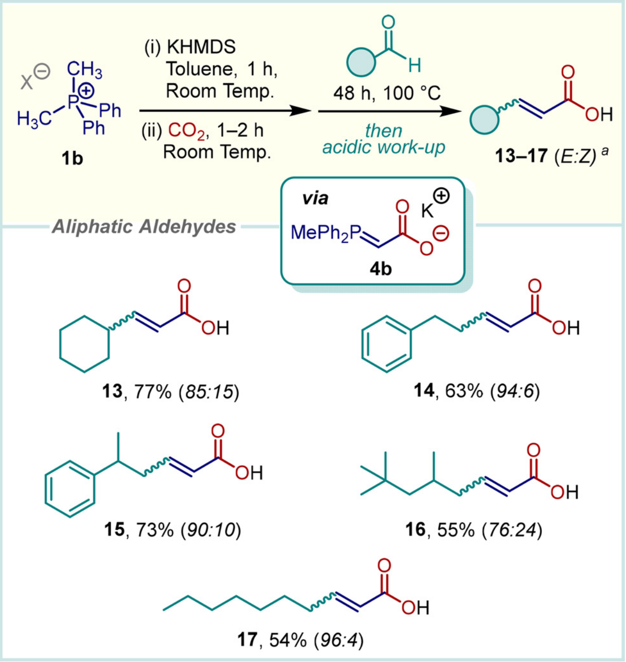
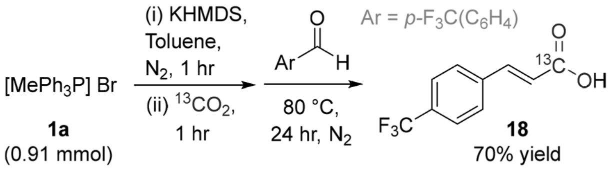


Fig. 3 Disubstituted aliphatic α,β-unsaturated carboxylic acids synthesised using $[Me_2Ph_2P]$ OTf. Isolated yields are shown. The *E* : *Z* ratios of alkenes are shown in parentheses. Reactions were conducted on *ca.* 1 mmol scale.

Application for isotopic labelling

The availability of novel CO_2 utilisation methods provides new ways to employ CO_2 as a chemical feedstock and one-carbon building block. One application in which this can be exploited to great effect is in the incorporation of isotopically labelled carbon atoms (^{13}C or ^{14}C, or indeed labelled oxygen atoms, ^{18}O) into compounds through use of isotopically labelled CO_2.[44–46] In order to demonstrate the efficacy of the Wittig CO_2 utilisation methodology for this purpose, ^{13}C-labelled CO_2 was employed in the synthesis of a representative α,β-unsaturated carboxylic acid, 4-(trifluoromethyl)cinnamic acid (**18**). $^{13}CO_2$ was used to react with ylide **2a** (generated from phosphonium salt **1a**) to produce carboxylate ylide **4a-^{13}C**, and this underwent reaction with 4-(trifluoromethyl)benzaldehyde at 80 °C to generate ^{13}C-labelled product **18** in an isolated yield of 70% (Scheme 6). This demonstrates the capacity of this method to enable facile incorporation of isotopically labelled atoms into products using labelled CO_2 (with CO_2 pressure at atmospheric pressure levels) and exemplifies the value of CO_2 as a chemical feedstock.



Scheme 6 Synthesis of ^{13}C-labelled 4-(trifluoromethyl)cinnamic acid using $^{13}CO_2$ in a Wittig CO_2 utilisation reaction.

Conclusion

We have succeeded in extending the applicability of our Wittig CO_2 utilisation methodology, developing three novel applications that had not previously been possible. The methodology was successfully applied to reactions of aliphatic aldehydes, avoiding significant competitive occurrence of aldol self-condensation, thereby allowing for the synthesis of α,β-unsaturated carboxylic acids bearing aliphatic substituents at the β-position for the first time. α-Substituted α,β-unsaturated carboxylic acids (each containing a trisubstituted C═C bond) were synthesised in good yields and with high *E*-selectivity, enabled by the increased reactivity of a more nucleophilic ylide. The methodology was also extended to ketones to access β-substituted α,β-unsaturated carboxylic acids, which are typically challenging substrates in Wittig reactions of stabilised ylides. The site of installation of both the carboxyl group and the alkene in these reactions is unambiguous; this approach thus enables utilisation of CO_2 while exploiting the unique advantages of the Wittig reaction to form three new carbon–carbon bonds in a one pot telescoped process. Finally, the methodology was shown to enable the generation of labelled α,β-unsaturated carboxylic acids through the use of labelled CO_2, providing a straightforward means of incorporating a labelled isotope into relatively complex products.

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 R. E. 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.; supervision, P. A. B. and G. P. M.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: synthetic details, experimental methods, and characterisation data including copies of NMR spectra. See DOI: https://doi.org/10.1039/d6ob00221h.

The authors have cited additional references within the SI.[47–73]

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