Continuous-flow generation of diazoesters and their direct use in S-H and P-H insertion reactions: synthesis of α-sulfanyl, α-sulfonyl and α-phosphono carboxylates

Hannah E. Bartrum,[†] David C. Blakemore,[§] Christopher J. Moody[†]* and Christopher J. Hayes[†]*

[†]*School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK and*

[§]*Pfizer Neusentis, The Portway Building, Granta Park, Cambridge, CB21 6GS, UK.*

chris.hayes@nottingham.ac.uk and c.j.moody@nottingham.ac.uk

Abstract

The synthesis of α-sulfanyl, α-sulfonyl and α-phosphono carboxylates has been achieved using a two-step procedure involving the in-flow generation of diazoesters from sulfonylhydrazones, via Bamford Stevens elimination, and then subsequent S-H, sulfinate and P-H carbene insertion reactions. The method for α-sulfonyl ester is particularly noteworthy as it represents a very atom economic ('green') way to access the products, and it completely avoids the use of alkyl halides.

Keywords

Diazoester; Metal carbenoid; S-H Insertion; P-H Insertion; Continuous flow.

Introduction

Both α-sulfonyl- and α-phosphonyl carboxylates are useful reagents in organic synthesis, participating in important reactions such as olefination.[1-5] The reagents are usually obtained from the parent carboxylate by α-halogenation, and subsequent reaction of the α-haloester with a sulfanyll, followed by *S*-oxidation, or with a trialkyl phosphite under Arbusov conditions. We now report a new unified approach to these important reagents utilizing metal carbene X-H insertion reactions.[6-8]

We recently reported the development of a highly efficient and safe in-flow process for the synthesis of diazoesters from arylsulfonylhydrazones via a Bamford Stevens reaction.[9] Furthermore, we

demonstrated that a two-step procedure could be employed in which the in-flow generated diazoesters were directly converted into a range of different α-alkoxy- and α-amino- acid derivatives by O-H and N-H carbene insertion reactions respectively. We now report further development of this methodology to embrace the much less common S-H, sulfinate and P-H carbene insertion reactions as a route to α-sulfide (path A), α-sulfonyl- (path B) and α-phosphonyl-carboxylates (path C) (Scheme 1).

Scheme 1. In-flow preparation of diazoesters and subsequent use in carbene S-H insertion (path A), sulfinate insertion (path B) and P-H insertion (path C).
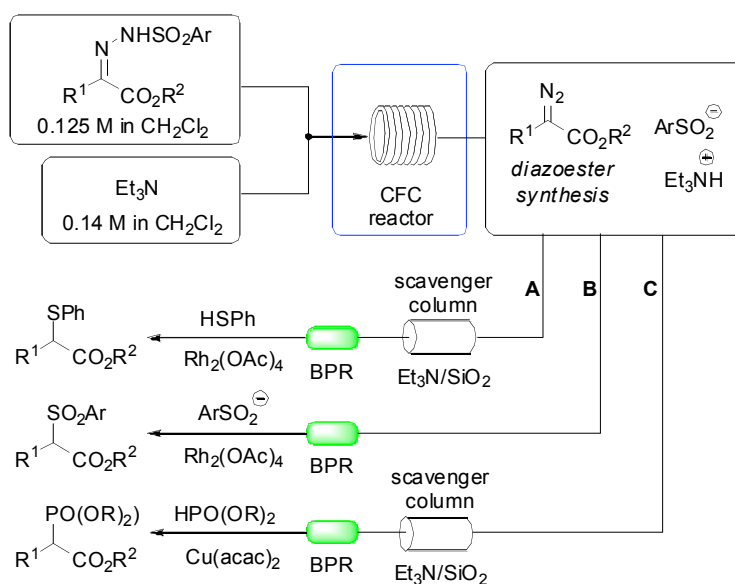

Results and Discussion

Our studies began by preparing the required arylsulfonylhydrazone precursors **1a-g** (Scheme 2) via the condensation of readily available α-ketoesters with arylsulfonylhydrazines as previously described.[9] We then turned our attention to developing the in-flow diazoester generation/S-H insertion process (path A, Scheme 1).[10-16] Diazoester generation from **1a-g** was carried out under our previously reported flow conditions,[9] which involved combining a stream of the arylsulfonylhydrazone (0.125 M in CH$_2$Cl$_2$) with a stream of triethylamine (0.14 M in CH$_2$Cl$_2$), followed by heating in a convection flow coil (CFC) reactor (80 ^{o}C, 10 min residence time) to effect the Bamford-Stevens elimination. The resulting flow stream was then passed through an in-line scavenger column (packed with silica/Et$_3$N) to remove the sulfinate byproduct generated during the Bamford Stevens reaction. After exiting the back pressure

regulator (250 psi), the output from the diazoester-generating flow process was then introduced to a hot solution of dichloromethane containing thiophenol and Rh$_2$(OAc)$_4$ to effect the carbene S-H insertion reaction (Scheme 2). The desired insertion products **2a-d** were isolated in reasonable yield over two-steps from the starting arylsulfonylhydrazones **1a-d**. In order to demonstrate the preparation of α-sulfonyl carboxylates the S-H insertion products, **2b** and **2d** were subsequently oxidized to the sulfones **4a** (98%) and **4b** (99%) respectively using standard conditions (mCPBA, CH$_2$Cl$_2$) (Scheme 3).

Scheme 2. S-H Insertion reactions of sulfanylphenol and 4-toluenesulfinic acid. [Ar = 4-tolyl unless otherwise stated. **1a**, R^1 = Ph, R^2 = Me; **1b**, R^1 = Ph, R^2 = c-Hex; **1c**, R^1 = 4-NO$_2$-C$_6$H$_4$, R^2 = Et; **1d**, R^1 = PhCH$_2$CH$_2$, R^2 = Et, Ar = 2,4,6-Me$_3$-C$_6$H$_2$; **1e**, R^1 = Ph, R^2 = i-Bu; **1f**, R^1 = Ph, R^2 = CH$_2$CH=CH$_2$.]
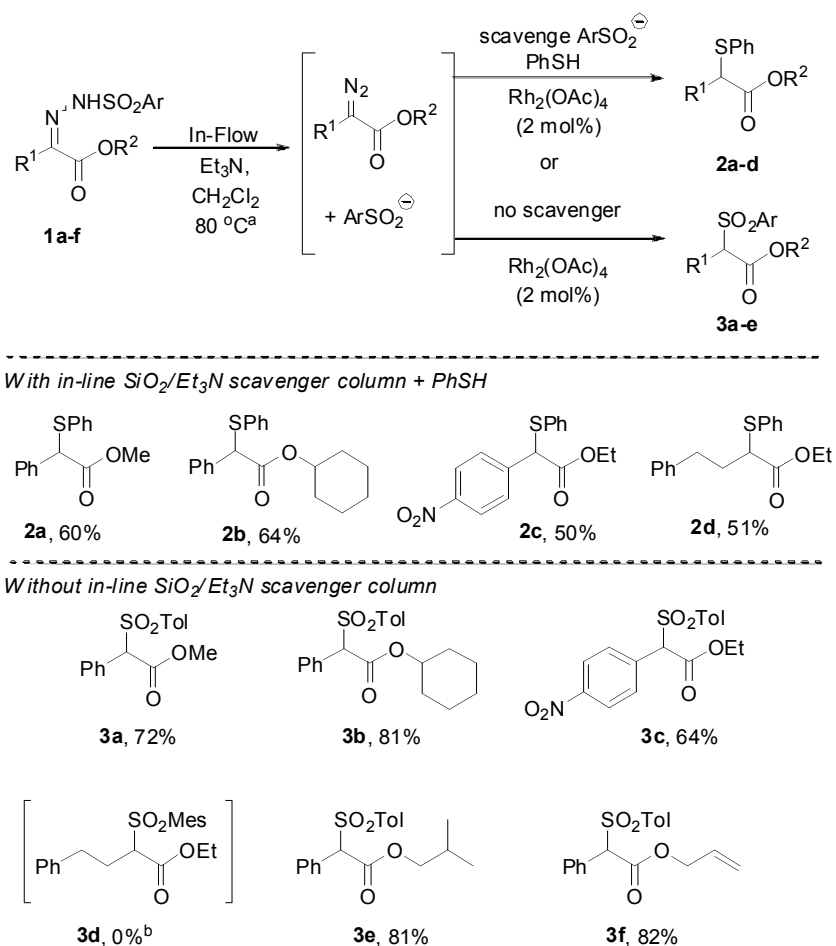
^{a} The CFC reactor was maintained at 99 ^{o}C for sulfonylhydrazone **1d**; ^{b} Alkene **6** produced in 95% (see Scheme 4).

**Scheme 3.** Sulfone formation via oxidation of sulfides.

3
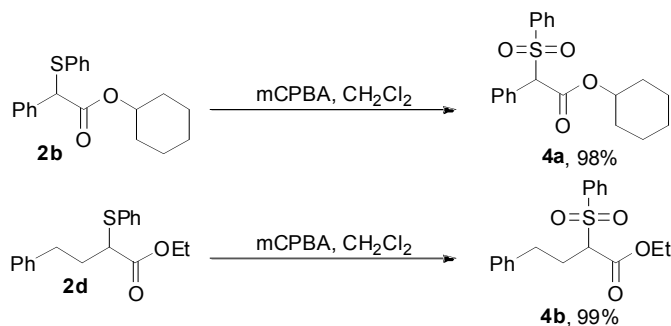
As triethylammonium 4-toluenesulfinate was the byproduct of the Bamford Stevens reactions, we wondered if it would participate in sulfinate carbene insertion reactions if it were not removed from the flow product stream. If successful, this would lead to a more direct entry to the desired α-sulfonyl carboxylate products, and the sulfide oxidation step (Scheme 3) would not be required. This would represent a very atom efficient synthesis of these products as N_2 would be the only byproduct formed from the starting arylsulfonylhydrazone. Fortunately, this sulfinate insertion process has precedent, and been reported to occur during the thermal decomposition of tosylhydrazones in basic media,[17] or by pyrolysis[18] or photolysis,[19] although the reported yields and substrate scope are poor. More recently Che and co-workers found that a limited number of sulfones were formed as byproducts in the ruthenium(II) porphyrin catalysed cyclopropanations of alkenes with tosylhydrazones.[20] Yu and co-workers have reported the use of Cu salts[21] (CuI, 20 mol%) to promote this transformation, while Barluenga and co-workers employed an iron catalyst.[22] Since both of these latter reactions require high reaction temperatures (110 °C) for efficient conversion, our safer in-flow diazoester formation and milder rhodium catalyzed reaction conditions could offer an advantage.

To this end we subjected tosylhydrazones **1a-f** to the in-flow diazoester forming process (path B, Scheme 1), but in this case no scavenger column was employed and the crude diazoester output, plus the toluenesulfinate byproduct, was added directly to a hot solution of 2 mol% $Rh_2(OAc)_4$ in dichloromethane, resulting in the formation of a range of α-sulfonyl esters **3** in generally good yields (Scheme 2). As the sulfonyl hydrazones **1** were initially prepared by condensation of commercially available α-keto esters and sulfonyl hydrazines, the only by-products generated during the entire 3-step

4

reaction sequence leading to α-sulfonyl esters **3** are water and nitrogen. This represents a remarkably simple and atom economic ('green') way to access the sulfonyl ester products, and completely avoids the use of alkyl halides. It is interesting to note that whilst the arylsulfonyl hydrazone **1d** did give the S-H insertion product **2d** (51%) when using sulfanylphenol (Scheme 2), it did not produce any of the expected sulfone product **3d** when sulfinate was used as the insertion partner. What happened instead was formation of the alkene **6** in 95% yield (Scheme 4) via 1,2-H shift of the intermediate metal carbene[23] to give **5**, followed by isomerization of the double bond under the basic reaction conditions[24,25] (Scheme 4). Similarly, the in-flow conversion of tosylhydrazone **1g** into its corresponding diazoester followed by treatment with $Rh_2(OAc)_4$ led to formation of β-sulfonyl carboxylate **7** in moderate yield (21%) (Scheme 4). Repeating the reaction as a one-pot batch process produced similar results (47%), and we propose that the β-sulfone **6** arises as a result of conjugate addition of the sulfinate byproduct to methyl acrylate[26] generated by Bamford Stevens reaction of tosylhydrazone **1g**.

Scheme 4. Attempted α-sulfone formation with alkyl arylsulfonyl-hydrazones [Ar = 2,4,6-Me$_3$-C$_6$H$_2$].
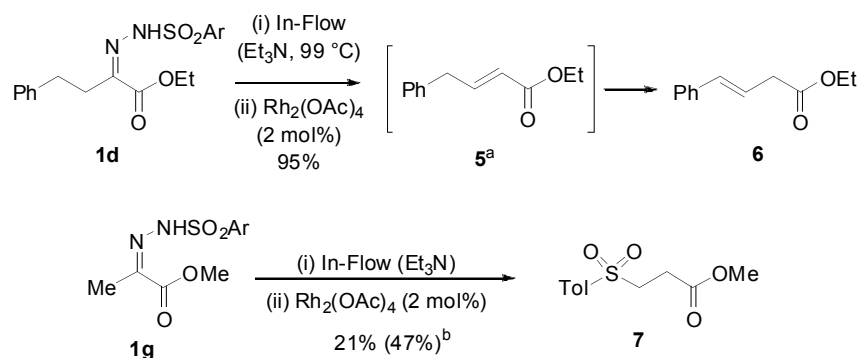

[a] Alkene **5** synthesized according to the literature procedure.[19] [b] Yield using batch process.

We next focused on developing a procedure for P-H insertion reactions to form α-phosphono carboxylates (path C, Scheme 1). At the outset of our work, the only report of such a transformation was by Arbuzov *et al.* who found that $Cu(acac)_2$ was an effective catalyst for P-H insertions on a range of diazocompounds.[27] However, the yields obtained were variable and the reaction proceeded in relatively poor yield (32 and 40%) for the only two diazoester examples explored. During the preparation of this

manuscript, Wu *et al.* published a one-pot method for the copper-catalysed insertion of in-situ generated diazo-compounds into H-phosphorus oxides,[28] but no diazoesters were included in their examples. As we already had good conditions developed for the in-flow formation of diazoesters, we initially focused on optimizing the P-H insertion reaction on pure diazoester **8** (Table 1), which was formed by elimination of the sulfonylhydrazone **1a**.

Table 1. Optimization of batch P-H insertion conditions
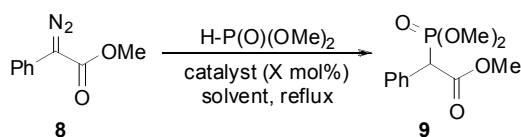
Entry	Catalyst	Solvent[a]	Yield (%)
1	Cu(acac)$_2$ (3 mol%)	toluene	63
2	Cu(acac)$_2$ (3 mol%)	CH$_2$Cl$_2$	66
3	Cu(OAc)$_2$ (3 mol%)	CH$_2$Cl$_2$	60
4	Rh$_2$(OAc)$_4$ (2 mol%)	CH$_2$Cl$_2$	-

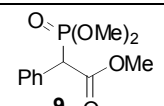[a]All reactions performed at reflux in the stated solvent

Applying the reported conditions to diazoester **8** (replacing benzene with toluene) gave the desired alkyl phosphonate **9** in acceptable yield (entry 1, Table 1). Changing the solvent to dichloromethane had no detrimental effect on the yield (entry 2, Table 1) and Cu(OAc)$_2$ proved to be equally effective as a catalyst (entry 3, Table 1). No desired product formation was observed by employing Rh$_2$(OAc)$_4$ as a catalyst (entry 4, Table 1).
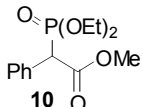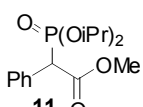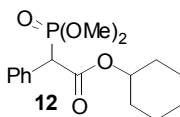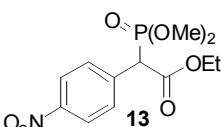
With Cu(acac)$_2$ and CH$_2$Cl$_2$ as the catalyst and solvent of choice, we next investigated the two-step procedure (path C, Scheme 1) starting with tosylhydrazone **1a**. Thus, in-flow treatment of tosylhydrazone **1a** with triethylamine in CH$_2$Cl$_2$ (including passage through a Et$_3$N/silica gel scavenger column to remove sulfinate) gave the corresponding diazoester. The output product stream was then

directly added to a boiling solution of the desired H-phosphonate and Cu(acac)$_2$ in CH$_2$Cl$_2$ (Table 2).

Initially we focused on optimizing the procedure for the formation of alkyl phosphonate **9**. Utilizing the

same conditions as those for the batch process (3 mol% Cu(acac)$_2$) resulted in isolation of the desired

product in 51% yield along with recovery of the diazoester intermediate **8**. Increasing the catalyst

loading to 5 mol% improved the yield to 67%, but the best results were achieved using 10 mol% of the

catalyst, which resulted in isolation of **9** in 76% yield over the two steps. This represents a substantial

increase in yield to that previously reported for the standard batch process.[27]
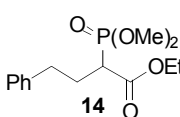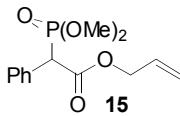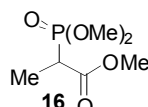
   The yield of the desired phosphonoacetate product decreased with increasing steric bulk of the alkyl

phosphite insertion partner, with the diethyl derivative **10** being isolated in only 31% yield and the

diisopropyl derivative **11** being isolated in 19% yield. We therefore continued to explore the reaction of

other diazoesters with dimethyl phosphite (Table 2, entries 4-8). The desired P-H insertion products

were formed in all cases via the two-step process, although the yields were generally moderate to poor.

In the case of the nitro derivative **13** a significant amount of intermediate diazoester was recovered. In

contrast to the attempted sulfinate insertion reactions, the sulfonylhydrazones **1d** and **1g** gave the

desired P-H insertion products **14** and **16** respectively, albeit in poor yields. The mass balance in the

reaction of **1d** was a 1:1 mixture of alkenes **5** and **6**, which suggests that the rate of P-H insertion is slow

compared to the rate of N$_2$ elimination and 1,2-H shift of the intermediate diazoester. Full conversion of

1g was observed, and it is likely that methyl acrylate accounts for the mass balance in the reaction, but

none was isolated due to its volatility.

Table 2. Dialkyl phosphonate formation

Entry	Hydrazone	H-P(O)(OR^3)$_2$	Product	Yield (%)
1	**1a**	H-P(O)(OMe)$_2$	**9**	76 (67)[a]

2	**1a**	H-P(O)(OEt)$_2$	**10**	31
3	**1a**	H-P(O)(O^{i}Pr)$_2$	**11**	19
4	**1b**	H-P(O)(OMe)$_2$	**12**	55
5	**1c**	H-P(O)(OMe)$_2$	**13**	26 (52)[b]
6	**1d**	H-P(O)(OMe)$_2$	**14**	23[c]
7	**1f**	H-P(O)(OMe)$_2$	**15**	51
8	**1g**	H-P(O)(OMe)$_2$	**16**	24

[a] 5 mol% Cu(acac)$_2$ used; added as two portions of 2.5 mol% catalyst with the second portion added after 4 h of reaction. [b] based on recovered starting material. [c] 69% of a 1:1 mixture of alkenes **5** and **6** also isolated.

   In conclusion we have shown that in-flow generated α-diazoesters can participate in S-H, sulfinate and P-H carbene insertion reactions to give α-sulfanyl-, α-sulfonyl- and α-phosphonyl carboxylate products. This represents a significant extension to our previously published O-H and N-H insertions,[9] and further demonstrates that in-flow generated α-diazoesters can be formed and used safely under flow chemistry conditions.

Experimental Section

General Flow Method A (S-H insertion): A solution of tosylhydrazone (0.25 mmol) in CH_2Cl_2 (2 mL) was injected into one of the 2 mL sample loops of the R2+ unit of a Vapourtec R2+/R4 reactor. The other 2 mL sample loop was loaded with a solution of triethylamine (0.28 mmol) in CH_2Cl_2 (2 mL). The valves of the loop were set to load and the reagents pumped through the system using CH_2Cl_2 as a system solvent at a flow rate of 0.200 mL/min (0.100 mL/min per pump). The reagents were combined in a T-piece before entering a 2 mL convection flow coil (CFC) reactor (inside diameter = 1 mm, length = 2.9 m) (PFA), which was maintained at 80 ºC (99 ºC for **1d**) (residence time (t_r) = 10 min) by the R4 unit. The product stream exiting the reactor was passed through an omnifit column (100 mm x 6.6 mm) loaded with silica treated with 20% Et_3N in CH_2Cl_2. A back pressure regulator (250 psi) was added in line after the reactor and the output (7.5 mL total volume) was added directly to a solution of $Rh_2(OAc)_4$ (2.2 mg, 5.0 μmol, 2 mol%) and thiophenol (26 μL, 0.25 mmol) in CH_2Cl_2 (2 mL) at reflux. Once the addition of diazoester was complete, the reaction mixture was heated at reflux for 18 h before being cooled to room temperature and concentrated *in vacuo*. The crude product was purified by column chromatography.

General Flow Method B (sulfinate insertion): A solution of tosylhydrazone (0.25 mmol) in CH_2Cl_2 (2 mL) was injected into one of the 2 mL sample loops of the R2+ unit of a Vapourtec R2+/R4 reactor. The other 2 mL sample loop was loaded with a solution of triethylamine (0.28 mmol) in CH_2Cl_2 (2 mL). The valves of the loop were set to load and the reagents pumped through the system using CH_2Cl_2 as a system solvent at a flow rate of 0.200 mL/min (0.100 mL/min per pump). The reagents were combined in a T-piece before entering a 2 mL convection flow coil (CFC) reactor (inside diameter = 1 mm, length = 2.9 m) (PFA), which was maintained at 80 ºC (99 ºC for **1d**) (residence time (t_r) = 10 min) by the R4 unit. A back pressure regulator (250 psi) was added in line after the reactor and the output (7.5 mL total volume) was directly added into a flask containing $Rh_2(OAc)_4$ (2.2 mg, 5.0 μmol, 2 mol%) in CH_2Cl_2 (2 mL) at reflux. Once the addition of diazoester was complete, the reaction mixture was refluxed

overnight before being cooled to room temperature and concentrated *in vacuo*. The crude product was then purified by column chromatography.

General Flow Method C (P-H insertion): As for General Flow Method A except the output (7.5 mL total volume) from the flow was added directly to a solution of Cu(acac)$_2$ (6.5 mg, 0.05 mmol, 10 mol%) and the H-phosphonate (1.25 mmol, 5 eq.) in CH$_2$Cl$_2$ (1 mL) at reflux. Once the addition of diazoester was complete, the reaction mixture was heated at reflux for 18 h before being cooled to room temperature and concentrated *in vacuo*. The crude product was purified by column chromatography.

Methyl 2-phenyl-2-(phenylsulfanyl)acetate, 2a

Following General Flow Method A, tosylhydrazone **1a** gave, after purification by column chromatography (2% EtOAc/petrol) compound **2a** (39 mg, 60%) as a colorless oil. R$_f$ 0.6 (40% EtOAc/petrol); ν_{max}(CHCl$_3$)/cm^{-1} 3089, 2954, 2845, 1738, 1584, 1496, 1483, 1454, 1439, 1345, 1304, 1286, 1148, 1088, 1075, 1025, 1003; δ_H (400 MHz; CDCl$_3$) 7.45-7.42 (2H, m), 7.39-7.35 (2H, m), 7.33-7.30 (3H, m), 7.28-7.25 (3H, m), 4.91 (1H, s), 3.68 (3H, s); δ_C (100 MHz; CDCl$_3$) 171.1 (C), 135.8 (C), 133.8 (C), 132.8 (CH), 129.1 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 56.5 (CH), 52.9 (CH$_3$); *m/z* (ESI) found 281.0600. (M+Na, C$_{15}$H$_{14}$NaO$_2$S requires 281.0607). Spectroscopic data matches that previously reported.[29]

Cyclohexyl 2-phenyl-2-(phenylsulfanyl)acetate, 2b

Following General Flow Method A, tosylhydrazone **1b** gave, after purification by column chromatography (1% EtOAc/petrol) compound **2b** (52 mg, 64%) as a colorless oil. R$_f$ 0.7 (40% EtOAc/petrol); ν_{max}(CHCl$_3$)/cm^{-1} 2940, 2861, 1726, 1584, 1496, 1483, 1454, 1440, 1352, 1304, 1286, 1149, 1120, 1089, 1075, 1037, 1010, 976; δ_H (400 MHz; CDCl$_3$) 7.48-7.44 (2H, m), 7.40-7.36 (2H, m), 7.34-7.23 (6H, m), 4.91 (1H, s), 4.80-4.72 (1H, m), 1.75-1.68 (2H, m), 1.66-1.59 (2H, m), 1.51-1.43 (1H, m), 1.39-1.25 (5H, m); δ_C (100 MHz; CDCl$_3$) 170.0 (C), 136.0 (C), 134.2 (C), 132.5 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 127.9 (CH), 74.2 (CH), 56.6 (CH), 31.4 (CH$_2$), 31.3 (CH$_2$),

25.4 (CH$_2$), 23.6 (CH$_2$), 23.5 (CH$_2$); *m/z* (ESI) found 349.1244. (M+Na, C$_{20}$H$_{22}$NaO$_2$S requires 349.1233).

Ethyl 2-(4-nitrophenyl)-2-(phenylsulfanyl)acetate, 2c

Following General Flow Method A, tosylhydrazone **1c** gave, after purification by column chromatography (3% EtOAc/petrol) compound **2c** (40 mg, 50%) as a colorless oil. R$_f$ 0.3 (20% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2984, 1732, 1607, 1530, 1493, 1645, 1369, 1349, 1322, 1290, 1148, 1111, 1095, 1068, 1025, 859; δ_H (400 MHz; CDCl$_3$) 8.16 (2H, d, *J* 8.8), 7.58 (2H, d, *J* 8.8), 7.35 (2H, dd, *J* 7.2 and 1.6), 7.30-7.26 (3H, m), 4.92 (1H, s), 4.21-4.12 (2H, m), 1.20 (3H, t, *J* 7.2); δ_C (100 MHz; CDCl$_3$) 169.4 (C), 147.8 (C), 143.4 (C), 133.7 (CH), 132.4 (C), 129.7 (CH), 129.3 (CH), 128.9 (CH), 123.9 (CH), 62.4 (CH$_2$), 56.0 (CH), 14.1 (CH$_3$); *m/z* (ESI) found 340.0611 (M+Na, C$_{16}$H$_{15}$NNaO$_4$S requires 340.0614).

Ethyl 4-phenyl-2-(phenylsulfanyl)butanoate, 2d

Following General Flow Method A, tosylhydrazone **1d** gave, after purification by column chromatography (4% EtOAc/petrol) compound **2d** (43 mg, 51%) as a colorless oil. R$_f$ 0.5 (20% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 3087, 2983, 2938, 2862, 1723, 1604, 1584, 1496, 1483, 1455, 1370, 1304, 1148, 1094, 1068, 1026, 864; δ_H (400 MHz; CDCl$_3$) 7.46-7.43 (2H, m), 7.34-7.25 (5H, m), 7.23-7.21 (3H, m), 4.16-4.10 (2H, m), 3.63 (1H, t, *J* 7.0), 2.77 (2H, t, *J* 7.6), 2.27-2.17 (1H, m), 2.12-2.03 (1H, m), 1.19 (3H, t, *J* 6.8); δ_C (100 MHz; CDCl$_3$) 172.2 (C), 140.7 (C), 133.3 (C), 133.1 (CH), 129.0 (CH),128.7 (CH), 128.6 (CH), 128.1 (CH), 126.3 (CH), 61.3 (CH$_2$), 50.1 (CH), 33.3 (CH$_2$), 33.2 (CH$_2$), 14.2 (CH$_3$); *m/z* (ESI) found 301.1258 (M+H, C$_{18}$H$_{21}$O$_2$S requires 301.1257). Found 323.1070 (M+Na, C$_{18}$H$_{20}$NaO$_2$S requires 323.1076).

Methyl 2-phenyl-2-tosylacetate, 3a

Following General Flow Method B, tosylhydrazone **1a** gave, after purification by column chromatography (12% EtOAc/petrol) compound **3a** (55 mg, 72%) as colorless needles, mp 122-124 °C.

R$_f$ 0.6 (40% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2955, 2928, 1746, 1598, 1495, 1456, 1348, 1321, 1127, 1083, 1007, 908, 868; δ_H (400 MHz; CDCl$_3$) 7.48-7.45 (2H, m), 7.40-7.25 (5H, m), 7.23-7.20 (2H, m), 5.09 (1H, s), 3.77 (3H, s), 2.41 (3H, s); δ_C (100 MHz; CDCl$_3$) 165.5 (C=O), 145.5 (C), 133.4 (C), 130.4 (CH), 130.1 (CH), 129.8 (CH), 129.3 (CH), 128.7 (CH), 128.1 (C), 75.3 (CH), 53.3 (CH$_3$), 21.8 (CH$_3$); *m/z* (ESI) found 327.0676. (M+Na, C$_{16}$H$_{16}$NaO$_4$S requires 327.0662). ^{1}H NMR data matches those previously reported.[30]

Cyclohexyl-2-phenyl-2-tosylacetate, 3b

Following General Flow Method B, tosylhydrazone **1b** gave, after purification by column chromatography (10% EtOAc/petrol) compound **3b** (75 mg, 81%) as pale yellow needles, mp 127-128 °C. R$_f$ 0.8 (50% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2935, 2861, 1732, 1597, 1496, 1331, 1193, 1183, 1143, 1128, 1083, 1035, 1010, 927, 865; δ_H (400 MHz; CDCl$_3$) 7.49-7.46 (2H, m), 7.38-7.34 (3H, m), 7.31-7.27 (2H, m), 7.21 (2H, d, *J* 8.0), 5.06 (1H, s), 4.84 (1H, tt, *J* 8.8, 4.4), 2.41 (3H, s), 1.85-1.75 (2H, m), 1.74-1.62 (2H, m), 1.47-1.22 (6H, m); δ_C (100 MHz; CDCl$_3$) 164.4 (C=O), 145.2 (C), 133.6 (C), 130.3 (CH), 130.0 (CH), 129.6 (CH), 129.2 (CH), 128.5 (CH), 128.2 (C), 75.5 (CH), 75.2 (CH), 31.2 (CH$_2$), 31.1 (CH$_2$), 25.2 (CH$_2$), 23.5 (CH$_2$), 25.4 (CH$_2$) and 21.7 (CH$_3$); *m/z* (ESI) found 395.1298. (M+Na, C$_{21}$H$_{24}$NaO$_4$S requires 395.1288).

Ethyl 2-(4-nitrophenyl)-2-tosylacetate, 3c

Following General Flow Method B, tosylhydrazone **1c** gave, after purification by column chromatography (10% EtOAc/petrol) compound **3c** (58 mg, 64%) as colorless needles, mp 122-124 °C. R$_f$ 0.6 (40% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2984, 2940, 2869, 1741, 1607, 1597, 1392, 1370, 1351, 1326, 1306, 1144, 1128, 1083, 1018, 908, 875, 860; δ_H (400 MHz; CDCl$_3$) 8.17 (2H, d, *J* 8.8), 7.65 (2H, d, *J* 8.8), 7.54 (2H, d, *J* 8.2), 7.28 (2H, d, *J* 8.2), 5.22 (1H, s), 4.28-4.16 (2H, m), 2.44 (3H, s), 1.22 (3H, t, *J* 7.2); δ_C (100 MHz; CDCl$_3$) 164.0 (C=O), 148.5 (C), 146.1 (C), 134.9 (C), 133.2 (C), 131.5 (CH), 129.8 (CH), 129.7 (CH), 123.5 (CH), 74.5 (CH), 63.0 (CH$_2$), 21.8 (CH$_3$) and 13.9 (CH$_3$); *m/z* (ESI)

found 364.0846. (M+H, $C_{17}H_{18}NO_6S$ requires 364.0849). Found 386.0658. (M+Na, $C_{17}H_{17}NNaO_6S$ requires 386.0669).

Isobutyl 2-phenyl-2-tosylacetate, 3e

Following General Flow Method B, tosylhydrazone **1e** gave, after purification by column chromatography (8% EtOAc/petrol) compound **3e** (70 mg, 81%) as colorless needles, mp 66-68 °C. R_f 0.8 (40% EtOAc/petrol); ν_{max}(CHCl$_3$)/cm^{-1} 2959, 2939, 2876, 1732, 1597, 1456, 1396, 1378, 1348, 1421, 1126, 1083, 1018, 998, 969, 945, 868; δ_H (400 MHz; CDCl$_3$) 7.50-7.46 (2H, m), 7.39-7.34 (3H, m), 7.31-7.26 (2H, m), 7.22-7.20 (2H, m), 5.08 (1H, s), 3.97 (1H, dd, J 10.6 and 7.0), 3.90 (1H, dd, J 10.6 and 7.0), 2.40 (3H, s), 1.92 (1H, *app* nonet, J 7.0), 0.88 (6H, d, J 7.0); δ_C (100 MHz; CDCl$_3$) 165.1 (C=O), 145.4 (C), 133.7 (C), 130.4 (CH), 130.1 (CH), 129.7 (CH), 129.3 (CH), 128.7 (CH), 128.2 (CH), 75.5 (CH), 72.6 (CH$_2$), 27.7 (CH), 21.8 (CH$_3$) and 19.1 (CH$_3$); *m/z* (ESI) found 369.1135. (M+Na, $C_{19}H_{22}NaO_4S$ requires 369.1131).

Allyl 2-phenyl-2-tosylacetate, 3f

Following General Flow Method B, tosylhydrazone **1f** gave, after purification by column chromatography (10% EtOAc/petrol) compound **3f** (68 mg, 82%) as colorless needles, mp 74-76 °C. R_f 0.7 (40% EtOAc/petrol); ν_{max}(CHCl$_3$)/cm^{-1} 2929, 1738, 1650, 1598, 1495, 1456, 1365, 1341, 1321, 1126, 1083, 1043, 1019, 987, 944, 869; δ_H (400 MHz; CDCl$_3$) 7.49-7.47 (2H, m), 7.38-7.26 (5H, m), 7.23-7.20 (2H, m), 5.84 (1H, ddt, J 16.8, 10.4 and 6.0), 5.30 (1H, *app* dq, J 16.8 and 1.6), 5.23 (1H, *app* dq, J 10.4 and 1.2), 5.11 (1H, s), 4.66-4.64 (2H, m), 2.41 (3H, s); δ_C (100 MHz; CDCl$_3$) 164.7 (C=O), 145.4 (C), 133.5 (C), 131.0 (CH), 130.4 (CH), 130.1 (CH), 129.8 (CH), 129.3 (CH), 128.7 (CH), 128.0 (C), 119.5 (CH$_2$), 75.4 (CH), 67.0 (CH$_2$) and 21.8 (CH$_3$); *m/z* (ESI) found 353.0832. (M+Na, $C_{18}H_{18}NaO_4S$ requires 353.0818).

Cyclohexyl 2-phenyl-2-(phenylsulfonyl)acetate, 4a

To a stirred solution of cyclohexyl 2-phenyl-2-(phenylsulfanyl)acetate, **2b** (107 mg, 0.33 mmol) in CH_2Cl_2 (9 mL) was added *m*CPBA (170 mg, 0.98 mmol) and the reaction was stirred at room temperature for 3 h (until TLC analysis indicated complete consumption of starting material). Sodium thiosulfate (5 mL, sat.) was added and the reaction was stirred for a further 15 min before the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried (MgSO$_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (5% EtOAc/petrol) to give the title compound, **4a** (116 mg, 98%) as a colorless oil. R$_f$ 0.3 (20% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2941, 2862, 1732, 1586, 1496, 1455, 1448, 1374, 1352, 1324, 1312, 1288, 1146, 1128, 1083, 1035, 1009, 982, 908, 867; δ_H (400 MHz; CDCl$_3$) 7.63-7.57 (3H, m), 7.44-7.40 (2H, m), 7.38-7.34 (3H, m), 7.32-7.26 (2H, m), 5.08 (1H, s), 4.86-4.80 (1H, m), 1.85-1.75 (2H, m), 1.74-1.65 (2H, m), 1.55-1.46 (1H, m), 1.45-1.23 (5H, m); δ_C (100 MHz; CDCl$_3$) 164.3 (C), 136.6 (C), 134.2 (CH), 130.4 (CH), 130.1 (CH), 129.7 (CH), 128.7 (CH), 128.6 (CH), 128.1 (C), 75.6 (CH), 75.4 (CH), 31.3 (CH$_2$), 31.2 (CH$_2$), 25.3 (CH$_2$), 23.6 (CH$_2$), 23.5 (CH$_2$); *m/z* (ESI) found 359.1331 (M+Na, C$_{20}$H$_{23}$O$_4$S requires 359.1312). Found 381.1129 (C$_{20}$H$_{22}$NaO$_4$S requires 381.1131).

Ethyl 4-phenyl-2-(phenylsulfonyl)butanoate, 4b

To a stirring solution of ethyl 4-phenyl-2-(phenylsulfanyl)butanoate, **2d** (19 mg, 58 µmol) in CH_2Cl_2 (1.5 mL) was added *m*CPBA (43 mg, 0.17 mmol) and the reaction was stirred at room temperature for 3 h (until TLC analysis indicated complete consumption of starting material). Sodium sulfanylsulfate (5 mL, sat.) was added and the reaction was stirred for a further 15 min before the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried (MgSO$_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (5% EtOAc/petrol) to give the title compound, **4b** (20.5 mg, 99%) as a colorless oil. R$_f$ 0.2 (20% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2934, 1734, 1604, 1449, 1371, 1324, 1145, 1084; δ_H (400 MHz; CDCl$_3$) 7.86-7.84 (2H, m), 7.67 (1H, tt, *J* 7.2 and 1.2), 7.57-7.53 (2H, m), 7.29-7.25 (2H, m), 7.23-7.18 (1H, m), 7.12-7.10 (2H, m), 4.12-4.06 (2H, m), 3.93 (1H, dd, *J* 10.8 and 4.0), 2.75-2.69 (1H, m), 2.63-2.56 (1H, m), 2.42-2.26 (2H, m), 1.16 (3H, t, *J* 7.2); δ_C (100 MHz; CDCl$_3$) 165.9 (C), 139.4

(C), 137.3 (C), 134.3 (CH), 129.5 (CH),129.1 (CH), 128.8 (CH), 128.6 (CH), 126.7 (CH), 70.2 (CH), 62.4 (CH_2), 33.0 (CH_2), 28.4 (CH_2), 14.0 (CH_3); *m/z* (ESI) found 333.1141 (M+H, $C_{18}H_{21}O_4S$ requires 333.1155). Found 355.0972 (M+Na, $C_{18}H_{20}NaO_4S$ requires 355.0975).

(*E*)-Ethyl 4-phenylbut-3-enoate, 6

Following General Flow Method B, tosylhydrazone **1d** gave, after purification by column chromatography (2% EtOAc/petrol) compound **6** and (*E*)-Ethyl 4-phenylbut-2-enoate, **5** as a 9:1 mixture (90 mg, 95%) as a colorless oil. R$_f$ 0.8 (40% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2982, 2938, 2309, 1732, 1654, 1600, 1496, 1150, 1391, 1371, 1349, 1319, 1300, 983, 966, 908, 864. Data for the major title compound, **6**: δ_H (400 MHz; CDCl$_3$) 7.40-7.36 (2H, m), 7.34-7.29 (2H, m), 7.26-7.21 (1H, m), 6.49 (1H, *app* d, *J* 15.6), 6.31 (1H, dt, *J* 15.6 and 7.0), 4.18 (2H, q, *J* 7.2), 3.25 (2H, dd, *J* 7.0 and 1.2), 1.29 (3H, t, *J* 7.2); δ_C (100 MHz; CDCl$_3$) 171.7 (C=O), 137.0 (C), 133.5 (CH), 128.6 (CH), 127.6 (CH), 126.4 (CH), 122.0 (CH), 60.9 (CH_2), 38.6 (CH_2) and 14.3 (CH_3); Data for the minor compound, **5**: δ_H (400 MHz; CDCl$_3$) 7.34-7.30 (2H, m), 7.24-7.21 (1H, m), 7.19-7.17 (2H, m), 7.10 (1H, dt, *J* 15.6 and 6.8), 5.81 (1H, dt, *J* 15.6 and 1.4), 4.18 (2H, q, *J* 7.2), 3.52 (2H, dd, *J* 6.8 and 1.4), 1.27 (3H, t, *J* 7.2); δ_C (100 MHz; CDCl$_3$) 166.6 (C=O), 147.4 (CH), 137.8 (C), 129.0 (CH), 128.8 (CH), 126.8 (CH), 122.5 (CH), 60.4 (CH_2), 38.6 (CH_2) and 14.4 (CH_3); *m/z* (ESI) found 213.0887. (M+Na, $C_{12}H_{14}NaO_2$ requires 213.0886). Spectroscopic data matches that previously reported.[24,31]

Isomerisation of Alkene 5

To a stirred solution of alkene **5**[24] (57 mg, 0.3 mmol) in CH$_2$Cl$_2$ (1 mL) was added triethylamine (46 µL, 0.33 mmol) and the resultant solution was heated at reflux for 18 h before being cooled to room temperature and concentrated *in vacuo*. Analysis of the ^{1}H NMR spectrum of the resultant oil indicated a mixture of alkenes **6** and **5** in a ratio of 7:1. Spectroscopic data matched that reported above.

Methyl 3-tosylpropanoate, 7

Following General Flow Method B, tosylhydrazone **1g** gave, after purification by column chromatography (20% EtOAc/petrol) compound **7** (13 mg, 21%) as colorless needles, mp 73-75 °C. (lit.[21] 72-73 °C). R_f 0.6 (40% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2954, 1739, 1599, 1456, 1365, 1319, 1304, 1149, 1134, 1088, 1055, 982; δ_H (400 MHz; CDCl$_3$) 7.78 (2H, d, J 8.2), 7.37 (2H, d, J 8.2), 3.64 (3H, s), 3.40 (2H, t, J 7.6), 2.74 (2H, t, J 7.6), 2.45 (3H, s); δ_C (100 MHz; CDCl$_3$) 107.7 (C=O), 145.2 (C), 153.7 (C), 130.2 (CH), 128.4 (CH), 52.4 (CH$_3$), 51.7 (CH$_2$), 27.8 (CH$_2$) and 21.8 (CH$_3$); m/z (ESI) found 243.0691. (M+H, C$_{11}$H$_{15}$O$_4$S requires 243.0686). Found 265.0508. (M+Na, C$_{11}$H$_{14}$NaO$_4$S requires 265.0505). Spectroscopic data matches those previously reported.[26]

Methyl 2-(dimethoxyphosphoryl)-2-phenylacetate, 9

Following General Flow Method C, tosylhydrazone **1a** and dimethyl phosphite gave, after purification by column chromatography (75% EtOAc/petrol) compound **9** (49 mg, 76%) as a colorless oil. R_f 0.1 (40% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2954, 2855, 1747, 1732, 1650, 1602, 1495, 1456, 1362, 1344, 1310, 1130, 1064, 988, 946, 889; δ_H (400 MHz; CDCl$_3$) 7.51-7.48 (2H, m), 7.38-7.31 (3H, m), 4.28 (1H, d, J 23.6), 3.76 (3H, s), 3.72 (3H, d, J 11.2), 3.66 (3H, d, J 11.2); δ_C (100 MHz; CDCl$_3$) 168.1 (C, d, J 4.0), 130.7 (C, d, J 9.0), 129.7 (CH, d, J 6.0), 128.8 (CH, d, J 2.0), 128.3 (CH, d, J 3.0), 54.2 (CH$_3$, d, J 6.0), 53.8 (CH$_3$, d, J 7.0), 53.1 (CH$_3$) and 51.7 (CH, d, J 135.0); δ_P (162 MHz; CDCl$_3$) 21.2; m/z (ESI) found 259.0739. (M+H, C$_{11}$H$_{16}$O$_5$P requires 259.0730). Found 281.0554. (M+Na, C$_{11}$H$_{15}$NaO$_5$P requires 281.0549). Spectroscopic data consistent with that previously reported.[32]

Methyl 2-(diethoxyphosphoryl)-2-phenylacetate, 10

Following General Flow Method C, utilising 5 mol% Cu(acac)$_2$, tosylhydrazone **1a** and diethyl phosphite gave, after purification by column chromatography (60% EtOAc/petrol) compound **10** (22 mg, 31%) as a colorless oil. R_f 0.2 (40% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2980, 2952, 2932, 2909, 1739, 1733, 1602, 1496, 1456, 1392, 1389, 1346, 1306, 1144, 1097, 1059, 978, 803, 885; δ_H (400 MHz; CDCl$_3$) 7.53-7.49 (2H, m), 7.37-7.31 (3H, m), 4.26 (1H, d, J 23.6), 4.10-4.03 (3H, m), 4.00-3.92 (1H, m), 3.75 (3H, s), 1.26 (3H, td, J 7.2 and 0.8), 1.19 (3H, td, J 7.2 and 0.8); δ_C (100 MHz; CDCl$_3$) 168.3

(C, d, *J* 4.0), 130.9 (C, d, *J* 8.0), 129.7 (CH, d, *J* 7.0), 128.7 (CH, d, *J* 2.0), 128.2 (CH, d, *J* 3.0), 63.7 (CH$_2$, d, *J* 7.0), 63.3 (CH$_2$, d, *J* 7.0), 52.9 (CH$_3$), 52.2 (CH, d, *J* 139.0), 16.4 (CH$_3$, d, *J* 6.0), 16.3 (CH$_3$, d, *J* 7.0); δ_P (162 MHz; CDCl$_3$) 18.6; *m/z* (ESI) found 287.1040. (M+H, C$_{13}$H$_{20}$O$_5$P requires 287.1043). Found 309.0857. (M+Na, C$_{13}$H$_{19}$NaO$_5$P requires 309.0862).

Methyl 2-(diisopropoxyphosphoryl)-2-phenylacetate, 11

Following General Flow Method C, utilising 5 mol% Cu(acac)$_2$, tosylhydrazone **1a** and diisopropyl phosphite gave, after purification by column chromatography (60% EtOAc/petrol) compound **11** (15 mg, 19%) as a colorless oil. R$_f$ 0.3 (40% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2983, 2954, 1738, 1602, 1456, 1386, 1347, 1302, 1145, 1102, 994, 898; δ_H (400 MHz; CDCl$_3$) 7.54-7.50 (2H, m), 7.36-7.29 (3H, m), 4.72-4.64 (1H, m), 4.63-4.49 (1H, m), 4.20 (1H, d, *J* 23.6), 3.76 (3H, s), 1.28-1.24 (9H, m), 1.04 (3H, d, *J* 6.8); δ_C (100 MHz; CDCl$_3$) 168.4 (C, d, *J* 4.0), 131.3 (C, d, *J* 8.0), 129.9 (CH, d, *J* 7.0), 128.5 (CH, d, *J* 2.0), 128.0 (CH, d, *J* 3.0), 72.3 (CH, d, *J* 7.0), 72.0 (CH, d, *J* 8.0), 52.8 (CH$_3$), 52.9 (CH, d, *J* 135.0), 24.4 (CH$_3$, d, *J* 3.0), 24.1 (CH$_3$, d, *J* 4.0), 23.8 (CH$_3$, *J* 5.0), 23.4 (CH$_3$, d, *J* 6.0); δ_P (162 MHz; CDCl$_3$) 26.5; *m/z* (ESI) found 315.1352. (M+H, C$_{15}$H$_{24}$O$_5$P requires 315.1356). Found 337.1171. (M+Na, C$_{15}$H$_{23}$NaO$_5$P requires 337.1175).

Cyclohexyl 2-(dimethoxyphosphoryl)-2-phenylacetate, 12

Following General Flow Method C, tosylhydrazone **1b** and dimethyl phosphite gave, after purification by column chromatography (75% EtOAc/petrol) compound **12** (45 mg, 55%) as a colorless oil. R$_f$ 0.2 (40% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2937, 2859, 1732, 1602, 1496, 1455, 1372, 1352, 1304, 1145, 1120, 1060, 1007, 821; δ_H (400 MHz; CDCl$_3$) 7.52-7.48 (2H, m), 7.37-7.30 (3H, m), 4.87-4.80 (1H, m), 4.25 (1H, d, *J* 23.6), 3.71 (3H, d, *J* 10.8), 3.67 (3H, d, *J* 10.8), 1.90-1.64 (4H, m), 1.53-1.20 (6H, m); δ_C (100 MHz; CDCl$_3$) 167.0 (C, d, *J* 4.0), 131.0 (C, d, *J* 9.0), 129.6 (CH, d, *J* 6.0), 128.7 (CH, d, *J* 2.0), 128.1 (CH, d, *J* 4.0), 74.5 (CH), 54.0 (CH$_3$, d, *J* 7.0), 53.7 (CH$_3$, d, *J* 7.0), 52.2 (CH, d, *J* 134.0), 31.4 (CH$_2$), 31.3 (CH$_2$), 25.4 (CH$_2$), 23.6 (CH$_2$), 23.5 (CH$_2$); *m/z* (ESI) found 327.1354. δ_P (162 MHz;

CDCl$_3$) 21.5; (M+H, C$_{16}$H$_{24}$O$_5$P requires 327.1356). Found 349.1174. (M+Na, C$_{16}$H$_{23}$NaO$_5$P requires 349.1175).

Ethyl 2-(dimethoxyphosphoryl)-2-(4-nitrophenyl) acetate, 13

Following General Flow Method C, tosylhydrazone **1c** and dimethyl phosphite gave, after purification by column chromatography (75% EtOAc/petrol) compound **13** (21 mg, 26%) as a colorless oil. R$_f$ 0.2 (40% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2985, 2958, 2855, 1738, 1607, 1531, 1494, 1462, 1369, 1351, 1322, 1289, 1147, 1111, 1058, 967, 900, 860; δ_H (400 MHz; CDCl$_3$) 8.22 (2H, d, J 8.4), 7.70 (2H, dd, J 8.4 and 2.0), 4.38 (1H, d, J 24.0), 4.31-4.20 (2H, m), 3.77 (3H, d, J 11.2), 3.73 (3H, d, J 11.2), 1.29 (3H, t, J 7.2); δ_C (100 MHz; CDCl$_3$) 166.6 (C, d, J 4.0), 147.8 (C), 138.3 (C, d, J 8.0), 130.7 (CH, d, J 6.0), 123.8 (CH, d, J 3.0), 62.7 (CH$_2$), 54.3 (CH$_3$, d, J 6.0), 54.1 (CH$_3$, d, J 6.0), 51.8 (CH, d, J 133.0), 14.1 (CH$_3$); δ_P (162 MHz; CDCl$_3$) 19.6; m/z (ESI) found 318.0733. (M+H, C$_{12}$H$_{17}$NO$_7$P requires 318.0737). Found 340.0559. (M+Na, C$_{12}$H$_{16}$NNaO$_7$P requires 340.0557).

Ethyl 2-(dimethoxyphosphoryl)-4-phenylbutanoate, 14

Following General Flow Method C, tosylhydrazone **1d** and dimethyl phosphite gave, after purification by column chromatography (75% EtOAc/petrol) compound **14** (17 mg, 23%) as a colorless oil. R$_f$ 0.2 (40% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2985, 2957, 2854, 1731, 1604, 1496, 1455, 1370, 1328, 1145, 1058, 883; δ_H (400 MHz; CDCl$_3$) 7.30-7.26 (2H, m), 7.22-7.15 (3H, m), 4.28-4.19 (2H, m), 3.78 (3H, d, J 10.4), 3.75 (3H, d, J 10.8), 2.99 (1H, ddd, J 22.8, 11.2 and 3.6), 2.78-2.69 (1H, m), 2.63-2.54 (1H, m), 2.38-2.32 (1H, m), 2.21-2.08 (1H, m), 1.30 (3H, t, J 7.2); δ_C (100 MHz; CDCl$_3$) 169.0 (C, d, J 5.0), 140.5 (C), 128.7 (CH), 128.6 (CH), 126.4 (CH), 61.7 (CH$_2$), 53.5 (CH$_3$, d, J 7.0), 53.4 (CH$_3$, d, J 7.0), 44.6 (CH, d, J 131.0), 34.4 (CH$_2$, d, J 5.0), 28.7 (CH$_2$, d, J 5.0), 14.3 (CH$_3$); δ_P (162 MHz; CDCl$_3$) 25.2; m/z (ESI) found 301.1202. (M+H, C$_{14}$H$_{22}$O$_5$P requires 301.1199). Found 323.1012. (M+Na, C$_{14}$H$_{21}$NaO$_5$P requires 323.1019).

Allyl 2-(dimethoxyphosphoryl)-2-phenylacetate, 15

Following General Flow Method C, tosylhydrazone **1f** and dimethyl phosphite gave, after purification by column chromatography (75% EtOAc/petrol) compound **15** (40 mg, 56%) as a colorless oil. R$_f$ 0.2 (40% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2989, 2957, 2855, 1738, 1733, 1650, 1602, 1496, 1456, 1362, 1344, 1304, 1139, 1059, 989, 943, 889; δ_H (400 MHz; CDCl$_3$) 7.53-7.49 (2H, m), 7.38-7.32 (3H, m), 5.89 (1H, ddt, J 17.2, 10.4 and 6.0), 5.31 (1H, dq, J 17.2 and 1.2), 5.23 (1H, dq, J 10.4 and 1.2), 4.72-4.60 (2H, m), 4.30 (1H, d, J 23.6), 3.72 (3H, d, J 10.8), 3.67 (3H, d, J 10.8); δ_C (100 MHz; CDCl$_3$) 167.3 (C, d, J 3.0), 131.5 (CH), 130.7 (C, d, J 8.0), 129.7 (CH, d, J 6.0), 128.8 (CH, d, J 3.0), 128.3 (CH, d, J 3.0), 118.9 (CH$_2$), 66.5 (CH$_2$), 54.2 (CH$_3$, d, J 7.0), 53.8 (CH$_3$, d, J 7.0), 51.9 (CH, d, J 135.0); δ_P (162 MHz; CDCl$_3$) 21.1; m/z (ESI) found 285.0875. (M+H, C$_{13}$H$_{18}$O$_5$P requires 285.0886). Found 307.0693. (M+Na, C$_{13}$H$_{17}$NaO$_5$P requires 307.0706).

Methyl 2-(dimethoxyphosphoryl)propanoate, 16

Following General Flow Method C, tosylhydrazone **1f** and dimethyl phosphite gave, after purification by column chromatography (EtOAc) compound **16** (12 mg, 24%) as a colorless oil. R$_f$ 0.1 (40% EtOAc/petrol); v_{max}(CHCl$_3$)/cm^{-1} 2989, 2956, 2854, 1732, 1602, 1458, 1382, 1321, 1161, 1059, 1002, 868, 839; δ_H (400 MHz; CDCl$_3$) 3.74-3.71 (3H, m), 3.70-3.68 (3H, m), 3.66 (3H, s), 2.98 (1H, dq, J 23.6 and 7.2), 1.35 (3H, dd, J 18.0 and 7.2); δ_C (100 MHz; CDCl$_3$) 170.1 (C, d, J 5.0), ==53.3 (CH$_3$, d, J 7.0)==, 52.6 (CH$_3$), 38.6 (CH, d, J 134.0), 11.6 (CH$_3$, d, J 6.0); δ_P (162 MHz; CDCl$_3$) 16.8; m/z (ESI) found 197.0592. (M+H, C$_6$H$_{14}$O$_5$P requires 197.0573). Found 219.0400. (M+Na, C$_6$H$_{13}$NaO$_5$P requires 219.0393). Spectroscopic data consistent with that previously reported.[33]

Supplementary Data Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. Supplementary data associated with this article can be found in the online version.

References

(1)   Wadsworth, W. S. *Org. React.* **1977**, *25*, 73.

(2)   Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

(3)   Mirk, D.; Grassot, J.-M.; Zhu, J. *Synlett* **2006**, 1255.

(4)   Alonso, D. A.; Nájera, C.; Varea, M. *Helv. Chim. Acta* **2002**, *85*, 4287.

(5)   Alonso, D. A.; Fuensanta, M.; Gómez-Bengoa, E.; Nájera, C. *Eur. J. Org. Chem.* **2008**, 2915.

(6)   Doyle, M. P.; McKervey, M. A.; Ye, T. Modern Catalytic Methods for Organic Synthesis with Diazo Compounds; John Wiley: New York, 1998.

(7)   Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811.

(8)   Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577.

(9)   Bartrum, H. E.; Blakemore, D. C.; Moody, C. J.; Hayes, C. J. *Chem. Eur. J.* **2011**, *17*, 9586.

(10)   Yates, P. *J. Am. Chem. Soc.* **1952**, *74*, 5376.

(11)   Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223.

(12)   Moody, C. J.; Taylor, R. J. *Tetrahedron Lett.* **1987**, *28*, 5351.

(13)   Brunner, H.; Wutz, K.; Doyle, M. P. *Monatsh. Chem.* **1990**, *121*, 755.

(14)   DelZotto, A.; Baratta, W.; Rigo, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3079.

(15)   Yue, Y. L.; Wang, Y. H.; Hu, W. H. *Tetrahedron Lett.* **2007**, *48*, 3975.

(16)   Zhang, Y. Z.; Zhu, S. F.; Cai, Y.; Mao, H. X.; Zhou, Q. L. *Chem. Commun.* **2009**, 5362.

(17)   Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735.

(18)   Henry, R. A.; Moore, D. W. *J. Org. Chem.* **1967**, *32*, 4145.

(19)   Lemal, D. M.; Fry, A. J. *J. Org. Chem.* **1964**, *29*, 1673.

(20)   Zhang, J. L.; Chan, P. W. H.; Che, C. M. *Tetrahedron Lett.* **2003**, *44*, 8733.

(21)   Feng, X.-W.; Wang, J.; Zhang, J.; Yang, J.; Wang, N.; Yu, X.-Q. *Org. Lett.* **2010**, *12*, 4408.

(22)   Barluenga, J.; Tomas-Gamasa, M.; Aznar, F.; Valdes, C. *Eur. J. Org. Chem.* **2011**, 1520.

(23)   Cox, G. G.; Haigh, D.; Hindley, R. M.; Miller, D. J.; Moody, C. J. *Tetrahedron Lett.* **1994**, *35*, 3139.

(24)   Bulger, P. G.; Moloney, M. G.; Trippier, P. C. *Org. Biomol. Chem.* **2003**, *1*, 3726.

(25)   Narahashi, H.; Yamamoto, A.; Shimizu, I. *Chem. Lett.* **2004**, *33*, 348.

(26)   Ivanova, S.; Aleksiev, D. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2010**, *186*, 38.

(27)   Polozov, A. M.; Polezhaeva, N. A.; Mustaphin, A. H.; Khotinen, A. V.; Arbuzov, B. A. *Synthesis* **1990**, 515.

(28)   Wu, L.; Zhang, X.; Chen, Q.-Q.; Zhou, A.-K. *Org. Biomol. Chem.* **2012**, *10*, 7859.

(29)   Nakamura, S.; Nakagawa, R.; Watanabe, Y.; Toru, T. *J. Am. Chem. Soc.* **2000**, *122*, 11340.

(30)   Hertler, W. R. *J. Org. Chem.* **1974**, *39*, 3219.

(31)   Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4555.

(32)   Geirsson, J. K. F.; Gudmundsson, B. Ö.; Sigurdardottir, R. *Acta Chemica Scandinavica* **1993**, *47*, 1112.

(33)   Nawrath, T.; Gerth, K.; Müller, R.; Schulz, S. *Chem. Biodiversity* **2010**, *7*, 2228.

Graphical Abstract