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Metal-free, hydroacylation of C=C and N=N bonds *via* aerobic C–H activation of aldehydes, and reaction of the products thereof†

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In this report, a thorough evaluation of the use of aerobically initiated, metal-free hydroacylation of various C=C and N=N acceptor molecules with a wide range of aldehydes is presented. The aerobic-activation conditions that have been developed are in sharp contrast to previous conditions for hydroacylation, which tend to use transition metals, peroxides that require thermal or photochemical degradation, or N-heterocyclic carbenes. The mildness of the conditions enables a number of reactions involving sensitive reaction partners and, perhaps most significantly, allows for α-functionalised chiral aldehydes to undergo radical-based hydroacylation with complete retention of optical purity. We also demonstrate how the resulting hydroacylation products can be transformed into other useful intermediates, such as γ-keto-sulfonamides, sultams, sultones, cyclic *N*-sulfonyl imines and amides.

Introduction

The development of methods to construct new chemical bonds efficiently in a selective manner whilst minimising energy usage and production of waste has, arguably, never been of greater importance.[1] Thus, the synthesis of complex molecules using environmentally benign transformations has become a major focus in organic synthesis.[1] Despite recent work on the development of more efficient chemical processes, it is still the case that numerous synthetic transformations are inherently limited as they employ a multi-step mode of reactivity, *i.e.* where a starting material **1** is converted to a desired product **4** *via* a number of intermediates, **2** and **3** (Fig. 1).[2]

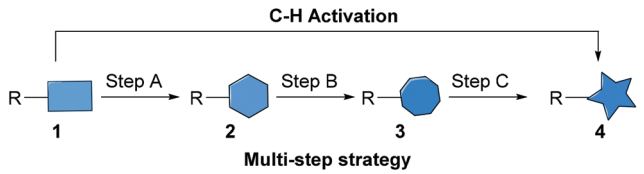

Fig. 1 Strategies for bond formation.

Such an approach depends on: (A) the ease of introduction of a precursor functional group into a starting material (**1**) to give intermediate **2**, (B) ease of precursor (**2**) conversion into an active species (**3**), and (C) selectivity and efficiency of the reaction of the active species to produce the desired product (**4**). Each step in the process introduces inefficiencies that multiply through the multi-step conversion and typically involve the use of additional reagents, which results in increased waste production. An appealing alternative to the modified substrate/reagent approach is that of C–H activation.[2,3] In particular, in recent years, there have been significant developments in remote C–H activation processes using transition metal catalysis.[4]

Although direct C–H activation has been used in the field of radical chemistry there are often significant problems with the selectivity of C–H abstraction,[5–7] and the more successful protocols tend to use a modified substrate/reagent strategy. Moreover, a significant number of the most widely used methods employ expensive, toxic and environmentally damaging reagents or catalysts, and/or large excesses of noxious reagents or solvents.[5–11] Nonetheless, it should still be appreciated that free radical processes have played an important role in synthetic organic chemistry and such methods can offer a complementary approach to the more vigorous conditions often required for two electron processes.[5,12]

In view of the limitations of current strategies toward radical-based C–H activation, we became interested in developing an alternative. Upon examination of the generally accepted mechanism for the auto-oxidation of aldehydes to carboxylic acids, we were intrigued to note that it evokes the formation of

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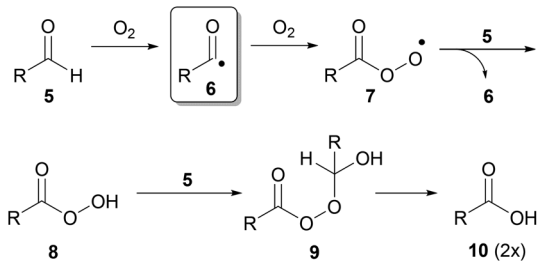
†Electronic supplementary information (ESI) available: ^{1}H, ^{13}C NMR and chiral HPLC spectra (where applicable) of all novel compounds and compounds made by novel procedures. See DOI: 10.1039/c3ob41632a

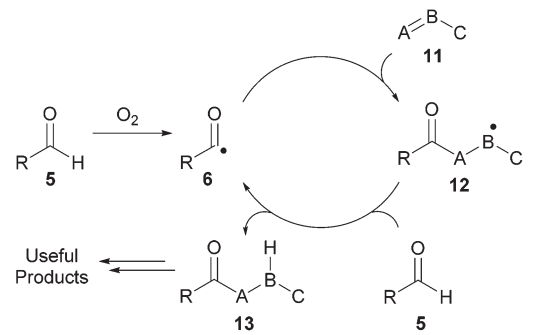


Scheme 1 Aldehyde auto-oxidation pathway.

an acyl radical **6** from an aldehyde **5** *via* the action of molecular oxygen (Scheme 1).[13] In this pathway, the acyl radical **6** reacts with molecular oxygen to form peracyl radical **7**, which then abstracts an H-atom from another molecule of aldehyde regenerating acyl radical **6**. The resultant peroxyacid **8** then reacts with another molecule of aldehyde to afford **9**, which undergoes decomposition to yield two molecules of carboxylic acid **10**.[13]

Although the synthetic applications of acyl radicals are well established[8] and technologies exist for radical based hydroacylation using polarity reversal catalysis or metals,[14–18] there has been limited work on the synthetic applications of aldehyde auto-oxidation.[8,19–21] We have recently described the radical hydroacylation of vinyl sulfonates, sulfones and phosphonates, α,β-unsaturated esters and azodicarboxylates using acyl radicals generated *via* the aldehyde auto-oxidation pathway.[22–26] Efficient C–C and C–N bond formation was achieved under benign conditions by the trapping of acyl radicals (**6**) generated from aldehydes (**5**) with radical acceptors (**11**) to initiate a chain reaction process, leading to the formation of hydroacylation product **13** (Scheme 2). We also described some of the utility of the derived hydroacylation products **13** in a range of further transformations.[24,26]

Herein, we report a thorough evaluation of the use of aerobically initiated hydroacylation with a wide range of aldehydes and double bond acceptor molecules. In our analysis, we examine aldehyde functional group tolerance with the various acceptors and the significance of the rate of aldehyde auto-oxidation on yield. Further evidence for the radical nature of the pathway is also provided. In addition, a series of methods by which the hydroacylation products can be transformed into other useful intermediates, such as γ-keto-sulfonamides, sultams, sultones, cyclic *N*-sulfonyl imines and amides, are also described.



Scheme 2 Mechanism for aerobically initiated hydroacylation.

Results and discussion

Aerobic auto-oxidation of aldehydes to carboxylic acids

Central to our methodology is the aerobic C–H activation of aldehydes. Thus, we sought to explore the rate at which different aldehydes auto-oxidise to their corresponding carboxylic acids (Table 1). To achieve this, a fixed volume of each aldehyde (500 μL) was stirred in the same shaped vessel at the same stirring rate (300 rpm) and the ratio of aldehyde **5** to acid **10** assessed by ^{1}H NMR integration after 2 h. A simple set of aldehydes **5a–j**, a functionally diverse series of aldehydes **5k–t**, aromatic aldehydes **5u–w**, and enantiopure aldehydes **5x–y** were all evaluated under the reaction conditions.

Although it has recently been reported that certain aldehydes (*i.e.* fragrant aldehydes) auto-oxidise at a rate that is partially dependent on their structure,[27] there does not appear to be any obvious relationship between structure of aldehyde and rate of auto-oxidation in the series evaluated in this study. In fact, we observed that aldehydes bearing even minor structural changes brought about significant differences in the rate of acid formation (see Table 1, entries 2 and 24; and 4 and 7). Interestingly, certain aldehydes did not undergo any conversion, even after prolonged reaction times of 24 h (Table 1, entries 10, 19 and 20). Although aldehyde **5y** did undergo appreciable conversion, 32%, it was converted to acetaldehyde and acetic acid rather than its corresponding acid **10y** (Table 1, entry 25).

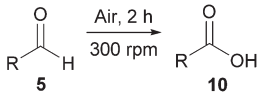
Hydroacylation of pentafluorophenyl vinyl sulfonate (PFP)

Studies toward developing an aerobically initiated hydroacylation protocol began with the hydroacylation of vinyl sulfonate **14**, which has previously been shown to be an excellent radical acceptor.[28] A structurally simple aldehyde that has a mid-range oxidation rate (see Table 1), *n*-butanal **5a**, was chosen as the aldehyde component. Initially a screen of solvents was carried out to determine the optimum solvent (Table 2).

Hydroacylation was most readily affected in ethereal-based solvents such as 1,4-dioxane and ethylene glycol dimethyl ether, and perhaps most significantly, on H_2O. Although the highest yield observed for the hydroacylation of **14** with **5a** was on H_2O, further optimisation of the reaction conditions for our hydroacylation protocol was also continued for 1,4-dioxane as solvent, since the use of H_2O would preclude the use of solid aldehydes. It should also be noted that, in all solvents, addition of radical inhibitor bis(1,1-dimethylethyl)-4-methylphenol (BHT), suppressed reaction significantly.

Following our study on the effect of varying solvent we proceeded to explore the effect of aldehyde stoichiometry on yield. To do this, aldehyde stoichiometry was varied between 1 and 10 equivalent(s) for hydroacylation of **14** with **5a** on H_2O and in 1,4-dioxane (Table 3).

Table 1 Auto-oxidation of aldehyde **5** to acid **10**



5 **10**

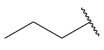
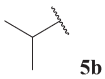
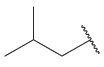
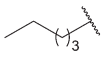
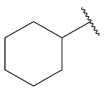
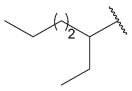
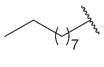
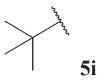
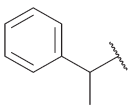
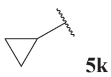
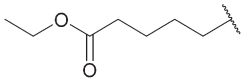
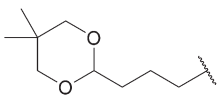
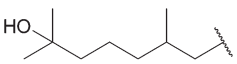
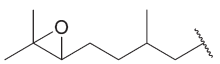
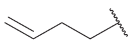
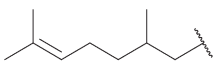
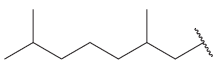
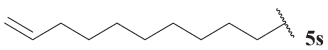
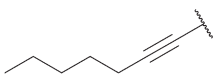
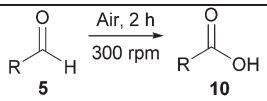
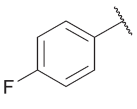
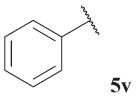
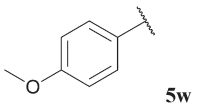
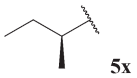
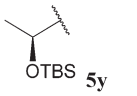
Entry	Aldehyde **5**	**5** : **10**[a]
1	 **5a**	1 : 0.37
2	 **5b**	1 : 1.04
3	 **5c**	1 : 0.39
4	 **5d**	1 : 0.27
5	 **5e**	1 : 0.34
6	 **5f**	1 : 0.50
7	 **5g**	1 : 0.04
8	 **5h**	1 : 1.54
9	 **5i**	1 : 0.99
10	 **5j**	1 : 0.00[b]
11	 **5k**	1 : 0.32
12	 **5l**	1 : 0.40
13	 **5m**	1 : 0.17
14	 **5n**	1 : 0.12
15	 **5o**	1 : 0.25
16	 **5p**	1 : 0.14
17	 **5q**	1 : 0.40
18	 **5r**	1 : 0.44
19	 **5s**	1 : 0.00[b]
20	 **5t**	1 : 0.00[b]

Table 1 *(Contd.)*

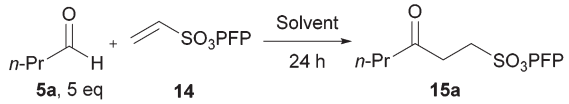


5 **10**

Entry	Aldehyde **5**	**5** : **10**[a]
21	 **5u**	1 : 0.34
22	 **5v**	1 : 0.32
23	 **5w**	1 : 0.02
24	 **5x**	1 : 0.12
25	 **5y**	1 : 0.00[c]

Conditions: aldehyde **5** (500 μL) stirred at 300 rpm at 21 °C for 2 h unless otherwise stated. [a] Ratio of aldehyde **5** to acid **10** after 2 h stirring of aldehyde **5** (500 μL) at 300 rpm determined through comparison of the ^{1}H NMR integration of aldehyde **5** and acid **10**. It should also be noted that not stirring, significantly reduced the rate of auto-oxidation. As certain aldehydes were contaminated with a minor amount of acid, the ratios quoted are relative to the initial ratio of aldehyde to acid (where applicable). [b] No conversion of aldehyde observed, even after 24 h. [c] 32% Conversion of aldehyde but no corresponding acid formation observed by integration of ^{1}H NMR relative to pentachlorobenzene as an internal standard.

Table 2 Hydroacylation of vinyl sulfonate **14** with aldehyde **5a** in various solvents



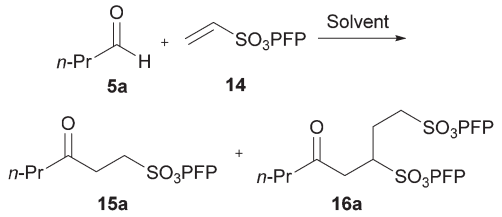
5a, 5 eq **14** **15a**

Solvent	Conversion of **14**/%	Yield **15a**/%
1,4-Dioxane	100	65
Et_2O	40	13
CH_2Cl_2	82	39
$CH_3OCH_2CH_2OCH_3$	100	64
THF	64	28
PhMe	71	25
DMF	82	30
MeOH	12	4
H_2O	100	78

Conditions: *n*-butanal **5a** (5 mmol) and vinyl sulfonate **14** (1 mmol) were stirred at 300 rpm in solvent (1 mL) at 21 °C for 24 h.

In 1,4-dioxane, maximum yield of ketone **15a** was observed with 5 equivalents of aldehyde, whereas on H_2O there was no vast improvement in yield when using greater than 2 equivalents of aldehyde. As such, the use of 5 equivalents of

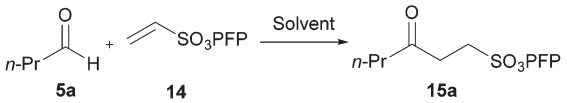
Table 3 Hydroacylation of vinyl sulfonate **14** with aldehyde **5a** with various equivalents of aldehyde **5a**



Solvent	5a/eq.	Conversion 14/%	Yield 15a[a]/%	15a : 16a[b]
1,4-Dioxane	10	100	64	1 : 0.12
	5	100	65	1 : 0.13
	4	100	57	1 : 0.16
	3	95	50	1 : 0.20
	2	75	37	1 : 0.27
	1	52	26	1 : 0.40
H_2O	10	100	80	1 : 0.04
	5	100	77	1 : 0.04
	4	100	79	1 : 0.03
	3	100	78	1 : 0.04
	2	100	78	1 : 0.05
	1	75	47	1 : 0.14

Conditions: *n*-butanal **5a** and vinyl sulfonate **14** (1 mmol) on H_2O or in 1,4-dioxane were stirred at 300 rpm for 24 h. [a] Determined by integration of ^{1}H NMR relative to pentachlorobenzene as an internal standard. [b] Determined by ^{1}H NMR integration.

Table 4 Hydroacylation of vinyl sulfonate **14** with aldehyde **5a** after various times



Solvent	Time/h	Yield 15a[a]/%
1,4-Dioxane	0.5	49
	1	65
	2	64
	3	65
	4	63
	6	65
	8	65
	16	66
	24	64
H_2O	0.5	60
	1	70
	2	75
	3	78
	4	79
	6	82
	8	79
	16	80
	24	81

Conditions for reactions in 1,4-dioxane: *n*-butanal **5a** (5 mmol) and vinyl sulfonate **14** (1 mmol) were stirred at 300 rpm in 1,4-dioxane at 21 °C for the time specified. Conditions for reactions on H_2O: *n*-butanal **5a** (5 mmol) and vinyl sulfonate **14** (1 mmol) were stirred at 300 rpm in H_2O at 21 °C for the time specified. [a] Determined by integration of ^{1}H NMR relative to pentachlorobenzene as an internal standard.

aldehyde in 1,4-dioxane, and 2 equivalents of aldehyde on H_2O were chosen as the optimal stoichiometries to proceed with. The major limitation on yield where fewer equivalents of aldehyde were employed was the increased formation of double addition product **16a**.

We next sought to evaluate reaction time by determining yield of ketone **15a** for the hydroacylation of **14** with **5a** in the H_2O and 1,4-dioxane conditions at 0.5, 1, 2, 3, 4, 6, 8, 16 and 24 h (Table 4). It was determined that the optimal reaction times in the 1,4-dioxane and H_2O conditions were 1 h and 3 h, respectively, with longer reactions having no significant effect on yield.

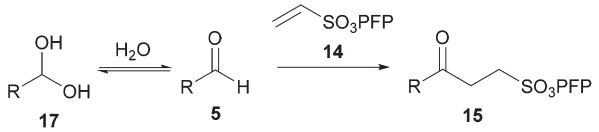
With our optimised conditions in hand we sought to evaluate the generality of our aerobically initiated hydroacylation protocol with respect to aldehyde auto-oxidation rate. Thus, aldehydes **5a–j** were specifically chosen to test this particular parameter as they exhibited a broad range of oxidation rates (see Table 1) and did not bear any complicating structural functionality. These aldehydes were also selected in view of their wide range of hydration equilibrium constants[29,30] and their broad range of solubilities in water,[31] in order to evaluate whether these parameters had any impact on yield of ketone in the water-based reaction conditions (Table 5).

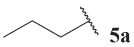
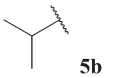
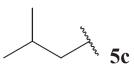
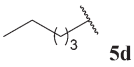
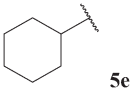
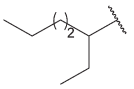
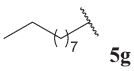
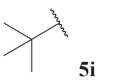
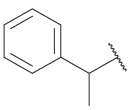
In both the 1,4-dioxane and water conditions, moderate to good yields of ketone were observed across the series with the exception of aldehydes **5b**, **5h** and **5j**. The absence of any strong correlation between yield of ketone and the extent of hydration and/or solubility, except in exceptional circumstances (*e.g.* acetaldehyde **5h**), was particularly pleasing as it showed that these parameters are fairly insignificant for efficient hydroacylation to transpire on water.

The moderate yields observed for the hydroacylation of isobutyraldehyde **5b** was attributed to the propensity of this aldehyde to undergo auto-oxidation rapidly, therefore resulting in poor trapping of its corresponding acyl radical by alkene **14**. This hypothesis is supported by the sub-optimal conversion of alkene **14** and complete conversion of aldehyde under the reaction conditions. A similar rationale may also be applied to explain the low yield of ketone **15h** observed on application of aldehyde **5h** in the 1,4-dioxane conditions. Interestingly, in the water-based conditions, the attempted hydroacylation of acetaldehyde **5h** afforded no ketone and gave no alkene conversion with complete conversion of aldehyde. This result can, however, be rationalised in that acetaldehyde is completely soluble in water[31] and is also known to readily react with water to form a hydrate. These characteristics of acetaldehyde thus prevent hydroacylation from ensuing when using water as solvent.

Aldehyde **5j**, which did not appear to auto-oxidise in our previous study (see Table 1), underwent no conversion in both reaction conditions (even after 72 h), and therefore resulted in 0% conversion of vinyl sulfonate **14** (see Table 5). Even heating to higher temperatures, increasing aldehyde loading or increasing reaction time did not improve conversion of aldehyde and/or yield of ketone **15j**.

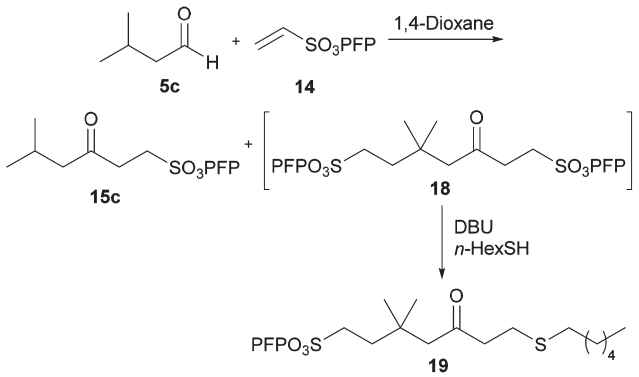
Table 5 Hydroacylation of vinyl sulfonate **14** with aldehydes **5a–j**



Aldehyde **5**	**5** : **17** in D_2O[a]	Solubility of **5**[c]/mass%	Yield **15** (H_2O)[d]/%	Yield **15** (1,4-dioxane)[d]/%
 **5a**	1 : 1.04	5.48	78	65
 **5b**	1 : 0.86	4.57	40 (60)	58 (95)
 **5c**	1 : 0.66	1.78	74	58
 **5d**	1 : 0.98	0.44	75	68
 **5e**	1 : 0.54	—	74	47
 **5f**	1 : 0.03[b]	0.05	83	69
 **5g**	1 : 0.12[b]	0.02	62	54
 **5h**	1 : 4.85	—	0 (0)	37 (60)
 **5i**	1 : 0.01[b]	—	54 (75)	5 (80)
 **5j**	1 : 0.03[b]	—	0 (0)	0 (0)

Conditions for reactions in 1,4-dioxane: *n*-butanal **5a** (5 mmol) and vinyl sulfonate **14** (1 mmol) were stirred at 300 rpm in 1,4-dioxane (1 mL) at 21 °C for the time specified in the ESI. Conditions for reactions on H_2O: *n*-butanal **5a** (2 mmol) and vinyl sulfonate **14** (1 mmol) were stirred at 300 rpm in H_2O (1 mL) at 21 °C for the time specified in the ESI. [a] Ratio determined by ^1H NMR integration in D_2O. [b] Due to poor solubility of aldehyde in D_2O, a DMSO–D_2O (1 : 1) mixture was used. [c] Solubility of aldehyde in H_2O at 30 °C. [d] All reactions proceeded with 100% conversion of **14** unless otherwise stated in parenthesis.

The generally higher yields observed on water may be attributed to the higher concentration of reagents in the water-based reaction conditions, perhaps due to a hydrophobic effect. This may result in the radical intermediates under these conditions having a shorter lifetime, resulting in less unfavourable unimolecular degradation pathways ensuing. This hypothesis may also be supported by the noticeably lower yields of ketone observed when using α-substituted aldehydes **5e** and **5f** and α,α-disubstituted aldehyde **5i** in the 1,4-dioxane conditions. Presumably, their corresponding acyl radicals, in the 1,4-dioxane conditions, have a longer lifetime and undergo more unfavourable decarbonylation. This is particularly evident for the hydroacylation of pivaldehyde **5i** where 58% of decarbonylation addition product was observed and only 5% of hydroacylation product was isolated. Further support for this hypothesis is the noticeably lower yield observed in 1,4-dioxane for the hydroacylation of **14** with isovaleraldehyde **5c**. The low yield of ketone **15c** was due to the formation of species **18**, which is almost certainly derived from acyl radical addition to **14**, followed by intramolecular hydrogen atom abstraction, addition to another molecule of vinyl sulfonate **14** and intermolecular H-atom abstraction. Although we were unable to isolate ketone **18**, we were able to carry out an elimination–addition sequence to afford ketone **19**, and therefore indirectly confirm its structure (Scheme 3).

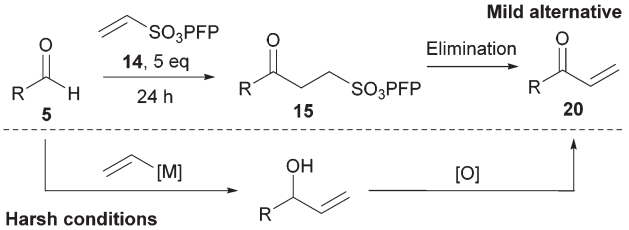


Scheme 3 Formation of by-product **18** in the 1,4-dioxane conditions and elimination–addition on ketone **18** to afford species **19**.

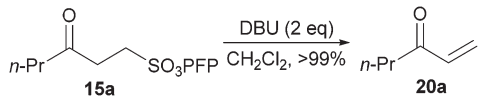
Synthetic utility of γ-keto-PFP-sulfonates

The disposition of the functional groups in a γ-keto-PFP-sulfonate motif strongly suggests that this bi-functional motif has appreciable potential for further manipulation. The carbonyl group is a versatile moiety that can be used in various synthetic transformations and, through the work pioneered by our group, PFP-sulfonates have been shown to be useful alternatives to sulfonyl chlorides for the synthesis of sulfonamides.[32–35]

a. Elimination of PFP-sulfonate to form enones. From the outset, the elimination of sulfonate from ketone **15** to form enone **20** was seen as a highly desirable transformation as, in conjunction with the hydroacylation chemistry, it represents a mild overall method of converting an aldehyde to an enone (Scheme 4). This is particularly relevant as, at present, aldehydes are commonly converted to enones *via* the addition of a



Scheme 4 An alternative route to gain access to enones from aldehydes.



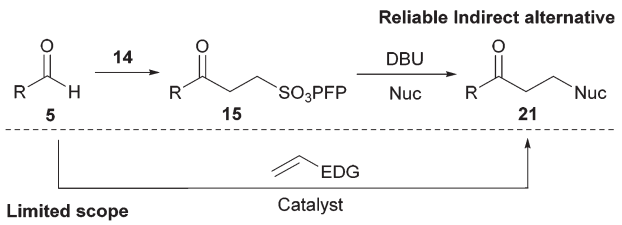
Scheme 5 Elimination of sulfonate from **15a** to form enone **20a**.

vinylic metal species to form an allylic alcohol, which is then oxidised (Scheme 4),[36] *i.e.* relatively harsh reaction conditions. Thus, a mild alternative to achieve the same overall transformation is highly attractive.

Keto-sulfonate **15a** was chosen as our model γ-keto-PFP-sulfonate to explore elimination to an enone. Encouragingly, elimination was achieved under basic conditions *via* the application of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2 equivalents). Quantitative conversion of keto-sulfonate **15a** to enone **20a** was readily confirmed by ^{1}H NMR, relative to pentachlorobenzene as an internal standard (Scheme 5).[37] However isolation was not effected due to the rapid polymerisation of terminal enones upon concentration after purification. Ketone **15a** was also subjected to a range of acidic conditions (acetic acid, *para*-toluenesulfonic acid and pyridinium *para*-toluenesulfonate) in various solvents (*i.e.* CH_2Cl_2, $CHCl_3$, MeOH, Et_2O, PhMe and THF), but was found to be highly stable with complete recovery of **15a** being observed in all cases.

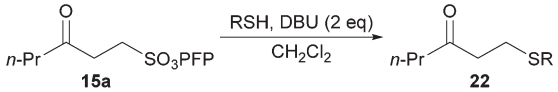
b. Elimination–addition as an indirect alternative to the hydroacylation of electron-rich alkenes. We envisaged that the conjugate addition of nucleophiles to the enones generated by elimination of sulfonate from keto-sulfonates may provide an indirect, reliable alternative to the hydroacylation of electron rich alkenes (Scheme 6). Current strategies toward the hydroacylation of electron rich alkenes require the use of a polarity reversal catalyst and are often low to moderate yielding.[8,16,38,39] Moreover, as elimination is essentially quantitative and there is a plethora of literature on the conjugate addition of various nucleophiles to enones,[40] we believe we can access motifs such as **21** rapidly and in high yields.

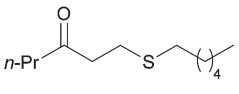
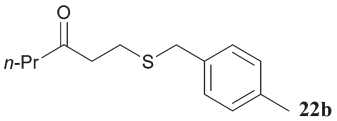
Through our strategy, it should also be possible to access a variety of unsymmetrical ketones, which would otherwise represent a significant challenge to current methods for the hydroacylation of electron rich alkenes, due to insurmountable polarity mis-match. A case in point is the direct hydroacylation of vinyl sulfides, a transformation that has, to the best of our knowledge, no literature precedent despite the emergence of thiol polarity reversal catalysis.[38] Encouragingly, however, the indirect hydroacylation–elimination–addition strategy



Scheme 6 An indirect alternative to the hydroacylation of electron-rich alkenes.

Table 6 Conversion of ketone **15a** to γ-keto-sulfides **22**



γ-Keto-sulfide **22**	Isolated yield/%
 **22a**	98
 **22b**	97

Conditions: ketone **15a**, DBU (2 eq.), thiol (1.3 eq.), CH_2Cl_2, 21 °C.

described above does provide access to these molecules, and in excellent yields (Table 6).

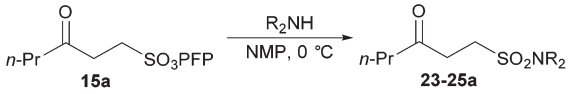
c. Formation of γ-keto-sulfonamides, sultams and sultones from γ-keto-PFP-sulfonates. We next explored the possibility of converting γ-keto-sulfonates into γ-keto-sulfonamides. To do this, initially we applied our previously reported conditions for sulfonamide synthesis from PFP-sulfonates (DBU, amine in THF)[33] to the conversion of PFP-sulfonate **15a** into its *n*-hexylamine sulfonamide analogue **23a**. However, perhaps unsurprisingly, keto-sulfonate **15a** underwent almost exclusive elimination to its corresponding enone under these reaction conditions. Application of a weaker base, triethylamine, also appeared to promote enone formation and generated minimal sulfonamide **23a** (*ca.* 10%).

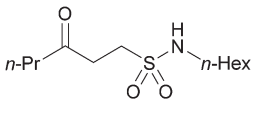
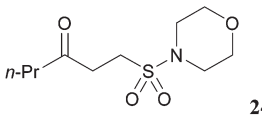
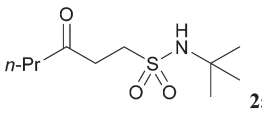
In an attempt to facilitate further formation of sulfonamide **23a** the use of more polar solvents was explored. Encouragingly, application of NMP as solvent gave desired sulfonamide **23a** in 45% yield, with the major side-product being enone derived. Lowering the temperature at which the amine was added, 0 °C, suppressed elimination and resulted in an improved yield of 64%. To further suppress elimination, an additional equivalent of the nucleophilic amine was used in place of triethylamine, as it did not promote elimination. To our delight, this resulted in a yield of 82%. The reaction protocol was then applied to a secondary amine and a sterically encumbered primary amine, morpholine and *tert*-butylamine, respectively (Table 7). Although this only afforded modest yields of sulfonamides **24a** and **25a**, the protocol provides reliable access to γ-keto-sulfonamides.

We also proceeded to show that secondary sulfonamide **23a** could be converted into sultam **26**, in a one-pot reductive-cyclisation protocol, in excellent yield (Scheme 7). It is envisaged that a wide range of similar sultams may be synthesised in an analogous manner.

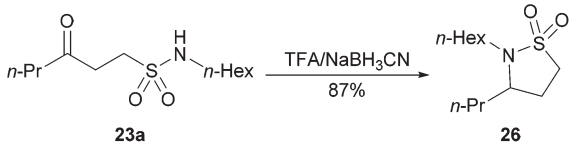
We next turned our attention to the synthesis of cyclic *N*-sulfonyl imines of the form of **27**. Previously, they have been accessed *via* a three step protocol reported by Freitag in 63–68% overall yield.[41] However, we were able to achieve direct access to *N*-sulfonylimine **27** *via* the bubbling of ammonia gas

Table 7 Conversion of ketone **15a** to sulfonamides **23–25a**

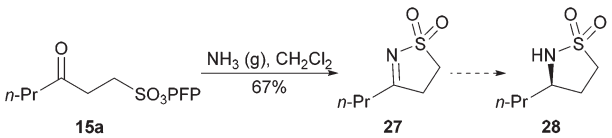


Sulfonamide	Isolated yield/%
 **23a**	82
 **24a**	32
 **25a**	40

Conditions: ketone **15a**, amine (2 eq.), NMP, 0 °C to 21 °C.



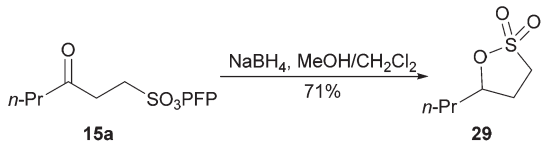
Scheme 7 Reductive cyclisation of **23a** to afford sultam **26**.



Scheme 8 Formation of cyclic *N*-sulfonylimine **27** from ketone **15a**.

into a solution of γ-keto-sulfonate **15a** in CH_2Cl_2 in 67% yield (Scheme 8). Unlike the protocol outlined by Freitag, this method represents a simple and mild route to cyclic *N*-sulfonylimines in which analogue synthesis should be facile. Furthermore, through the work pioneered by Zhou, access to 3-substituted chiral sultams of the form of sultam **28** should be facile.[42] The molecules generated by Zhou's asymmetric hydrogenation protocol are important organic synthetic intermediates and structural units of agricultural and pharmaceutical agents.[43]

Finally, we envisaged that access to sultones could be achieved by reduction of the ketone moiety in keto-sulfonate **15a**. Gratifyingly, sodium borohydride reduction of the carbonyl group in keto-sulfonate **15a** gave access to sultone **29** in good yield (Scheme 9).



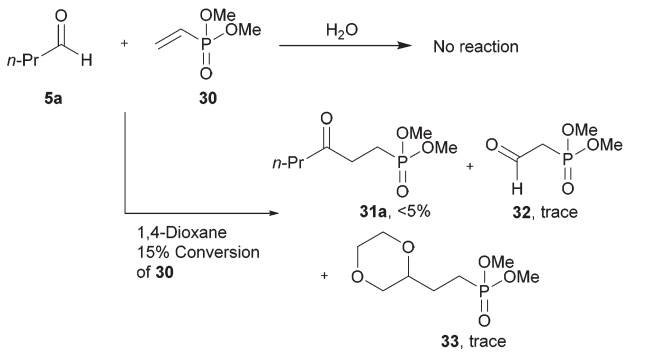
Scheme 9 Formation of sultone **29** from ketone **15a**.

Hydroacylation of vinyl phosphonates

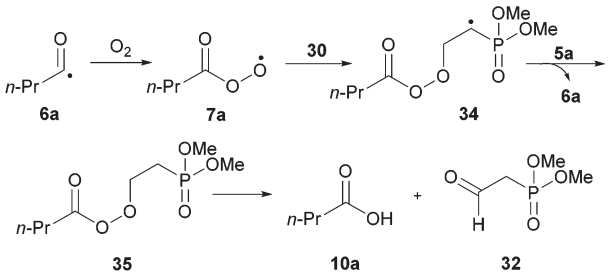
We were particularly interested in the hydroacylation of vinyl phosphonates as γ-ketophosphonates, and their corresponding phosphonic acids, have been established as useful tools in both synthetic chemistry[44,45] and biology as non-hydrolysable phosphate mimetics.[46–49] Thus, we applied our optimised protocols for the efficient hydroacylation of vinyl sulfonate **14** to the hydroacylation of vinyl phosphonate **30** (Scheme 10). As in the case for the optimisation of the hydroacylation of vinyl sulfonate **14**, *n*-butanal **5a** was chosen as the aldehyde component in the initial reactions.

Although no ketone was observed using the water-based conditions, γ-ketophosphonate **31a** was isolated using 1,4-dioxane as solvent, albeit in very low yield (Scheme 10). In both cases, complete conversion of aldehyde **5a** was observed. The lack of ketone observed in water was thought to be due to the water solubility of vinyl phosphonate **30**. The low yield in 1,4-dioxane was attributed to inefficient trapping of the acyl radicals generated under the reaction conditions by alkene **30**, as evidenced by the complete conversion of aldehyde and very low conversion of alkene, 15%. Careful examination of the crude ^{1}H NMR spectrum of the reaction in the 1,4-dioxane also indicated the formation of aldehyde **32** and phosphonate **33**. Phosphonate **33** is presumably formed *via* 1,4-dioxane radical addition to vinyl phosphonate **30**. Whereas aldehyde **32** is most likely the result of peracyl radical **7a** addition to vinyl phosphonate **30**, to form **34**, followed by aldehydic hydrogen atom abstraction to form peroxide **35**, which then decomposes to aldehyde **32** and an equivalent of butanoic acid **10a** (Scheme 11).

Despite the low yield observed for the hydroacylation of vinyl phosphonate **30** with *n*-butanal **5a** at 21 °C in 1,4-dioxane (Scheme 10) we were sufficiently intrigued to embark upon an optimisation study. As *n*-butanal had been completely converted to its corresponding acid under the reaction conditions and the conversion of alkene was very low, we envisaged that



Scheme 10 Attempted hydroacylation of vinyl phosphonate **30** with *n*-butanal **5a** in 1,4-dioxane and water.



Scheme 11 Proposed mechanism for the formation of aldehyde **32**.

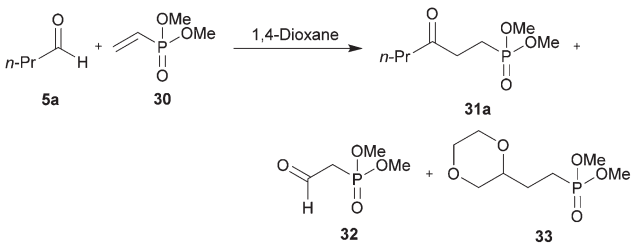
controlling exposure of the reaction mixture to molecular oxygen was key to achieving efficient hydroacylation. Moreover, this would also allow us, to some extent, suppress the formation of aldehyde **32**. We rationalised that control of the dissolved molecular oxygen concentration and exposure of the reaction mixture to air could be readily achieved by varying reaction temperature and the surface area to volume ratio (Table 8).

Gratifyingly, increasing the reaction temperature had a dramatic impact on yield of γ-ketophosphonate **31a** with optimal yield afforded at 60 °C, 70%, at 1.00 mol dm^{-3} (Table 8, entry 7); heating to higher temperatures did not affect yield significantly (Table 8, entries 10 and 11). The increase in yield with increasing temperature was attributed to the lower concentration of dissolved molecular oxygen. This promotes acyl radical trapping by vinyl phosphonate **30** rather than with molecular oxygen, resulting in higher conversion of alkene and a higher yield of γ-ketophosphonate **31a**. The lower yields observed at 60 °C at concentrations above and below 1.00 mol dm^{-3} may be rationalised by increased formation of aldehyde **32** and phosphonate **33**, respectively. The higher surface area to volume ratio at higher concentrations results in an increased exposure to air and hence promotes the likelihood of an acyl radical being trapped by molecular oxygen rather than by an alkene, thus lowering the yield of γ-ketophosphonate **31a** and decreasing the **31a : 32** ratio (Table 8, entries 5–7). Unsurprisingly, at lower concentrations, a decreased **31a : 33** ratio was observed due to the greater relative concentration of 1,4-dioxane to vinyl phosphonate **30**, consequently, lowering the yield of γ-ketophosphonate **31a** and increasing the yield of yield of **33** (Table 8, entries 7–9).

With optimised conditions in-hand, we then examined the scope of hydroacylation of vinyl phosphonate **30**. The same set of functionally simple aldehydes that exhibit a broad range of auto-oxidation rates, **5a–j**, employed in the analysis of vinyl sulfonate **14** (see Table 5) were applied to reaction with **30**.

In general, moderate to good yields were observed across the aldehyde series. The major exceptions to this were the relatively low yields observed for aldehydes **5b** and **5h**, and the absence of ketone formed on application of aldehydes **5i** and **5j**. The low yields observed for aldehydes **5b** and **5h** may be rationalised by the propensity of these aldehydes to undergo rapid auto-oxidation, thus resulting in inefficient acyl radical trapping by alkene **30**. This hypothesis is supported by the complete conversion of aldehyde and low conversion of alkene observed in both cases. The absence of the formation of γ-ketophosphonate **31i** for the hydroacylation of vinyl phosphonate **30** with pivaldehyde **5i** was due to the significant amount of *tert*-butyl radical addition that took place under the reaction conditions, resulting in the formation of dimethyl

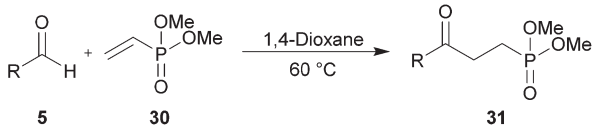
Table 8 Hydroacylation of vinyl phosphonate **30** with aldehyde **5a** at various temperatures and concentrations



Entry	*T*/°C	[**30**][a]/mol dm^{-3}	Surface area/cm^2 : volume[b]/cm^3	Conversion **30**[c]/%	**31a : 32 : 33**[c]	Isolated yield **31a**/%
1	20	1.00	1 : 0.32	15	—	<5
2		0.25	1 : 1.29	15	—	<5
3	40	1.00	1 : 0.32	60	—	35
4		0.25	1 : 1.29	65	—	25
5	60	5.00	1 : 0.06	100	1 : 0.27 : 0.07	61
6		2.00	1 : 0.16	100	1 : 0.19 : 0.08	67
7		**1.00**	1 : 0.32	**100**	**1 : 0.18 : 0.09**	**70**
8		0.50	1 : 0.64	100	1 : 0.16 : 0.10	60
9		0.25	1 : 1.29	100	1 : 0.10 : 0.14	55
10	80	1.00	1 : 0.32	100	—	69
11		0.25	1 : 1.29	100	—	57

Conditions: vinyl phosphonate **30** (1 mmol), *n*-butanal **5a** (5 mmol), 1,4-dioxane (see table), temperature (see table), 24 h. [a] Concentration of **30** refers to initial concentration of **30** in 1,4-dioxane before addition of **5a**. [b] Surface area refers to surface area exposed to air. [c] Determined by integration of ^{1}H NMR relative to pentachlorobenzene as an internal standard.

Table 9 Hydroacylation of vinyl phosphonate **30** with aldehydes **5a–j**



5 **30** **31**

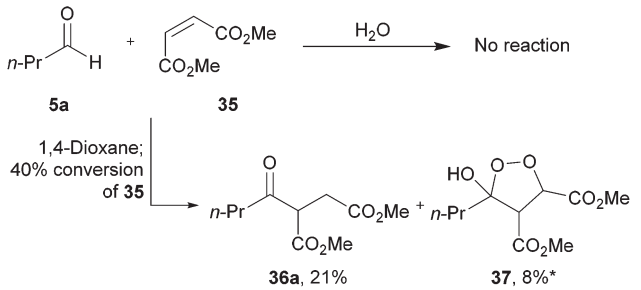
Aldehyde **5**	Conversion **30**/%	Isolated yield **31**/%[a]
5a	100	70
5b	65	40
5c	100	65
5d	100	72
5e	100	60
5f	100	52
5g	100	55
5h	38	21
5i	60	0[b]
5j	0	0

Conditions: vinyl phosphonate **30** (1 mmol), aldehyde **5** (5 mmol), 1,4-dioxane (1 mL), 60 °C, 24 h. [a] Isolated yield unless otherwise stated. [b] Dimethyl (3,3-dimethylbutyl)phosphonate isolated in 46% yield.

(3,3-dimethylbutyl)phosphonate in 46% yield (see Table 9 and ESI†). The *tert*-butyl radical is presumably derived from decarbonylation of the acyl radical formed from pivaldehyde oxidation. Consistent with our previous study on the hydroacylation of vinyl sulfonate **14** (see Table 5), aldehyde **5j** gave 0% conversion of alkene since no aldehyde was oxidised.

Hydroacylation of α,β-unsaturated esters

We next applied our methodology to the hydroacylation of α,β-unsaturated esters to generate 1,4-dicarbonyls, which are extremely useful intermediates. To investigate this, we initially applied our optimised protocols for the efficient hydroacylation of vinyl sulfonate **14** to the hydroacylation of 1,2-diester alkene **35** (Scheme 12), which has classically shown promise as an acyl radical acceptor.[8] As in the case for the hydroacylation of vinyl sulfonate **14** and vinyl phosphonate **30**, *n*-butanal was selected as the aldehyde component in these reactions.

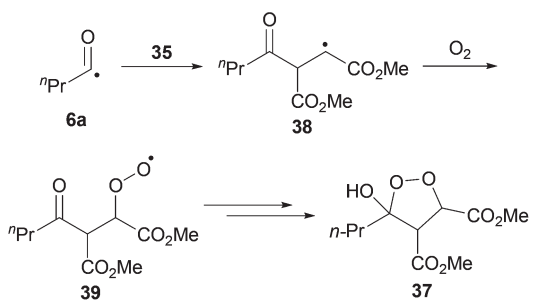


Scheme 12 Attempted hydroacylation of alkene **35** with *n*-butanal **5a** in 1,4-dioxane and water. *Determined by integration of ^{1}H NMR relative to pentachlorobenzene as an internal standard by analogy with similar products.

We were pleased to isolate ketone **36a** in the 1,4-dioxane conditions, albeit in low yield. However, no ketone was isolated from the water-based conditions. The lack of ketone under the water conditions was thought to be due to inefficient trapping of the acyl radical with alkene **35** as complete conversion of aldehyde and low conversion of alkene was observed under the reaction conditions. This may be a consequence of the exposure to molecular oxygen in the water conditions being much higher than in 1,4-dioxane, and too high to be compatible with alkene **35**. Also isolated from the crude reaction mixture in the 1,4-dioxane conditions was cyclic peroxide **37**, which is presumably derived from addition of molecular oxygen to the adduct radical formed by addition of acyl radical **6a** to alkene **38**, to form **39**, which then undergoes cyclisation and H-atom abstraction to form the cyclic peroxide (Scheme 13).

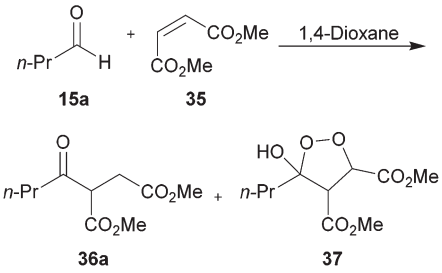
As in the case for the hydroacylation of vinyl phosphonate **30**, in the 1,4-dioxane conditions, *n*-butanal had been completely converted under the reaction conditions and the conversion of alkene was very low. Thus, we again rationalised that controlling the exposure of the reaction mixture to molecular oxygen by manipulating reaction temperature and concentration would be vital for efficient hydroacylation.

Increasing the temperature from 20 °C to 60 °C gave an increase in the yield of ketone **36a**, although heating to higher temperatures led to decomposition of the ketone product (Table 10). The increase in yield observed at higher temperature was thought to be a consequence of the lower concentration of dissolved molecular oxygen in solution. This would



Scheme 13 Proposed mechanism for the formation of peroxide **37**.

Table 10 Hydroacylation of alkene **35** with aldehyde **5a** at various temperatures



Temperature/°C	Conversion **35**/%[a]	Yield **36a**/%[a]	**36a** : **37**[a]
20	40	21	1 : 0.38
40	60	27	1 : 0.25
60	**60**	**35**	**1 : 0.19**
80	85	24	1 : 0.15

Conditions: alkene **35** (1 mmol), *n*-butanal **5a** (5 mmol), 1,4-dioxane (0.5 mL), temperature, 8 days. [a] Determined by integration of ^{1}H NMR relative to pentachlorobenzene as an internal standard.

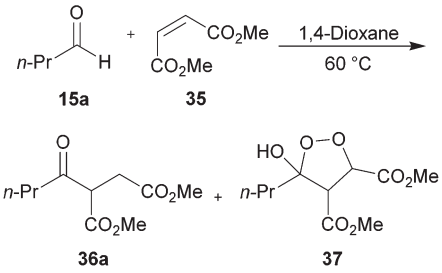
result in a higher conversion of alkene **35** as an acyl radical would more likely be trapped by an alkene than react with molecular oxygen; thus resulting in a higher yield of **36a**. Moreover, the lower concentration of molecular oxygen also decreased the **36a** : **37** ratio from 1 : 0.38 to 1 : 0.15 in the 20–80 °C range. This is likely to be a consequence of adduct radical **38** in the reaction mechanism (see Scheme 13) having a greater propensity to abstract an aldehydic hydrogen atom than undergo addition to molecular oxygen; thus suppressing formation of peroxide and encouraging formation of ketone **36a**.

It was also reasoned that the surface area to volume ratio may have a significant impact on the exposure of the reaction medium to air, and thus, the effect of changing surface area : volume was explored (Table 11). For reasons analogous to those discussed for vinyl phosphonate **30**, as the surface area to volume ratio decreased, higher conversion of alkene **35**, decreased formation of cyclic peroxide **37**, and a higher yield of ketone **36a** was observed. Optimal yield for the hydroacylation of dimethyl maleate **35** with *n*-butanal **5a** was observed at 0.33 mol dm^{-3}.

A similar trend in yields, to that obtained for the hydroacylation of dimethyl maleate **35** with *n*-butanal **5a** with respect to changing surface area:volume, was observed for the hydroacylation of diethyl maleate **40** and dimethyl fumarate **41** with *n*-butanal **5a** (Table 12). The good yields observed for the hydroacylation of diethyl maleate **40** and dimethyl fumarate **41** also showed that the efficiency of the hydroacylation protocol is, to some extent, independent of the nature of the ester and/or alkene geometry (*E*/*Z*).

With a view to increase the scope of 1,4-dicarbonyls that can be formed by our methodology, we applied our optimised conditions to the hydroacylation of 1,1-diester alkene **43** and 2-alkoxy-1,1-diester alkene **45**. Gratifyingly, very good yields of ketones **44a** and **46a**, respectively, were obtained (Scheme 14).

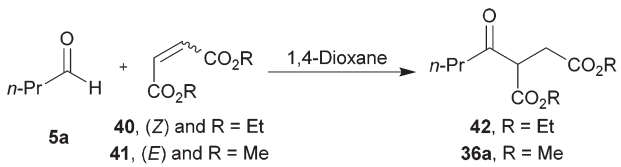
Table 11 Hydroacylation of alkene **35** with aldehyde **5a** at various concentrations



[**35**][a]/ mol dm^{-3}	Surface area / cm^2 : volume[b]/cm^3	Conversion[c]/%	Yield **36a**[c]/%	**36a** : **37**[c]
5.00	1 : 0.06	50	37	1 : 0.34
2.00	1 : 0.16	60	35	1 : 0.22
1.00	1 : 0.32	85	50	1 : 0.07
0.50	1 : 0.64	100	64	1 : 0.05
0.33	**1 : 0.96**	**100**	77	**1 : 0.04**
0.25	1 : 1.29	100	74	1 : 0.03
0.20	1 : 1.61	100	70	1 : 0.03

Conditions: alkene **35** (1 mmol), *n*-butanal **5a** (5 mmol), 1,4-dioxane (see table), 60 °C, 8 days. [a] Concentration of **35** refers to initial concentration of **35** in 1,4-dioxane before addition of **5a**. [b] Surface area refers to surface area exposed to air. [c] Determined by integration of ^{1}H NMR relative to pentachlorobenzene as an internal standard.

Table 12 Hydroacylation of alkenes **40** and **41** with aldehyde **5a** at various concentrations

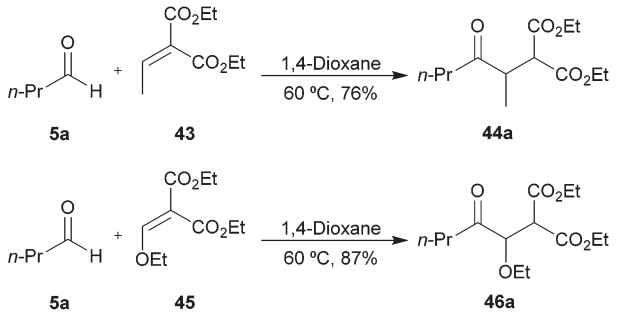


[Alkene][a]/ mol dm^{-3}	Surface area / cm^2 : volume[b]/cm^3	Isolated yield **42**/%	Isolated yield **36a**/%
2.00	1 : 0.16	47	30
0.33	1 : 0.96	68	62
0.20	1 : 1.61	55	50

Conditions: alkene (1 mmol), *n*-butanal **5a** (5 mmol), 1,4-dioxane (see table), 60 °C, 8 days. [a] Concentration of alkene refers to initial concentration of alkene in 1,4-dioxane before addition of **5a**. [b] Surface area refers to surface area exposed to air.

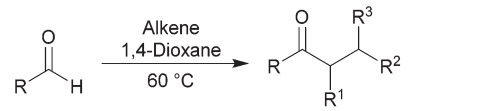
We were particularly encouraged by the excellent yield of ketone **46a** since it demonstrates the mild nature of our protocol as one might imagine that this species is prone to elimination under ionic conditions. Thus, our protocol gives us access to products that would otherwise be challenging to synthesise *via* alternative ionic-based methods.

Having established optimised conditions for the hydroacylation of a range of α,β-unsaturated esters with *n*-butanal **5a**, we next explored aldehydes with a range of auto-oxidation rates, **5a–j** (Table 13).



Scheme 14 Hydroacylation of alkenes **43** and **45** with aldehyde **5a**.

Table 13 Hydroacylation of alkenes **35**, **43** and **45** with aldehydes **5a–j**



5

36, R^1, $R^2 = CO_2Me$ and $R^3 = H$
44, $R^1 = Me$ and R^2, $R^3 = CO_2Et$
46, $R^1 = OEt$ and R^2, $R^3 = CO_2Et$

Entry	Aldehyde **5**	Ketone **36**	Ketone **44**	Ketone **46**
1	**5a**	70	76	87
2	**5b**	21	42	0
3	**5c**	57	60	85
4	**5d**	76	72	87
5	**5e**	56	74	24
6	**5f**	25	52	0
7	**5g**	60	72	89
8	**5h**	0	0	0
9	**5i**	0	0	0
10	**5j**	0	0	0

Conditions: alkene (1 mmol), aldehyde **5** (5 mmol), 1,4-dioxane (3 mL), 60 °C.

In all cases, and perhaps as expected, aldehydes that rapidly auto-oxidise to acid (*i.e.* aldehydes **5b**, **5h** and **5i**, see Table 1) gave low or no yield of ketone due to inefficient trapping of their corresponding acyl radicals by alkenes compared to the rate of direct auto-oxidation. Moreover, in concert with our previous studies, aldehyde **5j**, yielded no ketone and underwent no observable conversion to acid.

As expected, owing to the more electrophilic nature of 1,1-diester alkene **43** compared with 1,2-diester alkene **35** and the inherently more electrophilic adduct radical formed upon acyl radical addition, higher yields were generally observed for the hydroacylation of alkene **43** over alkene **35**. It was also notable that reaction with 1,2-diester alkene **35** over 1,1-diester alkene **43** appeared to be more sensitive to steric hindrance, as evidenced by the yields observed for reaction with a variety of α-substituted aldehydes (Table 13, entries 2, 5 and 6).

Interestingly, we were able to isolate various sensitive ketones, formed by the hydroacylation of alkene **45** with linear aldehydes **5a**, **5c**, **5d** and **5g** in excellent yields (Table 13, entries 1, 3, 4 and 7). However, reaction with α-substituted aldehydes afforded no or very low yields (Table 13, entries 2, 5 and 6). These results perhaps further highlight the sensitivity of acyl radical addition to highly substituted alkenes. Nevertheless, an array of valuable ketones were synthesised using our protocol.

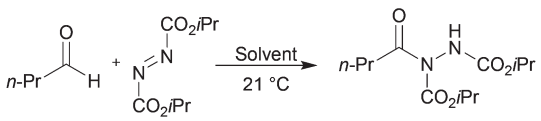
Hydroacylation of azodicarboxylates

Eager to extend our methodology to C–N bond formation, we applied our optimised conditions for the hydroacylation of vinyl sulfonate **14** to the hydroacylation of azodicarboxylate **47** employing *n*-butanal as the aldehyde component.

Using either 1,4-dioxane or water as solvent, excellent yields of acyl hydrazide **48a** were observed (Table 14, entries 1 and 7). Given the high yields achieved and the lack of appreciable side-products, except butanoic acid, we took the opportunity to assess whether aldehyde stoichiometry could be reduced whilst maintaining high yield (Table 14).

Using 1,4-dioxane as solvent we saw a significant decrease in yield on reducing the quantity of aldehyde (Table 14, entries

Table 14 Hydroacylation of DIAD **47** with aldehyde **5a** in 1,4-dioxane and water



5a **47** **48a**

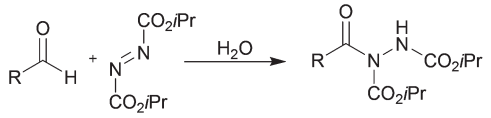
Entry	Solvent	**5a**/eq.	**47**/eq.	Isolated yield **48a**/%
1	1,4-Dioxane	5	1	94
2		2	1	80
3		1.5	1	72
4		1	1	64
5		1	1.2	65
6		1	2	67
7	H_2O	2	1	92
8		1.5	1	90
9		1	1	70
10		1	1.2	90
11		1	2	91

Conditions for 1,4-dioxane: DIAD **47**, *n*-butanal **5a**, 1,4-dioxane, 21 °C, 24 h. Conditions for H_2O: DIAD **47** and *n*-butanal **5a**, H_2O, 21 °C, 24 h.

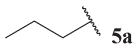
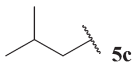
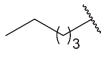
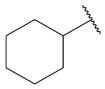
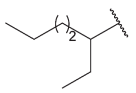
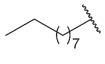
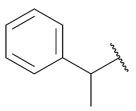
1–3). In contrast, reducing the **5a : 47** ratio from 2 : 1 to 1.5 : 1 in the water-based conditions resulted in similarly high yields (Table 14, entries 7 and 8). However, only modest conversion (70%) was achieved with stoichiometric reaction conditions (Table 14, entry 9). The lower yield observed on reaction with a 1 : 1 stoichiometry of **5a : 47** was attributed to conversion of diisopropyl azodicarboxylate **47** to diisopropyl hydrazinedicarboxylate. To counter this, the amount of diisopropyl azodicarboxylate **47** was increased (Table 14, entries 10 and 11), and gratifyingly, this afforded hydrazide **48a** in excellent yield, 90%, based on *n*-butanal as the limiting reagent. A similar approach was applied to using 1,4-dioxane as solvent, however, this brought limited success (Table 14, entries 4–6).

With our optimised conditions in hand, we sought to evaluate the tolerance of azodicarboxylate **47** to aldehydes with a range of auto-oxidation rates. To appraise this, aldehydes **5a–j** (1 equivalent) were reacted with azodicarboxylate **47** (1.2 equivalents) in H_2O (Table 15).

Table 15 Hydroacylation of DIAD **47** with aldehydes **5a–j**



5 **47** **48**

Aldehyde **5**	Isolated yield **48**/%
 **5a**	91
 **5b**	79
 **5c**	79
 **5d**	88
 **5e**	84
 **5f**	86
 **5g**	85
 **5h**	0
 **5i**	69
 **5j**	71

Conditions: DIAD **47** (1.2 mmol), aldehyde **5** (1 mmol), H_2O (1 mL), 21 °C for the time specified in the ESI.

Hydroacylation of azodicarboxylate **47** showed excellent tolerance of aldehydes with a broad range of auto-oxidation rates. Previously, our protocol has shown relatively poor tolerance for aldehydes that auto-oxidise rapidly, *i.e.* aldehydes **5b** and **5i**. However, when employing azodicarboxylate **47** as the acyl radical acceptor component, these aldehydes underwent efficient hydroacylation, even when using a single equivalent of aldehyde. As in the case for the hydroacylation of vinyl sulfonate **14**, under the water-based conditions, the use of acetaldehyde **5h** gave no conversion of the double bond acceptor species due to its high solubility in, and reactivity with, water. Perhaps most interestingly, aldehyde **5j**, which did not appear to auto-oxidise (see Table 1) and did not undergo any conversion with any of the other acceptors (see Tables 5, 9 and 13), afforded a good yield of acyl hydrazide **48j** (71%). These results seem to indicate that azodicarboxylates are exceptionally good acyl radical acceptors and/or that the adduct radicals generated from acyl radical addition to azodicarboxylates are exceptionally efficient aldehyde H-atom abstractors.

Synthetic utility of acyl hydrazides

We then sought to explore the synthetic utility of acyl hydrazides as acyl donors owing to the stabilised leaving group that would be released upon an addition–elimination reaction at the amide moiety. To do this, reaction of hydrazide **48a** with various amines was explored. Reaction with primary amines afforded the corresponding amides **49a–c** in excellent yields with concurrent isolation of diisopropyl hydrazinedicarboxylate **50** (Table 16). Unfortunately, however, treatment of hydrazide **48a** with bulkier amines such as morpholine and pyrrolidine resulted in low or no yield of amide **49**. Use of more polar solvents, such as DMF and NMP, did not improve yield and/or conversion.

Upon close examination of the crude reaction mixtures for the reaction of acyl hydrazide **48a** with secondary amines we were able to identify that the low yields of amides **49d–e** was due to attack of the amine at the carbamate ester, resulting in the formation of **51** (Scheme 15).

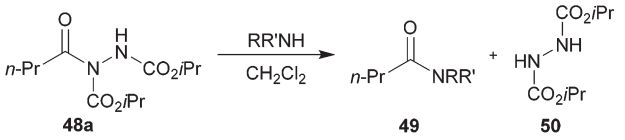
In an attempt to obviate this unfavourable side-reaction, Boc functionalised acyl hydrazide **52** was synthesised and submitted to the aminolysis reaction conditions with secondary amines morpholine and pyrrolidine. Gratifyingly, this significantly improved yield of tertiary amides **49d** and **49e** as it presumably suppressed attack at the carbamate (Table 17).

Application of functionalised aldehydes

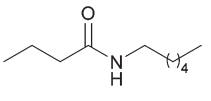
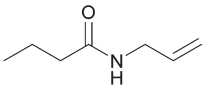
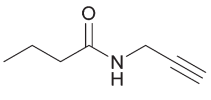
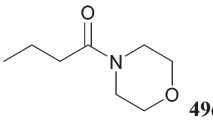
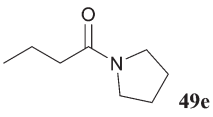
Having evaluated the tolerance of our hydroacylation protocol to aldehydes with a range of auto-oxidation rates in concert with various double bond acceptor moieties, we proceeded to appraise functional group tolerance. Thus, the hydroacylation of vinyl sulfonate **14**, vinyl phosphonate **30**, α,β-unsaturated ester **43** and azodicarboxylate **47**, under the optimised conditions that have been developed for each acceptor, with aldehydes **5k–5w** were evaluated.

To our delight, excellent tolerance of cyclopropyl, ester, acetal and alcohol functional groups was observed across all

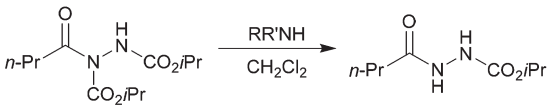
Table 16 Conversion of hydrazide **48a** to amide **49** with concurrent isolation of diisopropyl hydrazinedicarboxylate **50**



48a 49 50

Amide **49**	Isolated yield/%
 **49a**	96
 **49b**	95
 **49c**	98
 **49d**	19
 **49e**	25

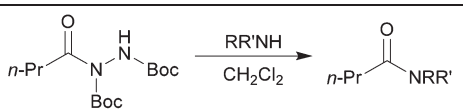
Conditions: acyl hydrazide **48a** and amine (2.5 eq.), CH_2Cl_2, 21 °C.



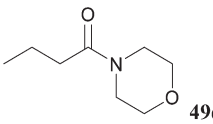
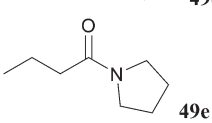
48a 51

Scheme 15 Formation of **51** derived from attack of amine on the carbamate of **48a**.

Table 17 Conversion of hydrazide **52** to amide **49**



52 49

Amide **49**	Isolated yield/%
 **49d**	59
 **49e**	75

Conditions: acyl hydrazide **52** and amine (2.5 eq.), CH_2Cl_2, 21 °C.

four double bond acceptors (Table 18, entries 1–4). Although epoxide-bearing aldehyde **5o** showed excellent tolerance of acceptors **30**, **43** and **47**, no ketone was isolated on reaction with vinyl sulfonate **14** (Table 18, entry 5). In this case, although alkene was completely consumed under the reaction conditions, only a polymeric substance could be observed in the crude ^{1}H NMR. Consistent with a radical mechanism was the poor tolerance of our methodology to aldehydes bearing alkenes (Table 18, entries 6 and 7), presumably due to polymerisation under the reaction conditions. The only exception to this was the moderate yields observed when using azodicarboxylate as acceptor; further testament to azodicarboxylates being excellent radical acceptors and/or their acyl radicals adducts being excellent chain propagators. To probe whether it was specifically the alkene functionality that limited yield of hydroacylation product, the corresponding reduced aldehyde of citronellal, **5r**, was employed under each of the reaction conditions (Table 18, entry 8). As aldehyde **5r** provided good to excellent yields of hydroacylation product in all cases, and as it has a similar auto-oxidation rate to citronellal **5q**, this supports the theory of poor tolerance of alkene functional groups specifically. Consistent with our previous results, aldehydes **5s** and **5t**, which did not appear to undergo oxidation in our auto-oxidation study, only underwent reaction with azodicarboxylate **47** (Table 18, entries 9 and 10).

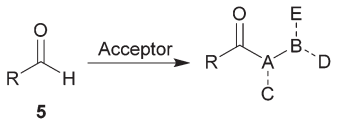
The tolerance of aromatic aldehydes under our optimised conditions was evaluated with electron-poor, -neutral and -rich aldehydes **5u–w** (Table 18, entries 11–13). In general, our hydroacylation protocol showed poor tolerance to aromatic aldehydes, with the only exception being observed for the hydroacylation of azodicarboxylate **47**; further evidence of the exceptional propensity of azodicarboxylates to undergo efficient hydroacylation. The major obstacle to efficient hydroacylation with the alkene based double bond acceptors was centred on low conversion of alkene, unfavourable polymerisation and 1,4-dioxane addition products. These side-reactions are likely to be a consequence of inefficient aromatic acyl radical trapping by alkenes, perhaps due to unfavourable steric interactions and/or inefficient aldehyde H-atom abstraction by the resultant acyl radical-alkene adduct radical species.

Application of enantiopure aldehydes

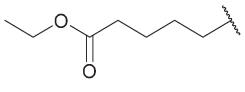
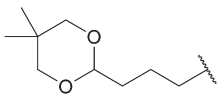
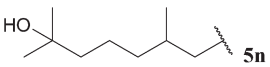
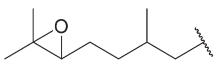
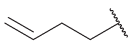
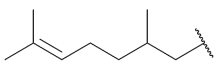
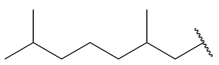
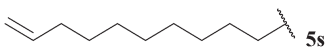
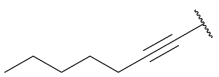
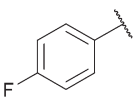
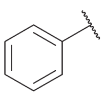
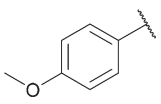
Due to acyl radicals being σ-type radicals we envisaged that aldehydes bearing α-stereocentres would undergo hydroacylation with preservation of enantiopurity. Thus we evaluated the use of chiral non-racemic aldehydes **5x** and **5y** in our hydroacylation protocol. As valuable enantiopure aldehydes would almost certainly not be employed when a vast excess of aldehyde is required (*e.g.* 5 equivalents), hydroacylation with chiral aldehydes **5x** and **5y** was only analysed on reaction with vinyl sulfonate **14** and azodicarboxylate **47** where only 2 and 1 equivalent(s) is/are employed, respectively (Table 19).

To our delight, aldehyde **5x** underwent efficient hydroacylation with both vinyl sulfonate **14** and DIAD **47**, and most importantly, with exceptional retained enantiomeric excesses (ree). Although no ketone could be isolated for reaction of

Table 18 Hydroacylation of vinyl sulfonate **14**, vinyl phosphonate **30**, α,β-unsaturated ester **43** and azodicarboxylate **47** with aldehydes **5k–5w**



5

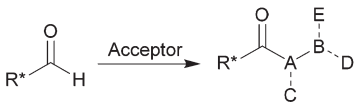
Entry	Aldehyde **5**	Vinyl sulfonate **14**[a]	Vinyl phosphonate **30**[a]	1,1-Diester alkene **43**[a]	DIAD **47**[a]
1	 **5k**	64	57	62	87
2	 **5l**	68	67	71	80
3	 **5m**	62	71	67	70
4	 **5n**	81	74	68	82
5	 **5o**	0	62	60	74
6	 **5p**	0 (37)	20[b]	0	42
7	 **5q**	0 (32)	0	0	54
8	 **5r**	66	68	61	87
9	 **5s**	0 (0)	0 (0)	0 (0)	75
10	 **5t**	0 (0)	0 (0)	0 (0)	55
11	 **5u**	10 (35)	27 (55)	<5[b] (10)	75
12	 **5v**	8[b] (32)	<5[b] (40)	<5[b] (10)	79
13	 **5w**	<5[b] (10)	<5[b] (35)	<5[b] (10)	44

Conditions for the hydroacylation of vinyl sulfonate **14**: alkene **14** (1 mmol), aldehyde **5** (2 mmol), H_2O (1 mL), 21 °C for the time specified in the ESI. Conditions for the hydroacylation of vinyl phosphonate **30**: alkene **30** (1 mmol), aldehyde **5** (5 mmol), 1,4-dioxane (1 mL), 60 °C, 24 h. Conditions for the hydroacylation of 1,1-diester alkene **43**: alkene **43** (1 mmol), aldehyde **5** (5 mmol), 1,4-dioxane (1 mL), 60 °C for the time specified in the ESI. Conditions for the hydroacylation of DIAD **47**: DIAD **47** (1.2 mmol), aldehyde **5** (1 mmol), H_2O (1 mL), 21 °C for the time specified in the ESI. [a] All reactions proceeded with 100% conversion of acceptor unless otherwise stated in parenthesis. [b] Determined by integration of ^{1}H NMR relative to pentachlorobenzene as an internal standard by analogy with similar products.

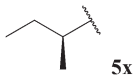
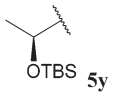
aldehyde **5y** with vinyl sulfonate **14**, acyl hydrazide **47y** could be isolated in good yield, and again, with excellent retained enantiomeric excess. These reactions represent to the best of our knowledge the first examples of hydroacylation achieved with a chiral aldehyde with retention of enantiomeric excess.

In concert with our auto-oxidation study, although all of aldehyde **5y** was consumed on reaction with vinyl sulfonate **14**, none of the corresponding acid was observed. The only species observed in the crude ^{1}H NMR were acetaldehyde **5h** and unreacted vinyl sulfonate **14**. One possible explanation for the formation of acetaldehyde **5h** is *via* decarbonylation of the corresponding acyl radical of aldehyde **5y**, followed by β-TBS-elimination. In the presence of azodicarboxylate, however, such a pathway may have been precluded, to some extent, by the rapid reaction of acyl radicals with azodicarboxylates.

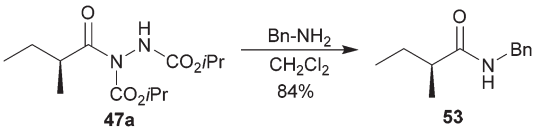
Table 19 Hydroacylation of vinyl sulfonate **14** and DIAD **47** with aldehydes **5x–y**



5

Aldehyde **5**	Vinyl sulfonate **14**[a]	DIAD **47**[a]
 **5x**	77, 97% ee	88, 98% ee
 OTBS **5y**	0 (25)	61, 99% ee

Conditions for the hydroacylation of vinyl sulfonate **14**: alkene **14** (1 mmol), aldehyde **5** (2 mmol), H_2O (1 mL), 21 °C for the time specified in the ESI. Conditions for the hydroacylation of DIAD **47**: DIAD **47** (1.2 mmol), aldehyde **5** (1 mmol), H_2O (1 mL), 21 °C for the time specified in the ESI. [a] All reactions proceeded with 100% conversion of acceptor unless otherwise stated in parenthesis.



47a **53**

Scheme 16 Conversion of hydrazide **47a** to amide **53**.

Having developed an effective protocol for the hydroacylation of acceptors using aldehydes bearing α-enantioenriched stereocentres in excellent ree, we proceeded to explore whether acyl hydrazide **47x** may be converted into an amide with high ree. To our delight, reaction with benzylamine afforded known amide **53** in good yield, and most significantly, with retention of stereochemical information (Scheme 16). We envisage that a range of enantioenriched amides may be prepared in similarly high enantiomeric excess.

Conclusions

In conclusion, we have described the use of aerobic aldehyde C–H activation for the construction of C–C and C–N bonds through the hydroacylation of vinyl sulfonates and phosphonates, α,β-unsaturated esters and azodicarboxylates. These reactions require no metal(s) and rely on only molecular oxygen in air for activation, therefore providing a clean, green route to hydroacylation. Of particular note is the hydroacylation of azodicarboxylates, which proceeded with aldehyde as limiting reagent, a stoichiometry not previously observed in the literature. Hydroacylation, in all acceptor cases, was shown to proceed in good yields for a range of aldehydes with respect to oxidation rate, as well as being tolerant of aldehydes bearing various functional groups. Moreover, the use of chiral aldehydes for hydroacylation, which has not been previously reported, was shown to be applicable to our aerobic activation protocol with exceptional retention of enantiomeric excesses observed in all cases. Throughout, we have observed products and patterns of reactivity that are most readily explained though a radical mechanism. In addition to using aerobic aldehyde C–H activation to affect hydroacylation of a range of acyl radical acceptors, the reactivity of the resultant hydroacylation products has also been demonstrated. The γ-keto-sulfonate motif may act as a precursor for the formation of γ-keto-sulfonamides, sultams, *N*-sulfonylimines and sultones. Perhaps most significantly, the γ-keto-sulfonate motif may undergo quantitative elimination to generate enones, providing a mild alternative route for the overall conversion of an aldehyde to an enone when taken in conjunction with the hydroacylation chemistry. Moreover, the hydroacylation–elimination–addition chemistry represents a powerful indirect alternative for the hydroacylation of electron rich alkenes, and the acyl hydrazide motif has also been highlighted as an intermediate for the construction of amides.

Experimental

General

All reagents were purchased from Aldrich or AlfaAesar and were used as received without further purification. All hydroacylation reactions were carried out in stoppered carousel tubes (15 cm × 2 cm) equipped with an octagon-shaped magnetic stirrer bar (12.7 mm × 3 mm). Where described below petrol refers to petroleum ether (40–60 °C). All reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates (254 μm). Flash column chromatography was carried out with Kiesegel 60M 0.04/0.063 mm (200–400 mesh) silica gel. ^{1}H NMR spectra were recorded at 300 MHz, 400 MHz, 500 MHz and 600 MHz and 13C NMR at 75 MHz, 100 MHz, 125 MHz and 150 MHz on a Bruker AMX300, AMX400, AMX500 and AMX600 at 21 °C temperature. The chemical shifts (δ) for ^{1}H and ^{13}C are quoted relative to residual signals of the solvent on the ppm scale. Coupling constants (J values) are reported in hertz (Hz). Mass spectra were obtained on a VG70-SE mass spectrometer. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FTIR Spectrometer operating in ATR mode. Optical rotations were measured using a Perkin Elmer 343 polarimeter. Chiral high performance liquid chromatography (HPLC) was performed on a Varian HPLC instrument equipped with a manual injector, binary pump, and a UV detector (214 nm) using CHIRALCEL® OD column (4.6 mm × 250 mm, 10 μm) from Chiral Technologies (West Chester, PA) eluting with hexane : i-PrOH.

Typical procedure for the hydroacylation of vinyl sulfonate 14 in 1,4-dioxane

To a solution of ethenesulfonic acid pentafluorophenyl ester **14** (1 mmol) in 1,4-dioxane (1 mL) was added aldehyde (5 mmol) and the reaction mixture stirred at 300 rpm at 21 °C until reaction was complete by TLC. PhMe (2 mL) was added

and the solvent removed *in vacuo* and the crude residue purified as described in the ESI† to afford the desired ketone sulfonate ester.

Typical procedure for the hydroacylation of vinyl sulfonate 14 in H_2O

To a solution of ethenesulfonic acid pentafluorophenyl ester **14** (1 mmol) in H_2O (1 mL) was added aldehyde (2 mmol) and the reaction mixture stirred at 300 rpm at 21 °C until reaction was complete by TLC. The solvent removed *in vacuo* and the crude residue purified as described in the ESI† to afford the desired ketone sulfonate ester.

Typical procedure for the synthesis of γ-keto-sulfides 22

To a solution of pentafluorophenyl 3-oxohexane-1-sulfonate **15a** (1 mmol) in CH_2Cl_2 (3 mL) was added thiol (1.3 mmol) and DBU (2 mmol), and the reaction mixture stirred at 300 rpm at 21 °C for 1 h. The solvent was removed *in vacuo* and the crude residue purified as described in the ESI† to afford the desired γ-keto-sulfide.

Typical procedure for the synthesis of sulfonamides 23–25a

To a solution of pentafluorophenyl 3-oxohexane-1-sulfonate **15a** (0.29 mmol) in NMP (2.5 mL) was added dropwise a solution of amine (0.58 mmol) in NMP (1 mL) at 0 °C. After addition was complete, the reaction mixture was warmed to 21 °C and stirred for 4 h. To work-up, the reaction mixture was diluted with Et_2O (20 mL), washed with sat. LiCl (3 × 20 mL), sat. $NaHCO_3$ (3 × 20 mL), 2 M HCl (3 × 20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the desired sulfonamide.

Typical procedure for hydroacylation of vinyl phosphonate 30

To a solution of vinyl phosphonate **30** (1 mmol) in 1,4-dioxane (1 mL) was added aldehyde (5 mmol) and the reaction mixture stirred at 300 rpm at 60 °C for 24 h unless otherwise stated in the ESI.† The reaction mixture was concentrated *in vacuo* and the crude residue purified as described in the ESI† to afford the desired γ-ketophosphonate.

Typical procedure for the hydroacylation of alkenes 35, 40, 41, 43 and 45

To a solution of alkene (1 mmol) in 1,4-dioxane (3 mL) was added aldehyde (5 mmol) and the reaction mixture stirred at 300 rpm at 60 °C for the time specified in the ESI.† The solvent removed *in vacuo* and the crude residue purified as described in the ESI† to afford the desired hydroacylation product.

Typical procedure for the hydroacylation of DIAD 47

To a mixture of azodicarboxylate (1.2 mmol) and H_2O (500 μL) was added aldehyde (1.0 mmol) and the reaction mixture stirred at 300 rpm at 21 °C for the time specified in the ESI.† The solvent was removed *in vacuo* and the crude residue purified as described in the ESI† to afford the desired hydroacylation product.

Typical procedure for the synthesis of amides 49a–c from acyl hydrazide 48a

To a solution of dipropan-2-yl 1-butanoylhydrazine-1,2-dicarboxylate **48a** (1 mmol) in CH_2Cl_2 (2 mL) was added amine (2.5 mmol) and the reaction mixture stirred at 300 rpm at 21 °C for 16 h. The solvent was removed *in vacuo* and the crude residue purified as described in the ESI† to afford the desired amide.

Typical procedure for the synthesis of amides 49d–e from acyl hydrazide 52

To a solution of di-*tert*-butyl 1-butanoylhydrazine-1,2-dicarboxylate **52** (1 mmol) in CH_2Cl_2 (2 mL) was added amine (2.5 mmol) and the reaction mixture stirred at 300 rpm at 21 °C for 16 h. The solvent was removed *in vacuo* and the crude residue purified as described in the ESI† to afford the desired amide.

Acknowledgements

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Notes and references

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