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C–H functionalisation of aldehydes using light generated, non-stabilised diazo compounds in flow†

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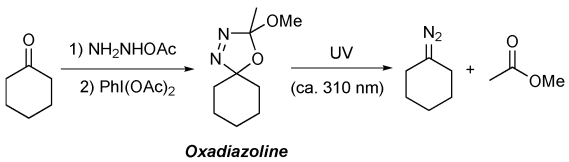
The difficulty in accessing and safely utilising non-stabilised diazo species has in the past limited the application of this class of compounds. Here we explore further the use of oxadiazolines, non-stabilised diazo precursors which are bench stable, in direct, non-catalytic, aldehyde C–H functionalisation reactions under UV photolysis in flow and free from additives. Commercially available aldehydes are coupled to afford unsymmetrical aryl–alkyl and alkyl–alkyl ketones while mild conditions and lack of transition metal catalysts allow for exceptional functional group tolerance. Examples are given on small scale and in a larger scale continuous production.

Diazo compounds have a long-standing history as extremely versatile tools for the creation of carbon–carbon and carbon–heteroatom bonds.[1–4] As a class of compounds, however, diazo derivatives are notorious for their toxic and hazardous nature, and associated difficulty in preparation and handling. These difficulties are compounded when the diazo moiety is not stabilised by either a proximal electron withdrawing group or π-system, meaning that the chemistry of non-stabilised diazo compounds is still a relatively underexplored area. The use of flow techniques as an enabling technology[5–8] can mitigate these classical issues to a large extent *via* the *in situ* generation and consumption of diazo compounds, so avoiding accumulation, allowing safer access under reproducible process windows.[9–19] Accordingly, our group has recently published a mild method for the generation of non-stabilised diazo compounds from oxadiazolines using UV light and their aryl–alkyl cross-coupling with boronic acids.[20]

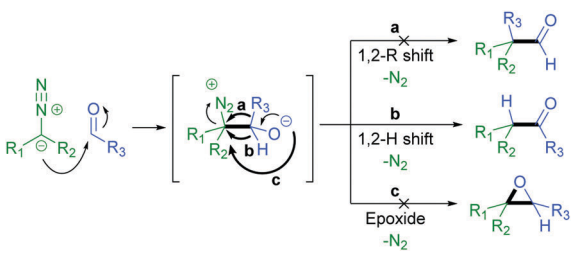
Oxadiazolines are prepared in a one-pot, two step procedure by the condensation of an alkyl ketone[21] with acetic hydrazide followed by cyclisation promoted by oxidants such as lead tetraacetate[22] or (diacetoxyiodo)benzene[23] or by electrochemical methods[24] (Scheme 1). Oxadiazolines are bench stable at room temperature but, when exposed to UV irradiation, decompose to form the relevant non-stabilised diazo compound and methyl acetate.[25,26] These compounds are particularly attractive for use in flow chemistry due to the certain safety issues outlined above, as well as the additional associated benefits that accrue under continuous processing conditions.



Scheme 1 Synthesis and UV photolysis of oxadiazolines.

The addition of a diazo compound to an aldehyde with subsequent 1,2-hydride shift affords the corresponding ketone product (Scheme 2).[27] We have previously reported the thermally activated insertion of diazo compounds into a formyl C–H bond to generate unsymmetrical ketones using tosylhydrazones as non-stabilised diazo precursors in 2014.[28]

Although a ubiquitous functional group, the synthesis of unsymmetrical ketones can still prove a synthetic challenge, making this an active area of research. In the recent literature, a number of methods coupling activated carbonyl substrates, such



Scheme 2 Mechanistic pathways available for diazo addition to an aldehyde.

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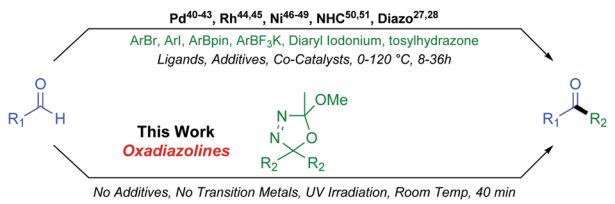
as acetyltrimethylsilanes,[29,30] acyl chlorides,[31,32] amides,[33–35] anhydrides,[36,37] phthalimides,[38] or carboxylic acids,[39] with various partners have been reported. Formation of unsymmetrical ketones directly from aldehydes is more desirable than from activated substrates but more challenging still. Direct formyl C–H insertion to create a new sp^2–sp^3 or sp^2–sp^2 carbon–carbon bond is achievable *via* Palladium,[40–43] Rhodium,[44,45] or Nickel[46–49] catalysed processes as well as through NHC mediated organocatalysis[50,51] or indeed diazo chemistry[27,28] (Scheme 3).

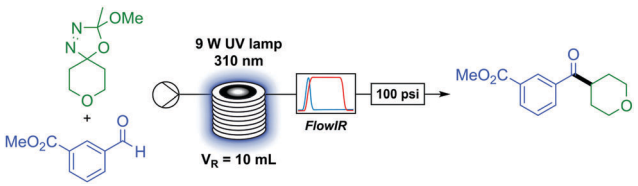
These existing methods afford valuable reactivity and useful chemistry. However, some drawbacks commonly encountered include long reaction times, occasionally harsh conditions, necessity for a plethora of additives, the presence of up to three catalysts, and relatively poor functional group compatibility due to the reactivities of associated transition metal catalysts. In this work, we extend our original oxadiazoline methodology and we report their very mild and rapid coupling with aldehydes to form unsymmetrical alkyl–alkyl and aryl–alkyl ketones with excellent functional group tolerance and resulting structural diversity.

Employing similar conditions to those of our previous work resulted in an excellent yield of the product ketone (Table 1, entry 1).[20] Removal of the DIPEA base resulted in no change to the reaction yield (Table 1, entry 2).[52] Reducing the residence time to 40 minutes resulted in a decrease in yield, however this could be increased again by raising the temperature of the reaction to 20 °C (Table 1, entries 3 and 4). Increasing the temperature to 30 °C resulted in a precipitous drop of the yield, presumably due to decomposition of the diazo intermediate (Table 1, entry 5). Reducing the equivalents of the oxadiazolines relative to the aldehyde from 2 to 1.1 resulted in a decrease in yield and no difference was observed on change of solvent (Table 1, entries 6, 7, and 8).



Scheme 3 Methods for direct aldehyde coupling reactions to form unsymmetrical ketones.

Table 1 Optimisation of aldehyde C–H addition reaction



Entry	[Oxadiaz] (M)	[Aldehyde] (M)	t_R (min)	T (°C)	Solvent	Yield[a] (%)
1[b]	0.1	0.05	80	10	CH_2Cl_2	94[c]
2	0.1	0.05	80	10	CH_2Cl_2	93
3	0.1	0.05	40	10	CH_2Cl_2	78
4	**0.1**	**0.05**	**40**	**20**	$\mathbf{CH_2Cl_2}$	**91**
5	0.1	0.05	40	30	CH_2Cl_2	28
6	0.06	0.05	40	20	CH_2Cl_2	72
7	0.06	0.05	40	20	MeTHF	70
8	0.06	0.05	40	20	Dioxane	70

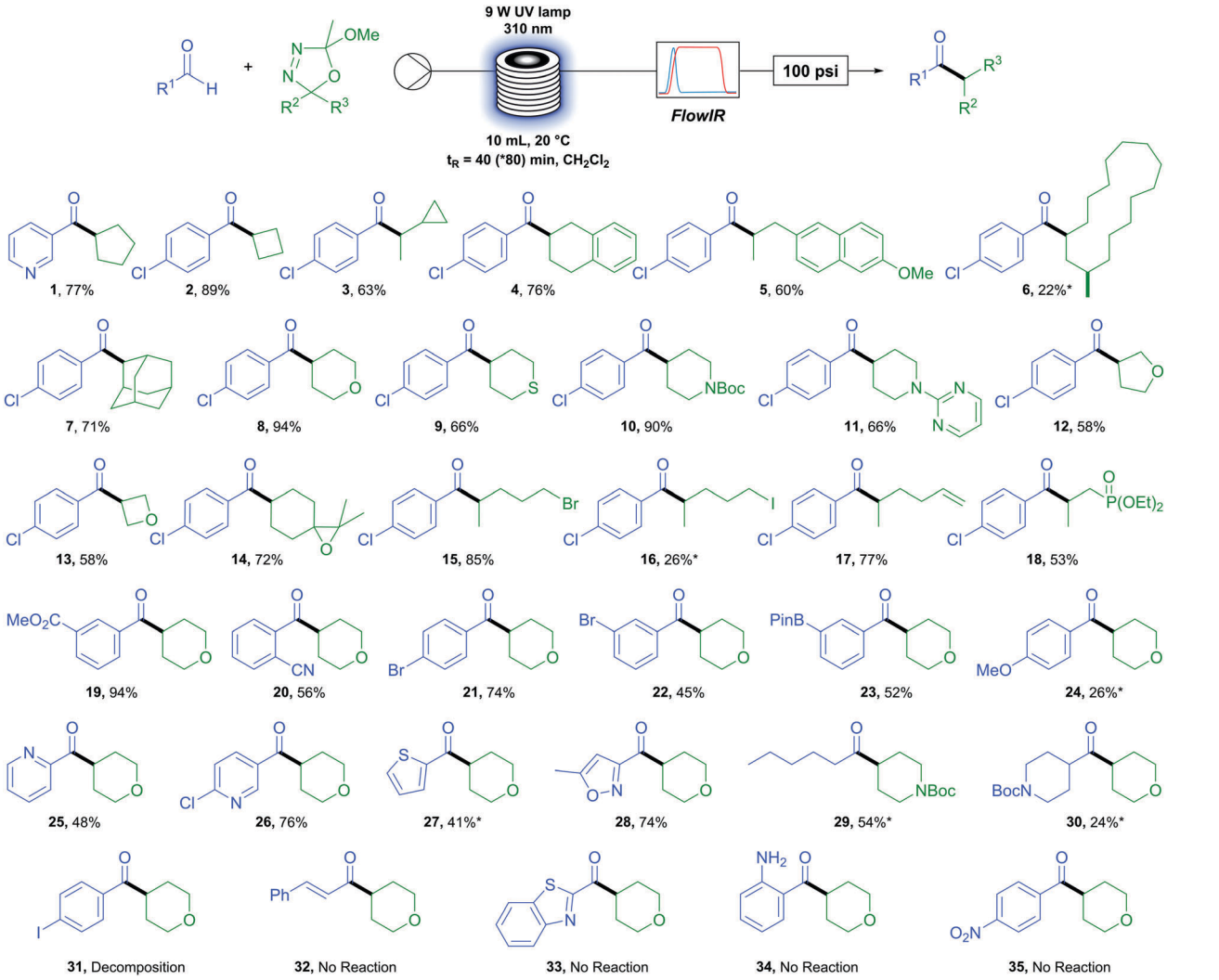
[a] GC yield unless stated otherwise. [b] 0.1 M DIPEA. [c] Isolated yield.

With optimised conditions in hand we began to investigate the scope of the transformation. The *in situ* generation and full consumption of diazo compounds in flow is an ideal case and one which, when screening new reactions, may not always hold. Inline IR[53,54] is a particularly advantageous analytical technique in diazo chemistry as diazo species have a unique IR stretch (*ca.* 2040 cm^{-1}) which, under our experimental setup, can be detected in a simple manner. As the IR is present upstream from the back-pressure regulator and system outlet (Table 1) if at any time the user observes a non-trivial concentration of diazo in the output of the reactor this can be simply dealt with through addition of an appropriate quenching agent (*i.e.* acetic acid) to the collection vessel *prior* to any diazo material exiting the system. An additional benefit of inline IR in this methodology is the detection of methyl acetate, which is produced in the breakdown of the oxadiazoline (Scheme 1) and can be used to observe the progress of the reaction.

We first sought to determine the generality of the oxadiazoline component (Table 2). A variety of carbon rings were tolerated, from cyclopentane (**1**) and cyclobutane (**2**) to an oxadiazoline incorporating a cyclopropane moiety (**3**). No ring-opened product was observed, serving as evidence of a polar rather than a radical process. Tetralin (**4**) and methoxy naphthyl (**5**) were viable substrates. An oxadiazoline derived from the macrocyclic natural product Muscone (**6**) also proved viable, albeit in low yield. A bulky adamantly group (**7**) reacted in good yield. Six membered saturated heterocycles tetrahydropyran (**8**), tetrahydrathiopyran (**9**), *N*-boc and *N*-pyrimidyl (**10** and **11**) piperidine reacted in moderate to excellent yields. Five- and four-membered saturated oxygen containing heterocycles tetrahydrofuran (**12**) and oxetane (**13**) reacted in more moderate yields. Functional group tolerance proved to be excellent, with examples of an epoxide (**14**), primary alkyl bromide and iodide (**15** and **16**), terminal alkene (**17**), and phosphonate ester (**18**) exemplifying the extremely mild conditions of this reaction and accessing products which would be otherwise difficult or impossible to access *via* metal-catalysed methods.

We next turned our attention to the aldehyde scope. Methyl ester (**19**) resulted in excellent yields while an *ortho*-nitrile group (**20**) displayed tolerance to bulk beside the reacting position in an aromatic system. Functional group tolerance is again excellent with *para*- (**21**) and *meta*-bromo (**22**) benzaldehydes as well as the synthetically useful boron-pinacol ester (**23**) which would otherwise be challenging to incorporate under transition metal catalysis.[55] However, the electron rich 4-methoxy benzaldehyde (**24**) resulted in a low yield. A variety of heterocyclic aldehydes were also successfully coupled. For example, several pyridyl containing aldehydes (**1**, **25** and **26**) as well as thiophene (**27**) and isoxazole (**28**). We were pleased to find that aliphatic aldehydes proceed although they appear more challenging than aromatic aldehydes, with hexanal (**29**) resulting

Table 2 Metal and additive free addition of non-stabilised diazo compounds to aldehydes in flow



in a moderate yield but cyclic *N*-boc piperidone carboxaldehyde (**30**) only a low yield.

When employing 4-iodobenzaldehyde (**31**) as the aldehyde coupling partner only decomposition to benzaldehyde was observed and the use of cinnamaldehyde (**32**), benzothiazole (**33**), and amino (**34**) or nitro (**35**) functional groups resulted in no reaction. In each case above, little or no conversion of the oxadiazoline was observed due to the absorbance of UV irradiation by the aldehyde. With this knowledge in hand, we found that a simple test can be carried out prior to performing the reaction which allows the user to determine the feasibility and potentially adjust conditions accordingly to maximise the yield. If the λ_{max} of the desired aldehyde coupling partner is at or above 310 nm (the wavelength of UV irradiation employed) then the reaction is unlikely to proceed (see Fig. S2, ESI†). We also found that, to some extent, this limitation can be overcome by lowering the concentration of the reactants and increasing the residence time of the reaction. This is demonstrated in the case of compound (**27**) (starting material aldehyde having a λ_{max} at 311 nm) where, under our standard operating conditions the yield was 16% but was increased to 41% by simply halving the reaction concentration and doubling the residence time.

As a flow process, the methodology is eminently scalable by simply running the reaction for longer. Without accumulation of any diazo intermediate, a four hour run under steady state at standard conditions provided 580 mg of ketone **19**, corresponding to a theoretical productivity of 3.48 g d^{-1}, with similar yield to the smaller scale run (91 to 94%) with this particular reactor set-up.

In conclusion, this work expands the scope and application of oxadiazolines as highly effective precursors to non-stabilised diazo compounds. Mild reaction conditions, short reaction times, and ease of continuous operation means this methodology offers a complementary alternative to existing literature procedures. In particular, the lack of transition metals or commonly used additives such as oxidants or bases allows for the incorporation of sensitive functional groups into the ketone products, laying groundwork for their immediate further functionalisation.

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Conflicts of interest

There are no conflicts to declare.

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52 Probing the role of the DIPEA in our previously published boronic acid coupling, we found the base to be essential in only a physical requirement to dissolve the boronic acid in dichloromethane. Further optimisation found that the amount of DIPEA could be reduced to 16 mol% in this solvent or removed entirely through use of a coordinating solvent such as THF. In the coupling of non-stabilised diazo compounds with boronic acids or aldehydes we find no evidence that the DIPEA stabilises the diazo intermediate as some have suggested.
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55 Boron-pinacol esters are significantly less reactive towards diazo compounds than their boronic acid or boroxine counterparts and we found only 3% yield each of addition to the Bpin of the starting material aldehyde or product.

