

5 Liquid- and Liquid–Liquid-phase Reactions – Addition and Elimination

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Addition and elimination reactions are one of the most important classes of reactions in organic synthesis because they serve as powerful tools for the construction of a variety of organic structures. This chapter provides an overview of elimination and addition reactions using microflow reactors.

5.1 Addition Reactions

Enolates are powerful carbon nucleophiles and addition of enolates to carbonyl groups (aldol reactions) serve as a useful method for C–C bond formation. The Mukaiyama aldol reactions involving fluoride ion-promoted addition of silyl enolates to aldehydes are very popular and are frequently employed in the construction of carbon skeletons in organic synthesis [1]. The Mukaiyama aldol reaction with the silyl enol ether of cyclohexanone and 4-bromobenzaldehyde can be performed based on the electroosmotic flow (EOF) technique with a four-channel microstructured flow reactor (channel dimensions $100 \times 50 \mu\text{m}$). The reactor was prepared using a standard fabrication procedure developed at the University of Hull [2, 3]. Based on GC–MS analysis, quantitative conversion of the starting material was achieved in 20 min, whereas in the case with a traditional batch system a quantitative yield was obtained only when an extended reaction time of 24 h was employed (Figure 5.1).

The aldol reactions of the silyl enol ethers of aromatic ketones such as acetophenone with 4-bromobenzaldehyde can also be carried out in a quantitative conversion using a microflow reactor (Scheme 5.1).

The reaction of an enolate with an acylating reagent often leads to the formation of a mixture of *O*- and *C*-acylated products [4]. Therefore, a large amount of work has been undertaken to explore and understand the reaction conditions that promote the regioselective acylation of enolates [5, 6]. Microflow reactors have also been used for selective *O*- and *C*-acylation. The reaction of the silyl enol ether of acetophenone with benzoyl fluoride using a microflow reactor under EOF conditions selectively gives the

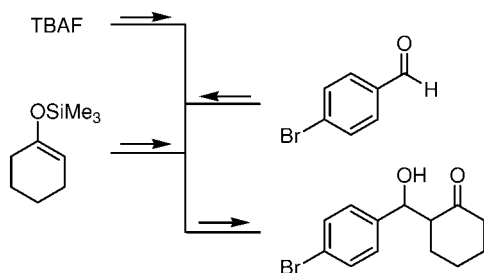
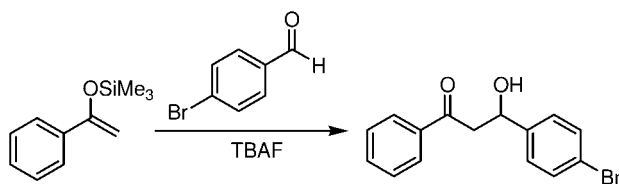


Figure 5.1 Addition of silyl enol ether of cyclohexanone to 4-bromobenzaldehyde in a microflow reactor.

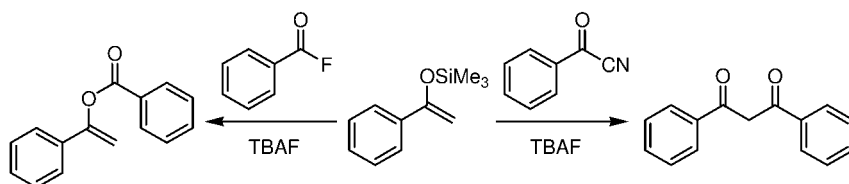


Scheme 5.1 Addition of the silyl enol ether of acetophenone to 4-bromobenzaldehyde in a microflow reactor.

O-acylated product with 100% conversion. The corresponding C-acylation is not obtained (Scheme 5.2) [7]. On the other hand, the use of benzoyl cyanide as an acylating agent selectively gives the C-acylation product with quantitative conversion.

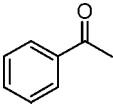

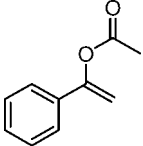
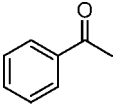

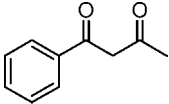
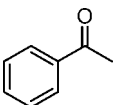
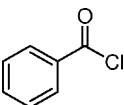
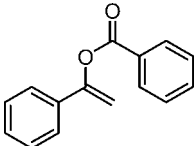
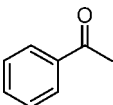
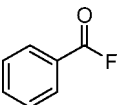
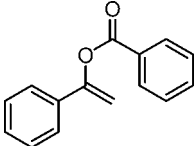
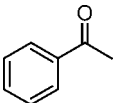
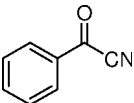
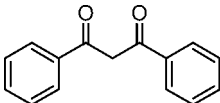
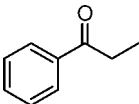
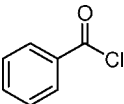
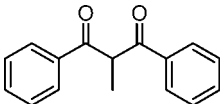
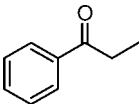
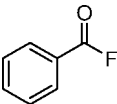
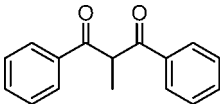
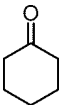
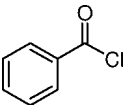
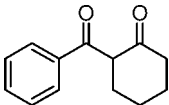
For comparison, macrobatch acylation reactions of the Li enolates prepared from the corresponding ketones using lithium bis(trimethylsilyl)amide (LiHMDS) of ketones are summarized in Table 5.1 [8]. The Li enolates are also generated *in situ* from the corresponding silyl enol ethers by the action of a catalytic amount of tetrabutylammonium fluoride (TBAF) and are acylated with an acylating agent such as an acyl halide or acyl cyanide. The regioselectivity of the acylations of both Li enolates and silyl enol ethers is dependent on both the type of ketone and the type of acylating agent.

Enolate generated by the treatment of 1,3-dicarbonyl compounds with diisopropylethylamine can react with α,β -unsaturated carbonyl compounds such as ethyl propiolate in a microflow reactor by the EOF technique to give a variety of 1,4-addition



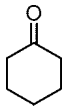
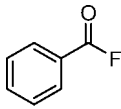
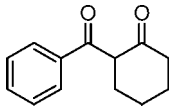
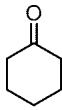
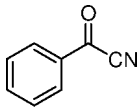
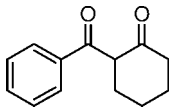
Scheme 5.2 Addition of the silyl enol ether of acetophenone to benzoyl fluoride or benzoyl cyanide in a microflow reactor.

Table 5.1 Acylation of a series of Li enolates and their respective silyl enol ethers.

Ketone	Acylation reagent	Product	Yield (%) Li enolate	Conversion (%) silyl enol ether
			89	–
			92	97
			56	–
			80	100
			93	98
			95	–
			96	99
			71	–

(Continued)

Table 5.1 (Continued)

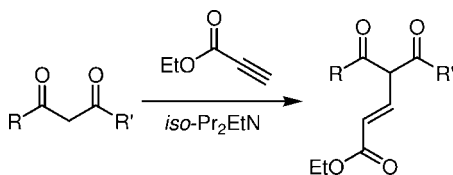
Ketone	Acyating reagent	Product	Yield (%) Li enolate	Conversion (%) silyl enol ether
			70	100
			89	95

products (Michael adducts), as shown in Table 5.2 [9]. The observed conversions in a microflow reactor under stopped-flow conditions are greater than those obtained in macro batch processes, although the conversions obtained under continuous flow conditions are lower.

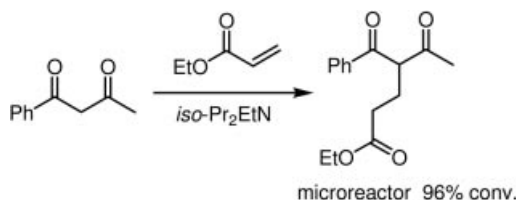
Ethyl acrylate also serves as a Michael acceptor and the reaction with 1-phenyl-1,3-butanedione gives the corresponding addition product in high conversion (Scheme 5.3) [10].

The Michael addition reactions of nitro compounds such as nitromethane to CF_3 -containing acrylates such as ethyl (*E*)-ethyl 3-(trifluoromethyl)acrylate using a microflow reactor (channel width 100 μm , depth ca. 40 μm and length 80 mm; flow rate 1 $\mu\text{l min}^{-1}$) has been reported. The reactions proceed smoothly in the presence of DBU as a base to afford the corresponding Michael adducts without any detectable formation of polymeric byproducts (Table 5.3) [11].

Table 5.2 1,4-Addition of enolates of 1,3-dicarbonyl compounds to ethyl propiolate.



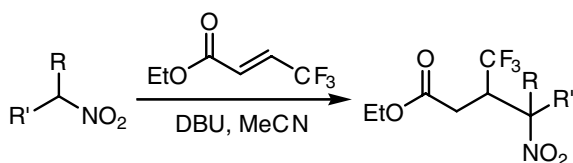
Reaction method	Conversion (%)		
	R,R' = CH ₃	R = Ph R' = CH ₃	R,R' = OEt
Batch	89	78	91
Continuous flow	56	15	41
Stopped-flow	95	100	100



Scheme 5.3 1,4-Addition to ethyl acrylate in a microflow reactor.

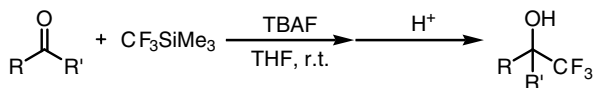
Trifluoromethylation of carbonyl compounds with trifluoromethyl(trimethyl) silane in THF also proceeds in a microflow reactor very rapidly (20 s) to give the corresponding trifluoromethylated products, whereas the corresponding flask reactions take 5 h (Table 5.4).

Table 5.3 Michael addition reaction with CF₃-containing acrylate.

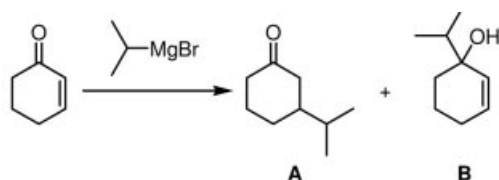


R	R'	Yield (%)
H	H	80
Me	Me	93
H	CO ₂ Et	90

Table 5.4 Trifluoromethylation of carbonyl compounds with trifluoromethyl(trimethyl) silane.



Carbonyl compound	Method	Reaction Time	Yield (%)
C ₆ H ₅ CHO	Microreactor	20 s	89
C ₆ H ₅ CHO	Batch	5 h	76
4-CF ₃ -C ₆ H ₅ CHO	Microreactor	20 s	83
4-CF ₃ -C ₆ H ₅ CHO	Batch	5 h	97
4-MeO-C ₆ H ₅ CHO	Microreactor	20 s	89
C ₉ H ₁₉ CHO	Microreactor	20 s	74
(<i>E</i>)-PhCH = HCHO	Microreactor	20 s	12
PhCOCH ₃	Microreactor	20 s	42
Cyclohexanone	Microreactor	20 s	7



Scheme 5.4 Reaction of cyclohex-2-enone with isopropylmagnesium bromide.

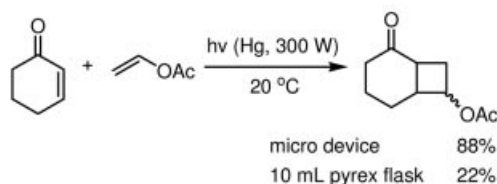
Addition reactions of Grignard reagents to carbonyl compounds are also performed in microflow reactors. For example, the reaction of cyclohex-2-enone with isopropylmagnesium bromide leads to the formation of both 1,4-adduct **A** and 1,2-adduct **B** (Scheme 5.4). It is noteworthy that the microflow reactor serves a beneficial tool for optimization of the reactions conditions. By testing 14 different reaction conditions, the yield was increased from 49% to 78% and the ratio of the regioisomers was improved from 65:35 to 95:5 [12, 13].

The photochemical [2 + 2] cycloaddition reaction is one of the most powerful and versatile methods for the formation of four-membered rings and has been extensively applied in organic synthesis [14]. Photochemical [2 + 2] cycloaddition reaction can be carried out in microflow reactors. For example, the reaction of cyclohexenones with vinyl acetates in a microflow reactor having glass-made microchannels of width 1000 μm and depth 500 μm under irradiation (300 W, Hg lamp) gives [2 + 2] cycloaddition products in good yield with a residence time of 2 h, which is remarkably short compared with that for a macro batch system using the same light source (Scheme 5.5) [15].

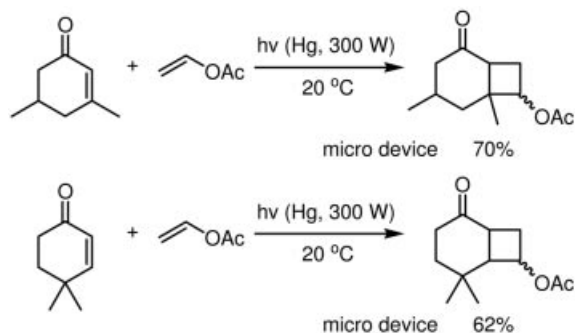
The reactions of 3,5-dimethylcyclohex-2-enone and 4,4-dimethylcyclohex-2-enone also proceed to give the desired [2 + 2] cycloadducts in 70% and 62% yields, respectively (Scheme 5.6).

The reaction can be applied to other olefinic substrates such as isopropenyl acetate and butyl vinyl ether. The reactions with cyclohex-2-enone give the corresponding cycloaddition products in 64 and 47% yields, respectively (Scheme 5.7).

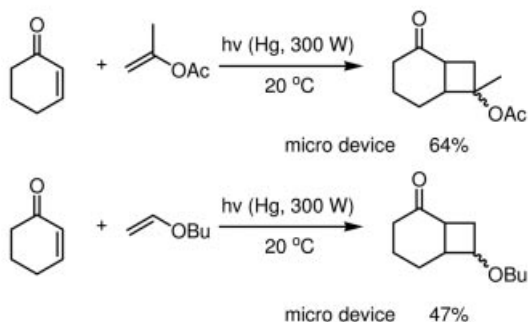
Intramolecular [2 + 2] photocycloaddition of 1-cyanonaphthalene derivatives in microflow reactors made of poly(dimethylsiloxane) (PDMS) has been developed. Both the efficiency and regioselectivity increased compared with those under batch conditions (Table 5.5) [16]. A glass-made microflow reactor is also effective for intramolecular photocycloaddition [17]. The efficiency and regioselectivity have been further improved.



Scheme 5.5 Photochemical [2 + 2] cycloaddition reaction of cyclohex-2-enone with vinyl acetate.



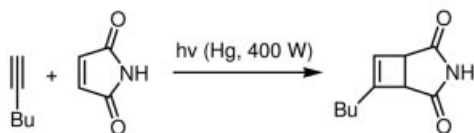
Scheme 5.6 Photochemical [2 + 2] cycloaddition reaction of 3,5-dimethylcyclohex-2-enone and 4,4-dimethylcyclohex-2-enone with vinyl acetate.



Scheme 5.7 Photochemical [2 + 2] cycloaddition reaction of 3,5-dimethylcyclohex-2-enone and 4,4-dimethylcyclohex-2-enone with vinyl acetate.

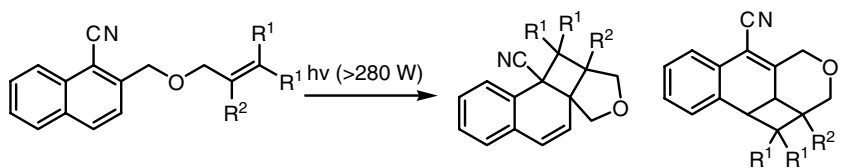
The [2 + 2] cycloaddition reaction of maleimide and 1-hexyne in a photochemical microflow reactor has also been reported. The development of flow reactors for continuous processes can allow large-scale reactions [18]. This reaction can be achieved with 83% conversion on a large scale (0.7 kg) (Scheme 5.8).

Photosensitized addition of methanol to (*R*)-(+)-(*Z*)-limonene in a microflow reactor has been reported (Scheme 5.9) [19]. The quantity of photoproducts, *cis*- and *trans*-4-isopropenyl-1-methoxy-1-methylcyclohexane, increases with increasing period



Scheme 5.8 The [2 + 2] cycloaddition reaction of maleimide and 1-hexyne.

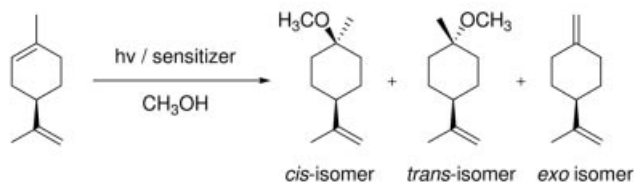
Table 5.5 Effect of microflow system on intramolecular [2 + 2] photocycloaddition.



R ¹	R ¹	Conditions	Solvent	Irradiation time (min)	Cycloadduct (%)		Conversion (%)
					[2 + 2]	[2 + 3]	
Me	Me	Batch	Benzene	240	55	45	65
Me	Me	Flow	Benzene	1	96	4	69
Me	H	Batch	Benzene	180	73	27	74
Me	H	Flow	Benzene	1	93	7	75
Me	H	Batch	Acetonitrile	50	72	28	77
Me	H	Flow	Acetonitrile	2.9	90	10	72
H	H	Batch	Acetonitrile	90	3	97	33
H	H	Flow	Acetonitrile	2.9	10	90	40

of irradiation by a mercury lamp and the diastereomeric excess of the photoadduct is slightly larger than that obtained in a batch reaction system. In the microflow system, the residence time of the substrate is very short and the reaction vessel does not retain the reaction products. These features may prevent subsequent side-reactions and increase the quantum yield of the photoreaction.

Radical addition to carbon–carbon unsaturated bonds has also been carried out in microflow reactors. Tributyltin hydride-mediated radical reactions of organic halides have been successfully carried out in a continuous microflow system [20]. Rapidly decomposing radical initiators such as V-65 and V-70 are fairly effective and the reactions proceed within a very short period of time. The continuous flow reaction system can be applied to gram-scale synthesis (7.6 g, 185 min) of a key intermediate for furofuran lignans (Figure 5.2).



Scheme 5.9 Photosensitized addition of methanol to (R)-(t)-(z)-limonene.

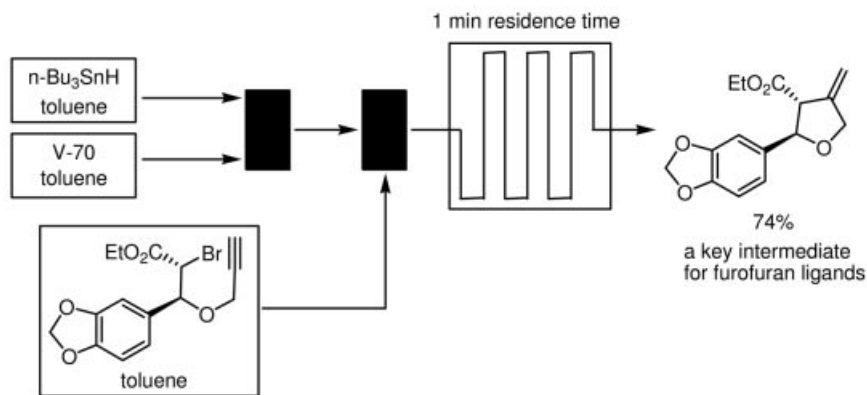


Figure 5.2 Gram-scale synthesis of a tetrahydrofuran derivative.

5.2 Elimination Reactions

Elimination is one of the most important types of reactions for making carbon–carbon multiple bonds in organic synthesis. However, only a few examples of elimination reactions in microflow reactors have been reported. β -Hydroxyketones provide the corresponding dehydrated products, α,β -unsaturated ketones, in almost quantitative yields under the microfluidic conditions, whereas conventional macro batch reactors give lower yields of the products due to recovery of the starting materials and formation of other hydrophobic byproducts (Figure 5.3) [21].

The microflow reaction has been successfully applied to a multikilogram synthesis of pristane, a biologically important natural product, which is now widely used as an adjuvant for monoclonal antibody production. The application of a continuous microflow system to the dehydration reaction as the key step can lead to the 5 kg-scale synthesis in 80% overall yield from farnesol (Figure 5.4). Finally, hydrogenation in the presence of 10% Pd/C under a hydrogen atmosphere provides pristane of 99% purity in 50–55% overall yield from farnesol.

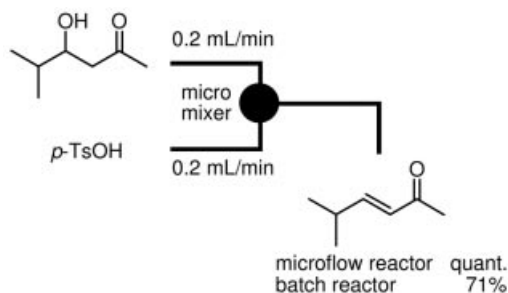


Figure 5.3 Microfluidic dehydration of β -hydroxyketone.

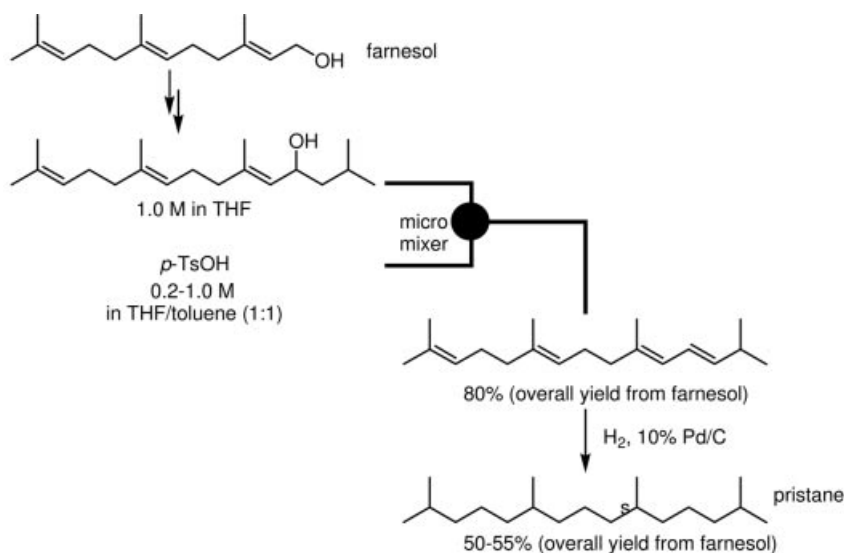
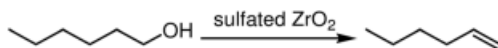


Figure 5.4 Synthesis of pristane.



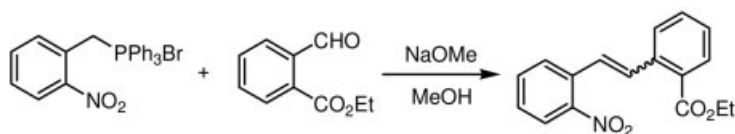
Scheme 5.10 Dehydration of 1-hexanol in a microstructured reactor.

Another example includes the use of a heated microreactor containing heterogeneous catalysis for the dehydration of alcohols to the associated alkene [22]. The dehydration of 1-hexanol to hexene at 155–160 °C has been carried out using an injection pump (Scheme 5.10). A conversion of 85–95% can be achieved without by-products. This compares favorably with the 30% conversion achieved by conventional reactors.

A microchannel reactor designed for periodic operation and a process to deposit alumina as a catalyst inside the reactor channels can also be used for the dehydration of 2-propanol to propene [23].

5.3 Addition–Elimination Reactions

Reactions involving sequential addition–elimination processes such as the Wittig reaction serve as useful methods for constructing organic molecules having carbon–carbon double bonds.



Scheme 5.11 Application of micro reactors to the Wittig reaction.

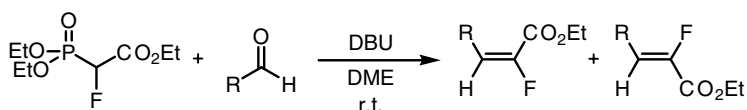
Microflow reactors have been successfully applied to the Wittig reaction. Several features such as stoichiometry and stereoselectivity of the reaction shown in Scheme 5.11 were investigated under EOF conditions. A conversion of 70% can be achieved when two equivalents of the aldehyde to the phosphonium salt are used [24, 25]. The stereochemistry of the products can be controlled by altering the voltages applied to the reagent reservoirs for EOF. The variation in the voltage can alter the relative reagents concentration within the device, producing *E/Z* ratios in the range 0.47–5.2 whereas the *E/Z* ratio is ca. 3 in a batch process.

The Horner–Wadsworth–Emmons reaction has also been carried out using a microflow reactor. In the example shown in Table 5.6, α -fluoro- α,β -unsaturated esters are obtained as a mixture of *E* and *Z* isomers. However, the *E:Z* ratio is not different from that obtained in the flask reaction [11].

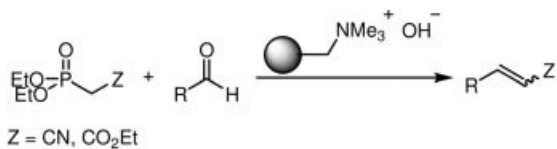
The Horner–Wadsworth–Emmons reaction can also be performed in the PASS (polymer-assisted, solution-phase synthesis) flow system. In this case, polymer-bound hydroxide ions in the flow reactor allow the preparation of alkenes in very high yield with minimal purification (Scheme 5.12) [26].

The Baylis–Hillman reaction, which is a two-component reaction with an activated alkene and a carbon electrophile, has been carried out using a microflow reactor

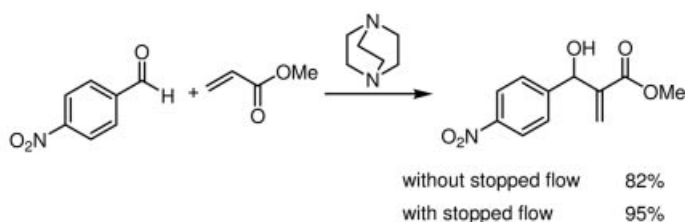
Table 5.6 Horner–Wadsworth–Emmons olefination for synthesis of fluorinated material.



R	Method	Yield (%)	Z:E
C ₆ H ₅	Microreactor	78	77:22
C ₆ H ₅	Batch	>99	70:30
4-CF ₃ -C ₆ H ₄	Microreactor	88	68:32
4-CF ₃ -C ₆ H ₄	Batch	86	64:36
4-MeO-C ₆ H ₄	Microreactor	58	74:26
4-MeO-C ₆ H ₄	Batch	>99	76:24
<i>n</i> -Nonyl	Microreactor	81	64:36
<i>n</i> -Nonyl	Batch	66	64:36



Scheme 5.12 Horner–Wadsworth–Emmons olefination in the PASS flow system.

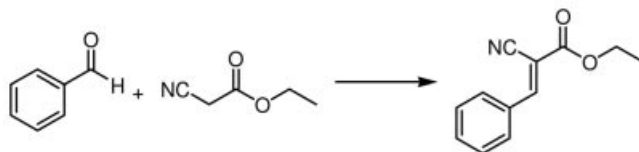


Scheme 5.13 The Baylis–Hillman reaction.

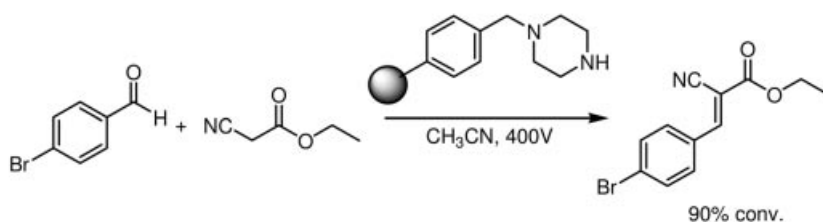
(Scheme 5.13) [27]. In the initial step, nucleophilic attack of an amine to an activated alkene takes place. In the next step, the resulting enolate reacts with an electrophile such as aldehydes to give the final products. The stopped-flow method gives better yields of the products in comparison with the continuous flow method.

The application of microflow reactors to the Knoevenagel condensation has been reported [28]. A layer of polydiallyldimethylammonium chloride (PDAMAC) is first coated on the surface of the microchannel. Then, a solution of negatively charged zeolite particles is passed through the channel, which absorbed onto the positively charged PDAMAC. These zeolite-coated microreactors can catalyze the Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate and the corresponding products are produced in yields up to 80% (Scheme 5.14).

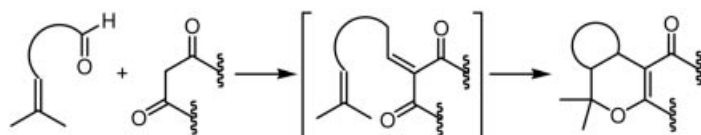
Knoevenagel condensation in a microflow reactor using immobilized piperazine on silica has also been reported. The condensation is carried out in an $800 \times 100 \mu\text{m}$ catalyst channel in borosilicate glass under the EOF conditions (Scheme 5.15) [29, 30]. Similar work with amine-functionalized silica coatings on microchannel walls has also been reported [31].



Scheme 5.14 Knoevenagel condensation.



Scheme 5.15 Knoevenagel condensation catalyzed by solid-supported piperazine.



Scheme 5.16 Knoevenagel condensation of an aldehyde with a 1,3-diketone and intramolecular hetero-Diels–Alder reaction.

A domino reaction involving Knoevenagel condensation of an aldehyde with a 1,3-dicarbonyl compound followed by the intramolecular hetero-Diels–Alder reaction with inverse electron demand has been carried out in a microflow reactor (Scheme 5.16) [32].

Four different compounds can be synthesized individually with conversions similar to those obtained in the corresponding macro batch reactions. As the residence time inside the chip increases, the conversion of the corresponding cycloadduct increases (Table 5.7).

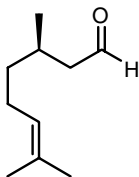
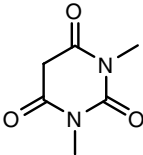
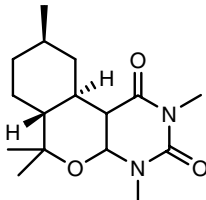
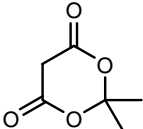
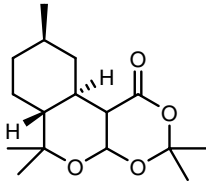
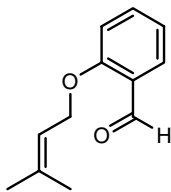
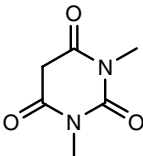
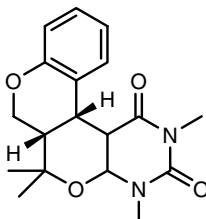
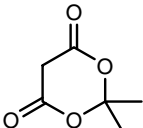
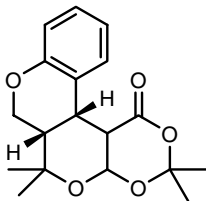
A multi-reaction experiment has been successfully carried out in a single chip reactor to obtain four different cycloadducts from the combinations of two different 1,3-dicarbonyl compounds and two different aldehydes.

The Hantzsch synthesis of 2-aminothiazoles [33] and the Knorr synthesis of pyrazoles [34], both of which involve addition–elimination sequences, have also been carried out in microflow reactors.

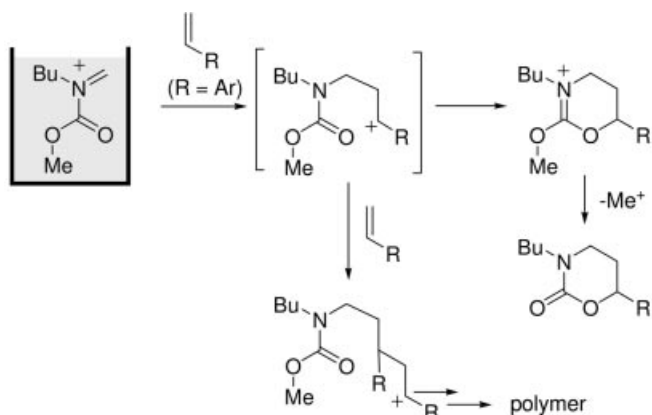
The [4 + 2] cycloaddition reaction of *N*-acyliminium ion pools [35–37] with styrene derivatives followed by the elimination of a methyl group has been successfully carried out in a microflow system containing a multi-lamination micromixer [38, 39] (Scheme 5.17).

The conventional reaction in a flask gives rise to the formation of significant amount of polymeric byproducts, although the yield of the cycloadduct depends strongly on the method of mixing, as shown in Table 5.8. The addition of styrene to an *N*-acyliminium ion pool (method A) gave the cycloadduct in 57% yield. The addition of an *N*-acyliminium ion pool to styrene (method B) gave the cycloadduct in only 20% yield and a significant amount of styrene polymer (ca. 80% based on styrene) was

Table 5.7 Knoevenagel condensation of an aldehyde with a 1,3-diketone and intramolecular hetero-Diels-Alder reaction.

Aldehyde	1,3-Diketone	Product	Conversion(%)		
			120 s	240 s	360 s
			59.5	66.0	68.0
			60.8	65.0	66.3
			66.1	67.5	75.1
			49.8	54.6	59.2

obtained, presumably because of the higher initial concentration of styrene. The simultaneous addition of two reaction components (method C) gave essentially the same results as method A. However, the use of the microflow system containing a multi-lamination micromixer led to a significant increase in the yield of cycloadducts (79%) at the expense of the amount of the polymer (ca. 20% based on styrene). Extremely fast 1:1 mixing by the micromixer seems to be responsible for the formation of the 1:1 adduct. Similar mixing effects were also observed for *p*-chloro- and *p*-methylstyrenes.



Scheme 5.17 [4 + 2] cycloaddition of *N*-acyliminium ion and alkenes and alkynes.

Table 5.8 Mixing effect of the reaction of *N*-acyliminium ion with styrenes.

Alkene	Cycloadduct	Yield (%)			
		Method A	Method B	Method C	Micromixing
		57	20	55	79
		43	12	54	70
		45	16	58	66

5.4

Conclusion

Addition reactions such as addition of enolates to carbonyl compounds, photochemical cycloaddition, radical addition and elimination reactions such as dehydration can be carried out in microflow reactors. Addition-elimination reactions such as Wittig reaction, Horner-Wadsworth-Emmons reaction, Baylis-Hillman reaction,

Knoevenagel reaction and [4 + 2] cycloaddition followed by elimination can be also carried out in microflow reactors.

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