catalysts

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Review

Recent Advances in Continuous-Flow Reactions Using Metal-Free Homogeneous Catalysts

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Abstract: Developments that result in high-yielding, low-cost, safe, scalable, and less-wasteful processes are the most important goals in synthetic organic chemistry. Continuous-flow reactions have garnered much attention due to many advantages over conventional batch reactions that include precise control of short reaction times and temperatures, low risk in handling dangerous compounds, and ease in scaling up synthesis. Combinations of continuous-flow reactions with homogeneous, metal-free catalysts further enhances advantages that include low-cost and ready availability, low toxicity, higher stability in air and water, and increased synthetic efficiency due to the avoidance of the time-consuming removal of toxic metal traces. This review summarizes recently reported continuous-flow reactions using metal-free homogeneous catalysts and classifies them either as acidic catalysts, basic catalysts, or miscellaneous catalysts. In addition, we compare the results between continuous-flow conditions and conventional batch conditions to reveal the advantages of using flow reactions with metal-free homogeneous catalysts.

Keywords: continuous-flow; micro-flow; micro-reactor; metal-free catalyst; organocatalyst; homogeneous reaction

1. Introduction

Developments that will result in high-yielding, low-cost, safe, scalable, and less-wasteful processes are the most important goals in synthetic organic chemistry. Continuous-flow reactions have garnered much attention due to many advantages over conventional batch reactions [1–15]. The advantages include (1) precise control of short reaction times, (2) precise control of reaction temperatures, (3) low risk in handling dangerous compounds, (4) ease in scaling up synthesis, (5) integration of in-line monitoring technology and optimization algorithms that enable the rapid and autonomous optimization of reaction conditions, and (6) integration of in-line purification technologies that enhance productivity and reduce footprint. Combinations of continuous-flow reactions with homogeneous catalysts further enhance their advantages such as a low catalyst loading and a short reaction time [16–22]. In particular, the use of metal-free catalysts has many benefits such as (1) low-cost and ready availability, (2) low toxicity, (3) higher stability in air and water, and (4) increased synthetic efficiency because there is no need for time-consuming removal of toxic metal traces [17,18]. Risi, Massi, and coauthors recently reviewed continuous-flow syntheses using organocatalysts [20]. Their review targeted both homogeneous and heterogeneous reactions and introduced representative examples of flow, metal-free, and homogeneous catalysis. In this review, we focused on continuous-flow reactions using metal-free homogeneous catalysts. Recent reports (2017–2020) are comprehensively summarized in the order of acidic catalysts, basic catalysts, and miscellaneous catalysts. In addition, we compared the results

between continuous-flow conditions and conventional batch conditions to reveal the advantages of the flow reactions using metal-free homogeneous catalysts.

2. Continuous-Flow Reactions Using Metal-Free Homogeneous Catalysts

2.1. Acidic Catalysts

2.1.1. Tropylium-Catalyzed Acetalization Reactions

Nguyen and coworkers reported metal-free acetalization reactions using tropylium salts as an organic Lewis acid [23]. Aromatic tropylium salts are recognized as stable analogues of tritylium salts [24]. The authors were the first to use tropylium ions as organic Lewis catalysts. Under optimized batch conditions, aldehyde **1** (0.83 M, 1.0 equiv.) was reacted with trialkyl orthoformate **2** (2.0 equiv.) in the presence of tropylium tetrafluoroborate **4** (5 mol%) at 70 °C for 5 h. A variety of acetal derivatives **5** were obtained (23 examples, up to 99% yield). The developed reaction was applied to continuous-flow synthesis (Figure 1). A syringe pump was used to inject a solution of **1** (0.08 M, 1.0 equiv.), either **2** (2.0 equiv.), or ethylene epoxide (**3**) (4 equiv., concentration was determined by ^{1}H NMR analysis), and **4** (1 mol%) in acetonitrile into the coils of a tubular reactor (temperature: 90 °C, residence time: 45 min) at a flow rate of 0.1 mL/min. The reactor was immersed in an oil bath, and connected to a back-pressure regulator (BPR, 100 psi). The developed flow protocol afforded desired acetals **5** or **6** (Figure 1; 10 examples, up to 99%) in yields that were equal to, or higher than, those using batch conditions (Table 1). Gram scale synthesis of acetals **5a**–**5c** was demonstrated. The amount of tropylium tetrafluoroborate catalyst was reduced from 5 to 1 mol% by employing flow conditions. The reaction time was shortened (45 min) by using heating conditions (90 °C). The use of the BPR allowed heating above the boiling point of acetonitrile. The flow reaction allowed the highly efficient multi-gram synthesis of a range of acyclic acetals including volatile or gaseous compounds such as acetaldehyde and ethylene epoxide. The authors cautioned that this reaction might be difficult to perform under batch conditions because of the use of gaseous reagents.

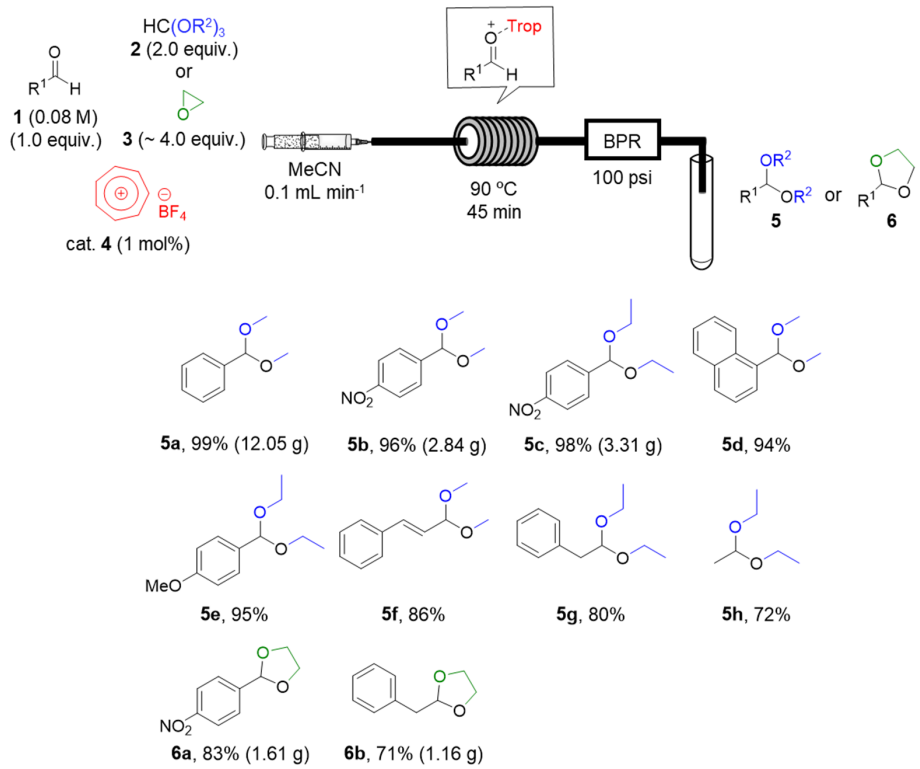

Figure 1. Tropylium-catalyzed acetalization reactions under continuous-flow conditions.

Table 1. Comparison between the continuous-flow conditions and conventional batch conditions of tropylium-catalyzed acetalization reactions.

Entry	Reactor	Concentration/M	Catalyst Loading/ mol%	Reaction Time	Temperature/°C	Product	Yield/%
1	batch	0.83	5	5 h	70	**5a**	92
2	flow	0.08	1	45 min	90	**5a**	99
3	batch	0.83	5	5 h	70	**5b**	91
4	flow	0.08	1	45 min	90	**5b**	96
5	batch	0.83	5	5 h	70	**5c**	99
6	flow	0.08	1	45 min	90	**5c**	98
7	batch	0.83	5	5 h	70	**5d**	90
8	flow	0.08	1	45 min	90	**5d**	94
9	batch	0.83	5	5 h	70	**5e**	95
10	flow	0.08	1	45 min	90	**5e**	95
11	batch	0.83	5	5 h	70	**5f**	75
12	flow	0.08	1	45 min	90	**5f**	86
13	batch	0.83	5	5 h	70	**5g**	36
14	flow	0.08	1	45 min	90	**5g**	80

2.1.2. Tritylium-Catalyzed Interrupted Povarov Reactions

Guo, Li, and coworkers reported *cis*-4-aminobenzodihydropyran synthesis using a tritylium-catalyzed interrupted Povarov reaction [25]. The family of triarylmethylium cations are stabilized as a result of delocalization of the positive charge over the three aromatic rings [26,27]. These researchers proposed and validated a mechanism of the Lewis acid-catalyzed reaction on the basis of the experimental data and prior study [28,29]. Salicylaldimine **11** is activated by complexation with tritylium ions to form the intermediate **12**, and it is attacked by the electron-rich alkene **9** (Figure 2). Under optimized batch conditions, a mixture of substituted salicylaldimine **11** (0.4 M, 1.0 equiv.), triphenylmethylium (tritylium) tetrafluoroborate (**10**) ($TrBF_4$, 1 mol%), and electron-rich alkene **9** (2.0 equiv.) in anhydrous THF was stirred at room temperature. The desired products **13** were obtained in good to excellent yields (13 examples, up to 92% and *cis*:*trans* = 95:5). The authors demonstrated a one-flow synthesis of benzodihydropyran **13a** from salicylaldehyde **7a**, aniline **8a**, and 2,3-dihydrofuran **9a** (Figure 2). Solutions of **7a** (1.1 M, 1.0 equiv.) and **8a** (1.0 equiv.) in THF were added to an arrowhead mixer. The combined mixture passed through a reaction tube at 60 °C for 2 min. The generated water was removed by passing the reaction mixture through an absorbent column. The resultant dehydrated solutions of imine **11a**, **9a** (1.0 equiv.), and 1 mol% of $TrBF_4$ (**10**) in THF were injected into a T-shape mixer. The resultant mixture was passed through a second reaction tube at 25 °C for 1 min. The desired product **13a** was obtained in an 88% yield (*cis*:*trans* = 90:10). On the other hand, a decreased yield and *cis*/*trans* selectivity of **13a** (60%, *cis*:*trans* = 70:30) were observed under the batch conditions even in the presence of MS4A (five beads) (Table 2). The authors speculated that the carbocations were either deactivated or decomposed by residual water generated during the imine formation step.

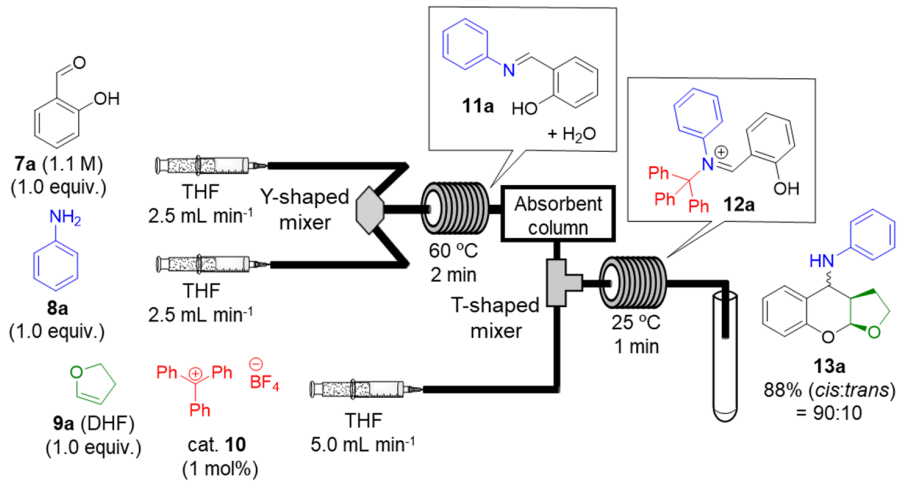

Figure 2. $TrBF_4$-catalyzed interrupted Povarov reaction under flow conditions.

Table 2. Comparison between the continuous-flow conditions and conventional batch conditions of $TrBF_4$-catalyzed interrupted Povarov reaction.

Entry	Reactor	Catalyst Loading/mol%	Reaction Time/min	Temperature/°C	Yield/%	*cis*:*trans*
1	batch	1	10 [a]	r.t.[d]	60	70:30
2	flow	1	2 [b], 1 [c]	60, 25	88	90:10

[a] Total time for imine formation and interrupted Pavarov reaction. [b] Time for imine formation. [c] Time for interrupted Pavarov reaction. [d] Room temperature.

2.1.3. Chlorination/Epoxidation of Biobased Glycerol

Monbaliu and coworkers reported the transformation of biobased glycerol into oxiranes (epichlorohydrin and glycidol) under continuous-flow conditions [30]. The developed approach allowed economically and environmentally favorable chlorination/epoxidation using organocatalysts and aqueous solutions of hydrochloric acid and sodium hydroxide. Carboxylic acids have been used as catalysts in the chlorination of glycerol [31]. Briggs and coworkers and Yin and coworkers separately revealed that the catalytic efficiency of carboxylic acids is influenced by their steric hindrance [32,33] rather than their p*K*a [33]. Less hindered carboxylic acids tended to exert higher catalytic activity. Monbaliu and coworkers screened a library of homogeneous carboxylic acid catalysts, and identified pimelic acid **15** as the best example. Solutions of glycerol (**14**) (neat, 1.0 equiv.) in water, aqueous hydrochloric acid (36 wt%, 6.0 equiv.), and **15** (10 mol%) were injected into a PEEK T-shape mixer (Figure 3). The reaction proceeded in a PFA capillary coil at 140 °C for 20 min under 8 bar. The desired 1,3-dichloro-2-propanol (**16**) was obtained in a 44% yield (Figure 3, >99% conversion, 81% cumulated yield).

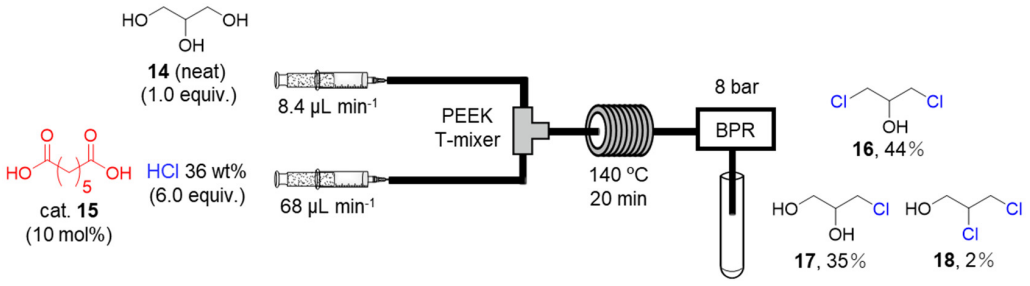

Figure 3. Chlorination of glycerol catalyzed in a flow of pimelic acid. Conversion and yield were determined by GC/FID (Gas Chromatography/Flame Ionization Detection) analysis.

Araujo Filho and coworkers reported the kinetics of sodium hydroxide-mediated epoxidation of 1,3-dichloro-2-propanol (**16**) under continuous-flow conditions [34]. Monbaliu and coworkers found that the upstream chlorination step directly concatenates the subsequent epoxidation step (Figure 4). The resultant mixture and an aqueous solution of sodium hydroxide (4 M, 1.5 equiv. with respect to HCl) were injected into a PEEK T-mixer and reacted in a PFA capillary coil at room temperature for 10 min under 5.2 bar. The resultant mixture along with methyl *tert*-butyl ether (MTBE, 320 µL min^{-1}) was then added to a second PEEK T-mixer. The biphasic solution was separated into an organic phase and an aqueous phase using a Zaiput Flow Technologies liquid–liquid separator (SEP-10) equipped with a hydrophobic membrane (pore size: 0.5 µm). The desired epichlorohydrin (**19**) and glycidol (**20**) were obtained in 44% and 30% yields, respectively (Figure 4, >99% conversion, 74% cumulated yield).

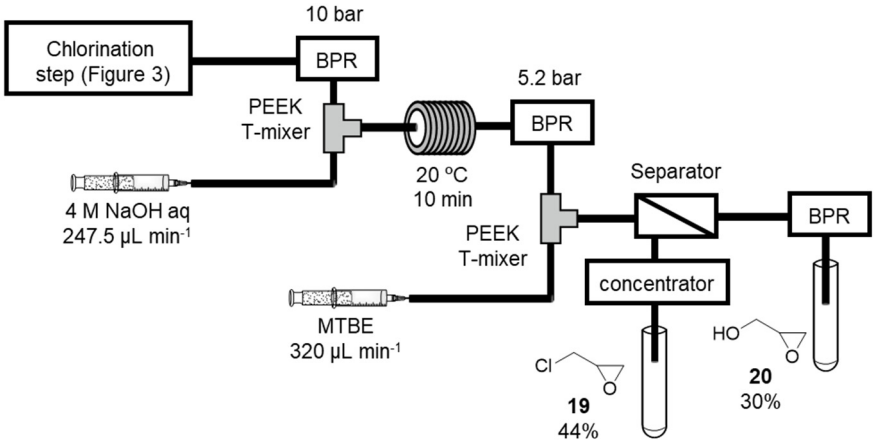

Figure 4. Transformation of glycerol into oxiranes by chlorination/epoxidation sequence under continuous-flow conditions. Conversion and yield were determined by GC/FID analysis.

2.1.4. Retro-Claisen-Type C–C Bond Cleavage of Diketones with Tropylium Catalyst

Nguyen, Koenigs, and coworkers reported a *retro*-Claisen-type reaction for the synthesis of ester derivatives from 1,3-dicarbonyl compounds using tropylium tetrafluoroborate as an organic Lewis acid [35]. Under optimized batch conditions, a mixture of 1,3-dicarbonyl compound **21** (neat, 1.0 equiv.) and nucleophile **22** (alcohol or amine, 2.0 equiv.) was reacted in the presence of tropylium tetrafluoroborate (**4**) (10 mol%) at 100 °C for 16 h. The use of trifluoroethanol (TFE) as a solvent (room temperature, 24 h) afforded comparable results. A variety of esters and amides **23** were obtained by the two developed protocols under batch conditions (20 examples, up to 99%). Under optimized flow conditions, solutions of 1,3-dicarobonyl compounds **21** (0.50 M, 1.0 equiv.) and tropylium tetrafluoroborate (**4**) (5 mol%), along with either alcohols or amine (1 M, 2.0 equiv.), in TFE were injected into a 10 mL tubular reactor and heated to 150 °C for 30 min (Figure 5). The desired products **23** were obtained in high to excellent yields (Figure 5; six examples, up to 93%). The developed flow protocol used a decreased amount of catalyst (Table 3), and enabled multi-gram scale synthesis.

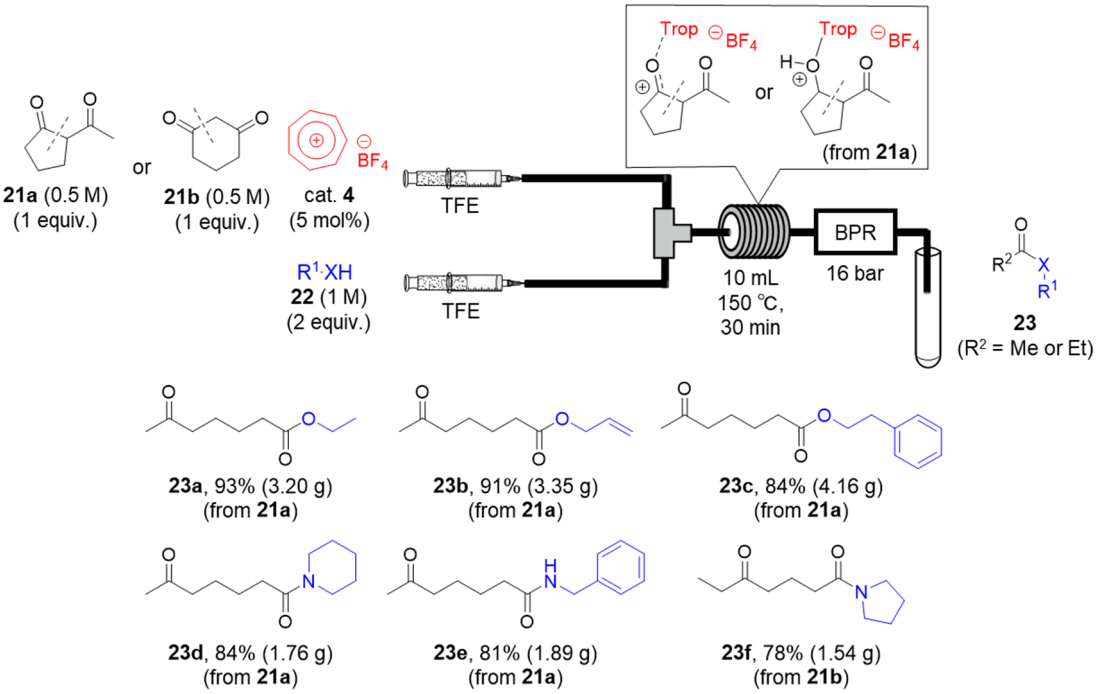

Figure 5. *Retro*-Claisen alcoholysis and aminolysis in flow.

Table 3. Comparison between the continuous-flow conditions and conventional batch conditions of *retro*-Claisen alcoholysis and aminolysis.

Entry	Reactor	Concentration/M	Catalyst Loading/mol%	Reaction Time	Temperature/°C	Product	Yield/%
1	batch	neat	10	16 h	100	**23a**	94
2	batch	1.67	10	24 h	r.t. [a]	**23a**	89
3	flow	0.25	5	30 min	150	**23a**	93
4	batch	neat	10	16 h	100	**23b**	97
5	batch	1.67	10	24 h	r.t. [a]	**23b**	85
6	flow	0.25	5	30 min	150	**23b**	91
7	batch	neat	10	16 h	100	**23c**	82
8	flow	0.25	5	30 min	150	**23c**	84
9	batch	neat	10	16 h	100	**23d**	85
10	flow	0.25	5	30 min	150	**23d**	84
11	batch	neat	10	16 h	100	**23e**	76
12	batch	1.67	10	24 h	r.t. [a]	**23e**	80
13	flow	0.25	5	30 min	150	**23e**	81
14	batch	neat	10	16 h	100	**23f**	70
15	flow	0.25	5	30 min	150	**23f**	78

[a] Room temperature.

2.1.5. Sustainable Continuous-Flow Synthesis of Allantoin

Allantoin is widely used in the cosmetic and pharmaceuticals industries. Monbaliu and Salvadeo optimized its synthetic protocol under continuous-flow conditions based on a rational Design of Experiments (DoE) approach [36]. Solutions of glyoxylic acid (**24**) (8.7 M, 2.5 equiv.) and urea **25** (3.2 M, 1.0 equiv.) in water were injected into a PEEK T-mixer and reacted in a PFA coil at 120 °C for 6 min under 6 bar. The complete conversion of urea **25** into the desired product **26** was accomplished (Figure 6). Glyoxylic acid was used as both a reactant and a Brønsted acid catalyst.

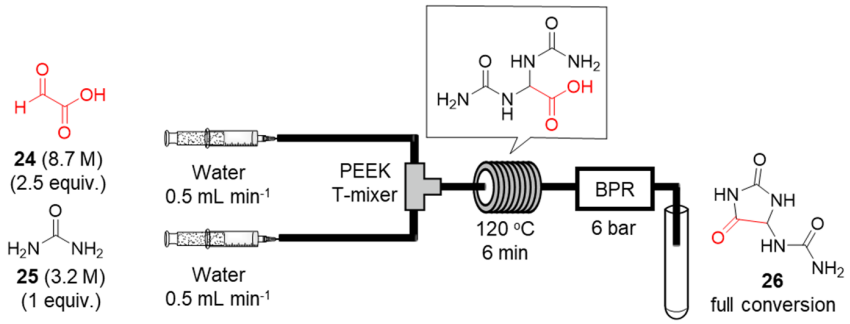

Figure 6. Continuous-flow synthesis of allantoin. Conversion was calculated via HPLC analysis.

2.1.6. Tropylium-Promoted Prenylation Reactions of Phenols in Flow

Nguyen and coworkers achieved a prenylation of phenols using tropylium tetrafluoroborate as an organocatalyst [37]. The developed continuous-flow approach enabled a metal-free, inexpensive, and multiple-gram scale synthesis of 2,2-dimethylchromans in a short reaction time. The proposed reaction mechanism included a hidden Brønsted acid catalytic pathway similar to that reported in a study by Hintermann and coworkers [38]. Under optimized batch conditions, 4-methoxyphenol (**27a**) (0.01 M, 1.0 equiv.), isoprene (**28**) (2.0 equiv.), and tropylium tetrafluoroborate (**4**) (10 mol%) were reacted in 1,2-dichloroethane (DCE) at 60 °C for 24 h. The desired product **29a** was obtained in a 60% yield. Under optimized flow conditions, a solution of phenol **27** (0.02 M, 1.0 equiv.) and **4** (2 mol%) in dichloromethane, and a solution of isoprene (**28**) (0.04 M, 2.0 equiv.) were injected into a 10 mL tubular reactor (temperature: 100 °C, residence time: 2 min) in a Vaportec R-series system (Figure 7). The desired prenylation products **29** were obtained in good to excellent yields (Figure 7; five examples, up to 96%). The flow reaction allowed quick access to 2,2-dimethylchromans with a decreased amount of catalyst. The observed yield of **29a** was higher compared with that of batch reactions (Table 4). In addition, the developed protocol enabled 20 mmol scale synthesis and afforded higher yields.

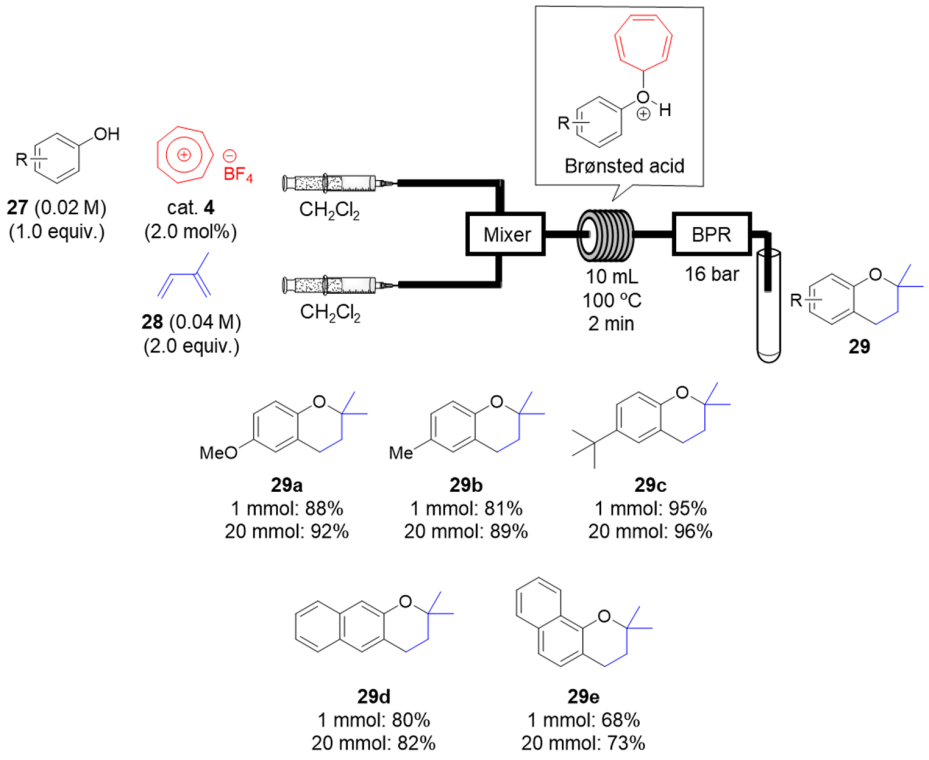

Figure 7. Tropylium-catalyzed prenylation reactions of phenols under continuous-flow conditions.

Table 4. Comparison between the continuous-flow conditions and conventional batch conditions of tropylium-catalyzed prenylation reactions.

Entry	Reactor	Catalyst Loading/mol%	Reaction Time	Temperature/°C	Product	Yield/%
1	batch	10	24 h	60	**29a**	60
2	flow	2	2 min	100	**29a**	88

2.2. Basic Catalysts

2.2.1. Organocatalytic α-Trifluoromethylthiolation of Silylenol Ethers

Benaglia, Rossi, and coworkers reported the organocatalytic α-trifluoromethylthiolation of silylenol ethers in the presence of a catalytic amount of Lewis base [39], on the basis of their previous study of an α-thiofunctionalization reaction [40]. Under optimized batch conditions, a mixture of silylenol ether **30** (0.1 M, 1.0 equiv.), tetrahydrothiophene (**31**) (THT, 10 mol%), and *N*-(trifluoromethylthio)saccharin (**32**) (1.0 equiv.) in acetonitrile was stirred at 80 °C for 5 h. The desired products **33** were obtained (4 examples, up to 75% conversion). The authors investigated continuous-flow conditions in order to improve the reaction efficiency (Figure 8). A mixture of silylenol ether **30** (0.2 M, 1.0 equiv.), THT (**31**) (10 mol%), and biphenyl as an internal standard (1.0 equiv.) in acetonitrile, along with a solution of *N*-(trifluoromethylthio)saccharin (**32**) (1.0 equiv.), were injected into a glass reactor (internal volume: 10 µL, temperature: 60 °C, residence time: 10 min, Labtrix® Start, Chemtrix). The desired products **33** were obtained (Table 5, Figure 8; four examples, up to 52% conversion). The productivity and space-time yields of **33a** via continuous-flow conditions were 1.5 and 200 times higher, respectively, than using batch conditions.

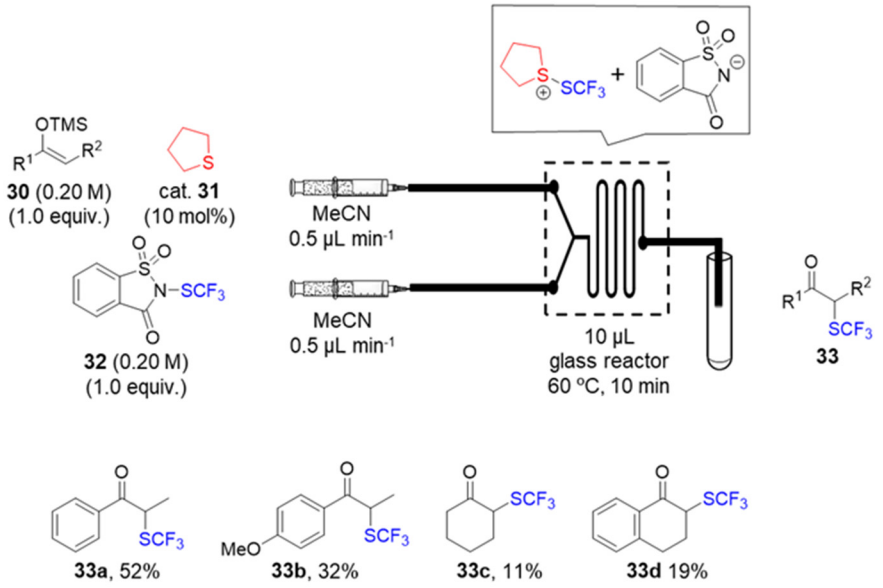

Figure 8. α-Trifluoromethylthiolation of silylenol ethers. The yield of **33a** was determined via ^{1}H NMR analysis or GC analysis, while the yields of **33b–d** were determined via ^{19}F NMR analysis.

Table 5. Comparison between the continuous-flow conditions and conventional batch conditions of α-trifluoromethylthiolation of silylenol ethers.

Entry	Reactor	Catalyst Loading/mol%	Reaction Time	Temperature/°C	Product	Conversion/%
1	batch	10	5 h	80	**33a**	74
2	flow	10	10 min	60	**33a**	52

2.2.2. Solvent-Free Organocatalytic Synthesis of Cyclic Carbonates

Monbaliu and coworkers reported the solvent- and metal-free organocatalyzed transesterification of dimethyl carbonate (DMC) with 1,2-diols under continuous-flow conditions [41]. DMC has attracted attention as a less-toxic carbonyl source [42–44]. However, there are only a limited number of reports on the carbonation of glycerol with DMC under continuous-flow conditions using homogeneous catalysts [45,46]. The authors screened reaction parameters including residence time, temperature, glycerol/DMC molar ratios, and the amounts of catalysts. The best catalyst was identified as 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (**36**) (Barton's base). Under optimized flow conditions, liquid 1,2-diols **34** (neat, 1.0 equiv.), DMC (**35**) (3.0 equiv.) and Barton's base (**36**) (1–2 mol%) were introduced into a T-mixer (Figure 9). The mixture was reacted in a coil reactor under conditions A–C (conditions A: 135 °C, 2 min, 1 mol% catalyst, 7 bar; conditions B: 160 °C, 4 min, 2 mol% catalyst, 7 bar; conditions C: 180 °C, 8 min, 2 mol% catalyst, 11 bar.) as shown in Figure 9. The desired products **37** were obtained (Figure 9; nine examples, up to 96%). The developed approach was applied to a pilot-scale synthesis that afforded 68.3 mol of glycerol carbonate per day (8 kg per day).

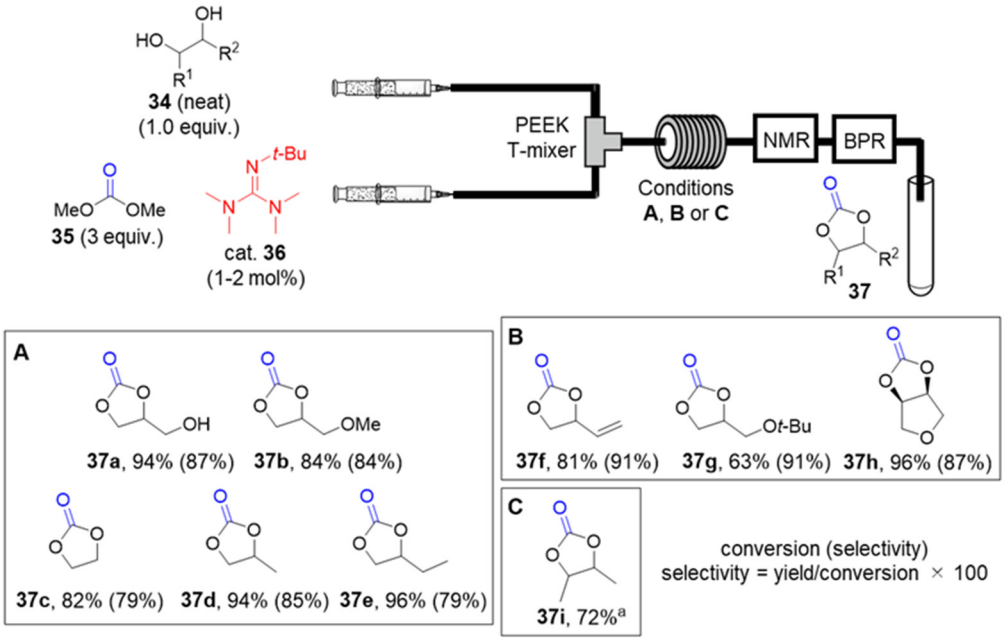

Figure 9. Chemical structures of synthesized cyclic carbonates. Conversions and yields were determined via GC/FID analysis and ^{1}H NMR analysis in $CDCl_3$ with mesitylene as an internal standard. [a] NMR yield.

2.2.3. Organocatalyzed Decarboxylative Trichloromethylation of Morita-Baylis-Hillman Adducts

Lindhardt and coworkers reported the organocatalyzed decarboxylative trichloromethylation of Morita–Baylis–Hillman (MBH) alcohols under continuous-flow conditions [47]. Tributylamine (TBA) was identified as a superior organocatalyst. On the basis of optimized batch conditions, the authors developed a continuous-flow protocol (Figure 10). Solutions of Morita-Baylis-Hillman alcohol **38** (0.2 M, 1.0 equiv.) and TBA (**39**) (1.5 equiv.) in chloroform, and trichloroacetic anhydride (**40**) (1.2 equiv.) also in chloroform, were injected into a T-connector, and the mixture was passed through a small premixing tubular reactor (room temperature, 2 min). The resultant mixture was then passed through a second heated tubular reactor (70 °C, 20 min). The desired products **41** were obtained in higher yields for all investigated entries compared with those of batch conditions (Figure 10; six examples, up to 86%). Scaled-up syntheses of **41e** and **41f** (more than 10 grams) were demonstrated. Optimized batch conditions required 20 h to complete the reaction, but higher temperatures were employed in the flow reaction, which shortened the reaction time to 20 min. The use of a 500 psi back-pressure regulator (BPR) avoided the vaporization of

chloroform and carbon dioxide, which can lead to an undesired segmentation of the flow. TBA worked as a base in the initial trichloroacetylation step and an organocatalyst in the subsequent decarboxylation step. Trichloroacetic anhydride was selected as the acetylation agent because it generated soluble salts (tributylammonium trichloroacetate) with TBA.

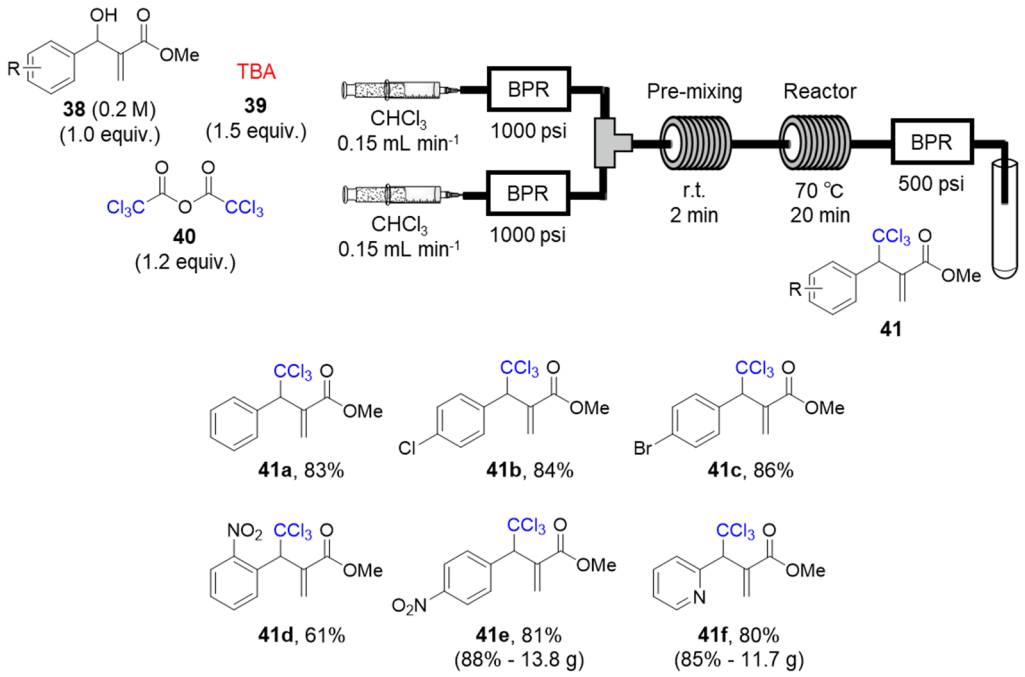

Figure 10. Telescoped decarboxylative trichloromethylation of MBH-alcohols under continuous-flow conditions.

2.2.4. Micro-Flow Synthesis of β-Amino Acid Derivatives via a Rapid Dual Activation Approach

The syntheses of β-amino acid derivatives have been demonstrated using rapid dual activation (<3.3 s) of both β-amino acid *N*-carboxy anhydride and alkyl chloroformate under micro-flow conditions [48]. A single-step micro-flow synthesis of amino acid *N*-carboxy anhydride was previously reported [49,50]. Solutions of β-phenylalanine-NCA (**42**) (0.30 M, 1.0 equiv.), isobutyl chloroformate (**43**) (1.0 equiv.), and *N*-methylmorpholine (2.0 equiv.) in CH_2Cl_2 were injected into a T-shape mixer at 20 °C (Figure 11). The resultant mixture was passed through a Teflon tube for 3.3 s. The reaction mixture and a solution of amine **44** (1.0 equiv.) and 4-dimethylaminopyridine (**45**) (DMAP, 10 mol%) in CH_2Cl_2 were injected into the second T-shape mixer at 20 °C and reacted in the Teflon tube for 7.0 s. A catalytic amount of DMAP activated the mixed carbonic anhydride moiety to generate a highly active acyl pyridinium cation **46**. The mixture was poured into a solution of amine (1.0–2.0 equiv.) or thiol (1.0 equiv.) and diisopropylethylamine (1.0 equiv.). The desired products **47** were obtained in good yields (Figure 11; nine examples, up to 90%). In addition, dihydrouracil synthesis was performed. The desired products **48a** and **48b** were obtained in good yields without a second nucleophile. The yield of the reaction was not reproducible under batch conditions due to batch-to-batch differences in the mixing efficiency.

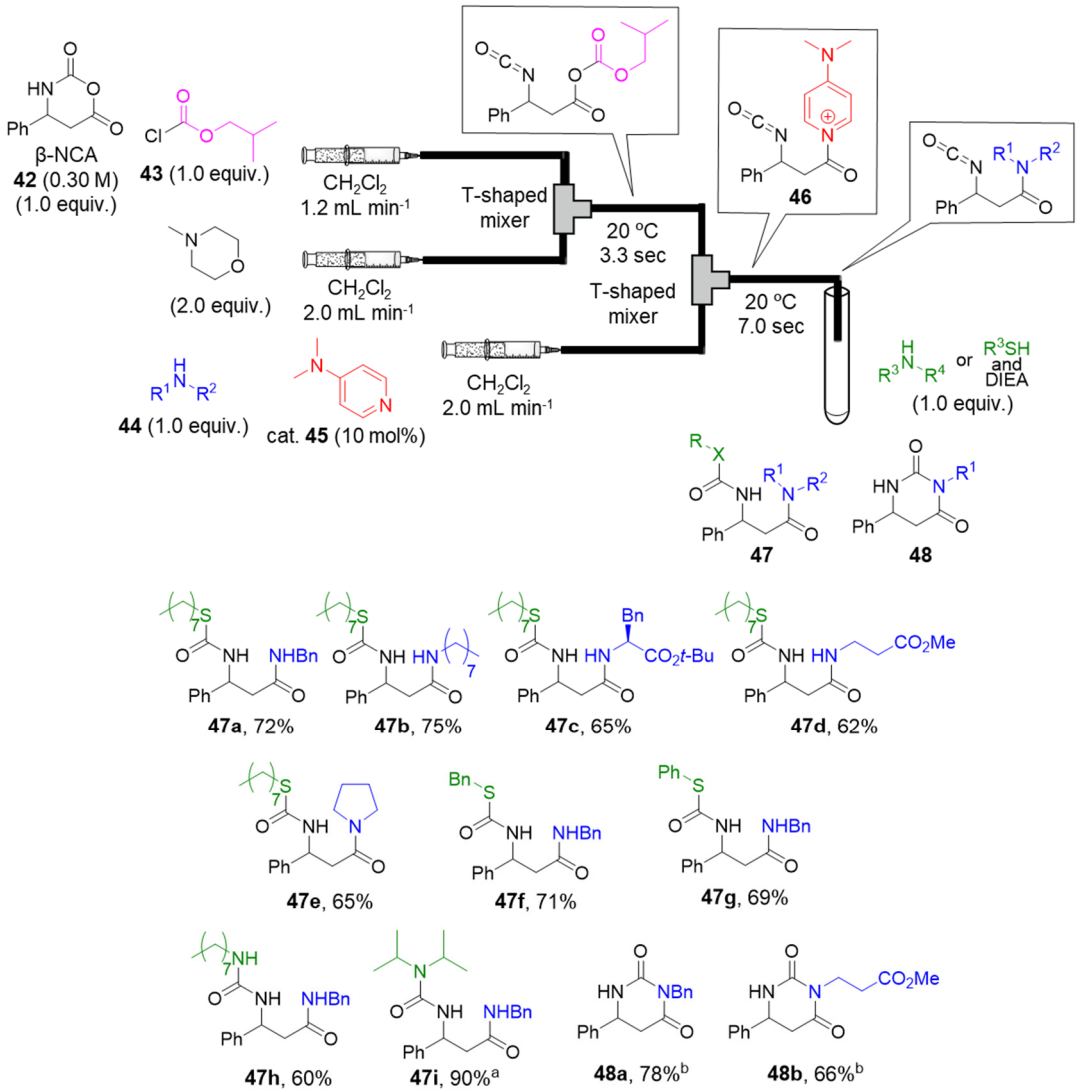

Figure 11. The synthesis of β-amino acid derivatives from β-NCA under micro-flow conditions. [a] 2.0 equiv. of diisopropylamine was used. [b] Cyclization was carried out at 100 °C for 2 h in toluene.

2.3. *Miscellaneous Catalysts*

2.3.1. Organocatalytic Synthesis of Cyclic Carbonates under Continuous-Flow Conditions

Monbaliu and coworkers reported an efficient organocatalytic process for the synthesis of cyclic organic carbonates from the corresponding 1,2-diols under continuous-flow conditions [51]. The authors used tetrabutylammonium bromide (**49**) as an inexpensive, air-stable, and less toxic organic catalyst (Figure 12). To a PEEK T mixer were injected 1,2-diols **34** (neat, 1.0 equiv.), **49** (3.5 mol%), and DMC (**35**) (2.25 or 3.0 equiv.). The mixture was then heated in a stainless-steel capillary coil at 180 °C for 3 min. The desired products **37** were obtained from a wide range of functionalized diols in good to excellent yields (Figure 12; 20 examples, up to 95%). The developed process allowed pilot-scale synthesis under continuous-flow conditions (76% yield, 13.6 kg per day).

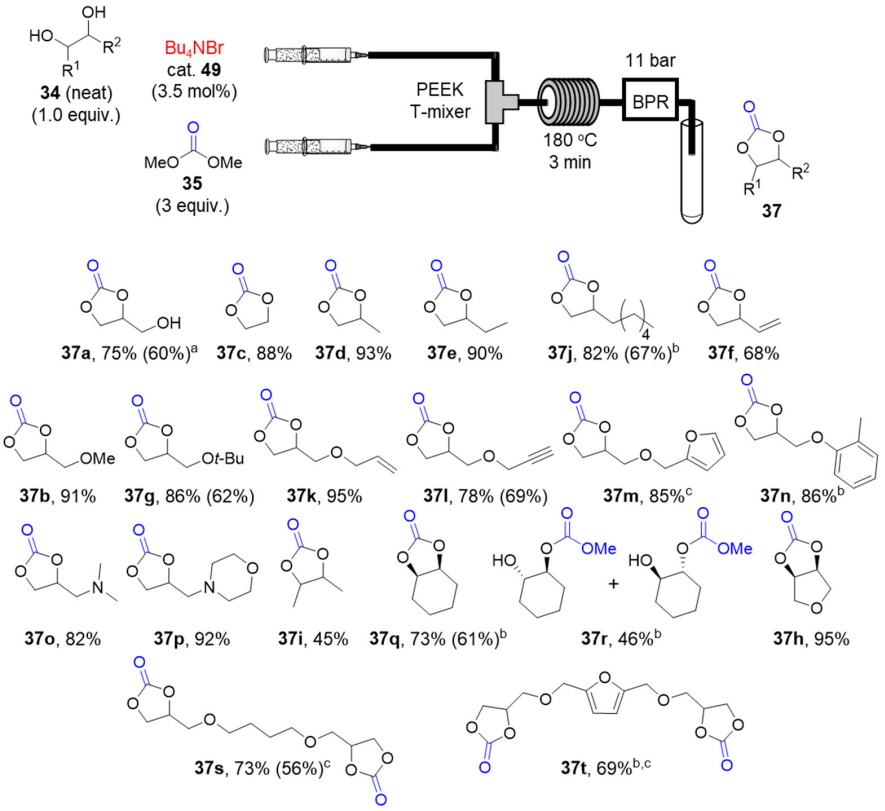

Figure 12. Carbonation of 1,2-diols under flow conditions. Yields were determined either via GC/FID analysis or ^{1}H NMR analysis with mesitylene as an internal standard (isolated yields are indicated in parentheses). [a] 2.25 equiv. of DMC. [b] Diol **34** was pumped as a solution in DMSO. [c] Residence time = 9 min.

2.3.2. Asymmetric Organocatalytic Aldol Reaction of a Hydrophobic Aldehyde

Gröger and coworkers reported the one-flow asymmetric organocatalytic aldol reaction of a hydrophobic aldehyde in an aqueous medium [52]. The authors previously developed a one-pot process under batch conditions [53], and the developed process was extended to continuous-flow synthesis. Under flow conditions, a solution of 3-chlorobenzaldehyde (**50**) (0.50 M, 1.0 equiv.) in 2-propanol and phosphate buffer with a solution of Singh's catalyst (**51**) (3.6 mol%) [54], acetone (**52**) (9.0 equiv.), 2-propanol, and phosphate buffer were injected into a T shape mixer and reacted in a Teflon tube at room temperature for 60 min (Figure 13). The desired product **53** was obtained in a 74% conversion and with an 89% ee. The flow process afforded almost equal or slightly better results than the batch process (Table 6; 67% conversion, 91% ee).

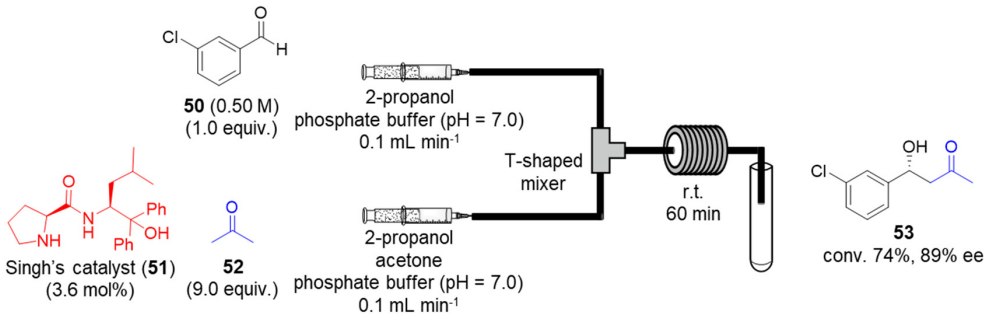

Figure 13. The asymmetric organocatalytic aldol reaction of a hydrophobic aldehyde in an aqueous medium under flow conditions. The conversions were determined via ^{1}H NMR analysis of the crude reaction mixtures. The ee was determined via HPLC analysis after preparative TLC (Thin-Layer Chromatography).

Table 6. Comparison between the continuous-flow conditions and conventional batch conditions of the asymmetric organocatalytic aldol reaction of a hydrophobic aldehyde in an aqueous medium.

Entry	Reactor	Catalyst Loading/mol%	Reaction Time/min	Temperature	Yield/%	ee/%
1	batch	3.6	60	r.t. [a]	67	91
2	flow	3.6	60	r.t. [a]	74	89

[a] Room temperature.

2.3.3. Organocatalytic Michael Addition of β-Ketoester to Nitroalkene

Benaglia and coworkers reported an organocatalytic Michael addition under continuous-flow conditions [55]. A solution of nitroalkene **54** (1 M, 1 equiv.) in toluene and a solution of β-ketoester **55** and Takemoto's catalyst **56** [56] in toluene was injected into a glass microreactor (internal volume: 15 µL, temperature: 80 °C, residence time: 15 min, Labtrix® Start, Chemtrix) using syringe pumps (total flow rate: 1 µL/min). The desired product **57** was obtained in a 45% isolated yield (Figure 14).

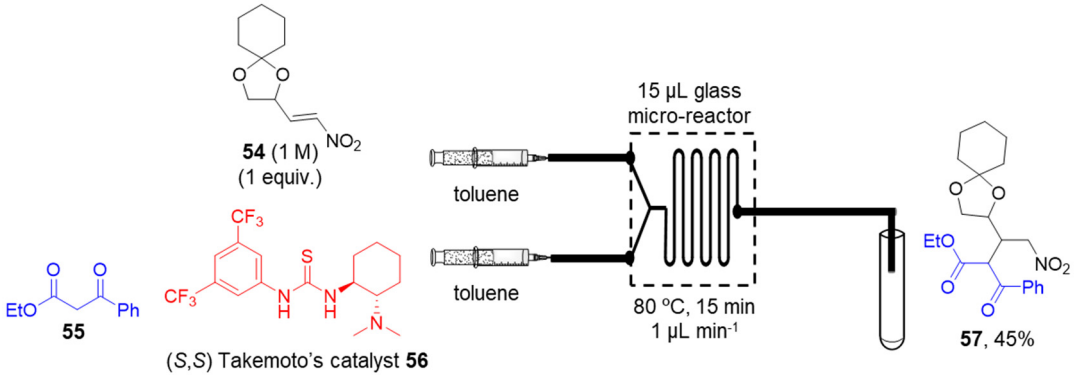

Figure 14. Organocatalyzed Michael addition to D-mannitol-derived enantiopure nitroalkene under flow conditions.

2.3.4. Exploration of an Enantioselective Organocatalyzed Rauhut-Currier Reaction and [3 + 2] Annulation under Flow Conditions Using Machine-Learning

Sasai, Takizawa, Washio, and coworkers developed a highly atom-economical enantioselective organocatalyzed Rauhut-Currier reaction [57] and [3 + 2] annulation [58] sequence of dienone with allenoate under micro-flow conditions using machine learning [59]. Optimization of the reaction conditions was supported by Gaussian process regression (GPR). Solutions of dienone **58** (0.02 M, 1.0 equiv.), allenoate **59** (2.0 equiv.), and a chiral phosphine catalyst **60** (20 mol%) in toluene were injected into a micro-mixer (Comet X-01) and reacted in a stainless-steel tube at 80 °C. The desired highly functionalized chiral spirooxindole analogues **61** were obtained within 26 s (Figure 15; 19 examples, up to 92%). On the other hand, a decreased yield and ee of **61a** (65%, 92% ee) were observed under the batch conditions (Table 7). The authors described that the rapid mixing under micro-flow conditions suppressed the undesired side reactions.

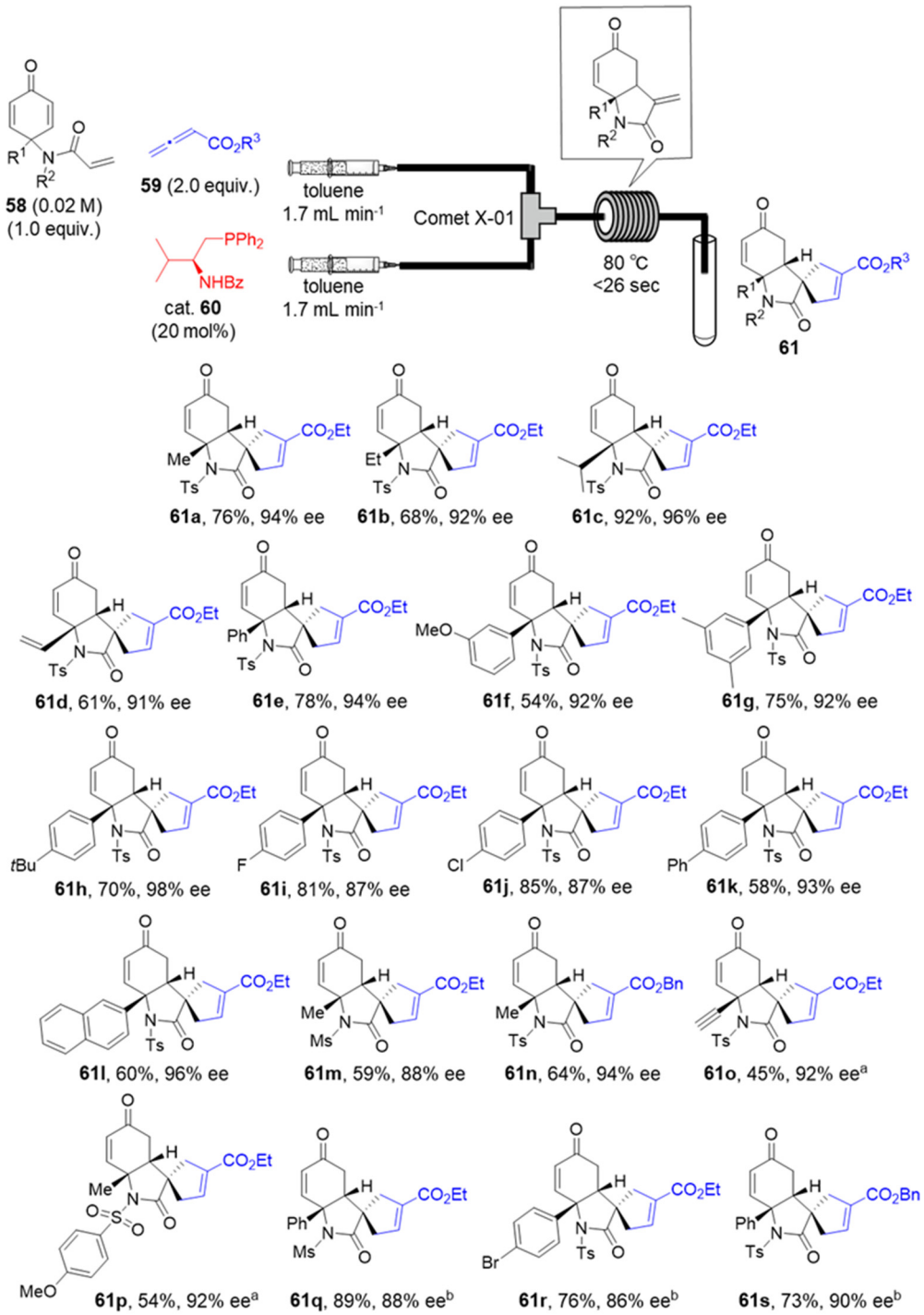

Figure 15. Rauhut-Currier reaction and [3 + 2] annulation sequence under flow conditions. Enantiomeric excess was determined via HPLC analysis. [a] 1.5 equiv. of allenoate **59**. [b] Residence time = 21 s (flow rate = 2.1 mL min^{-1}). [c] Yields were determined via ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

Table 7. Comparison between the continuous-flow conditions and conventional batch conditions of Rauhut-Currier reaction and [3 + 2] annulation sequence.

Entry	Reactor	Catalyst Loading/mol%	Reaction Time	Temperature/°C	Product	Yield/% [a]	ee/%
1	batch	20	<0.5 h	80	**61a**	65	92
2	flow	20	<26 s	80	**61a**	78	94

[a] Yields were determined via ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

2.3.5. N-Methylated Peptide Synthesis via Acyl N-Methylimidazolium Cation Generation Accelerated by a Brønsted Acid

Our group has developed efficient processes for the synthesis of peptides [60–64] using a rapid mixing technology of the micro-flow synthesis [1–4]. We recently developed the synthesis of high-yielding *N*-methylated peptides without severe racemization via *N*-methyl imidazolium cation formation in the presence of HCl [65]. The key to success was the addition of a catalytic amount of HCl. We speculated that a mixed carbonic anhydride coordinated with the proton would enhance the electrophilicity. Under optimized flow conditions, a solution of *N*-protected amino acid **62** (0.33 M, 1.0 equiv.), diisopropylethylamine (1.0 equiv.), dimethylbenzylamine **63** (5 mol%) in 1,4-dioxane, and isopropyl chloroformate **64** (1.0 equiv.) in 1,4-dioxane was injected into a T shape mixer (Figure 16). The mixed carbonic anhydride formation was completed at 60 °C in 5.0 s. The resultant mixture containing mixed carbonic anhydride and a solution of *N*-methylated amino acid **65** (1.0 equiv.), *N*-methyl imidazole (**66**) (NMI, 10 mol%), and HCl (**67**) (15 mol%) in 1,4-dioxane was injected into a T shape mixer and reacted in a Teflon tube at 60 °C for 2 min. The desired *N*-methylated peptides **70** were obtained in high yields (Figure 16; 16 examples, up to >99%). Our experimental results showed that the use of a catalytic amount of **63** containing two methyl groups was the most suitable for the formation of the mixed carbonic anhydride **68**. The use of highly electrophilic *N*-methylimidazolium cation **69** [66] enabled the amidation of sterically hindered *N*-methyl amino acids. We used NMI due its comparable reactivity, lower toxicity, and cost compared with that of DMAP [67]. A reduced (*ca.* 15%) yield was observed when the developed reaction was carried out under batch conditions. Surprisingly, the dimethylbenzyl amine-catalyzed mixed carbonic anhydride formation was extremely rapid, and was completed in 0.5 s (20 °C) using 10 mol% of the catalyst for a turnover frequency (TOF) of 14,400 h^{-1} [65]. We speculated that the micro-flow conditions successfully avoided an undesired decomposition of the unstable acyl ammonium cation, such as in decarboxylation, and, thus, flow conditions afforded higher yields compared with batch conditions.

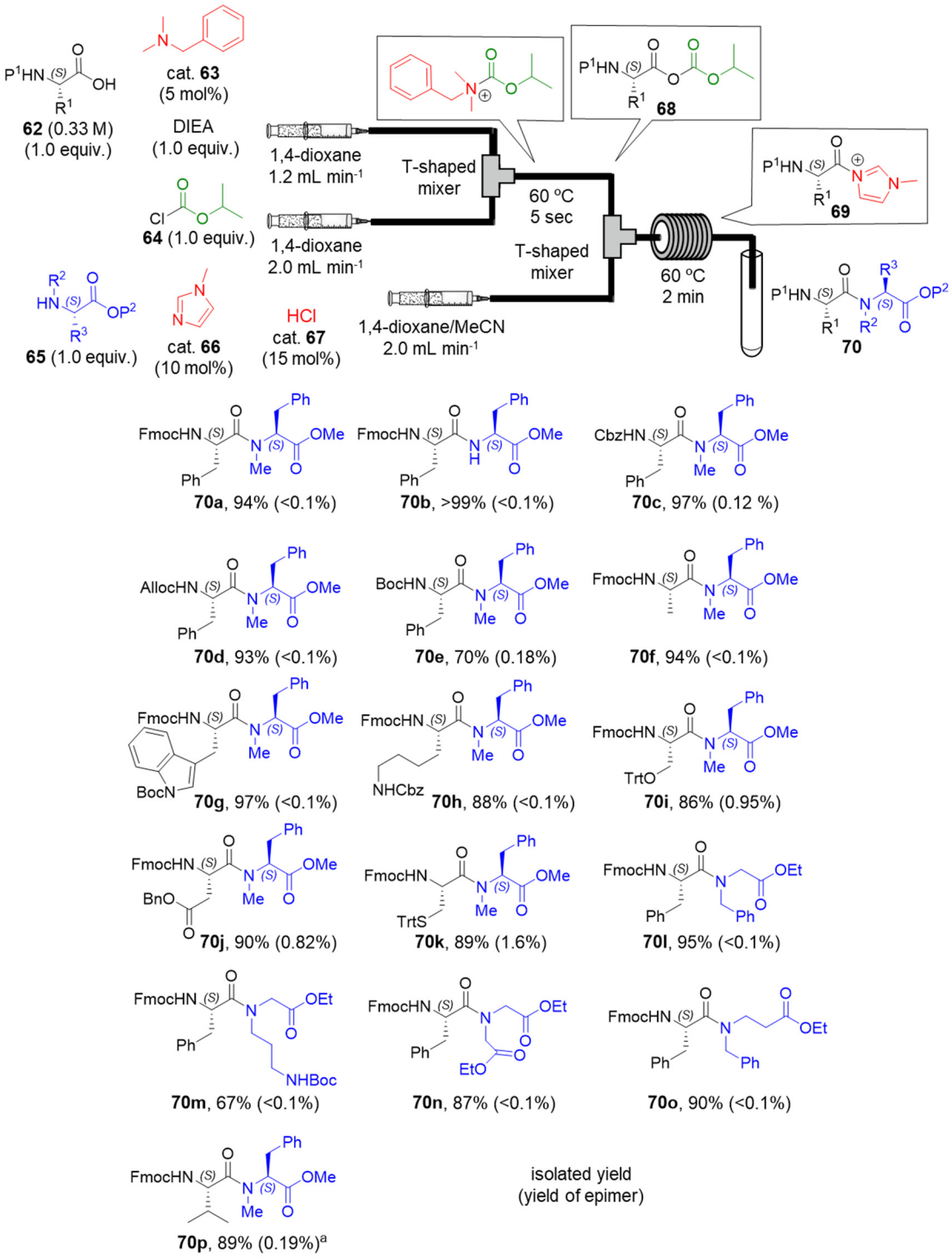

Figure 16. Amidation via acyl *N*-methylimidazolium cation generation under flow conditions. The yield of the epimer was determined via HPLC-UV analysis. [a] 1.3 equiv. of DIEA, 1.4 equiv. of 2,4-dimetyl-3-pentylchloroformate, 10 mol% of HCl was used.

3. Conclusions

This review summarized continuous-flow reactions that use metal-free homogeneous catalysts. The TOF of metal-free catalysts was usually lower than that of metal catalysts. Therefore, homogeneous reaction systems were usually preferable in order to avoid an undesired decrease in the turnover of metal-free catalysts. In addition, catalyst activity can be easily enhanced by heating above the boiling

points of solvents in a continuous-flow reactor using BPR. In particular cases, metal-free catalysts exerted a high TOF (see Section 2.3.5). The use of continuous-flow conditions is valuable to avoid undesired reactions whereby generated reaction intermediates are unstable. The future combination of continuous-flow reactions that use metal-free homogeneous catalysts and in-line monitoring technology is highly desirable in order to more rapidly acquire reaction data. The obtained data is valuable for determining kinetic parameters that might afford insights into reaction mechanisms. In addition, the integration of optimization algorithms enables a rapid and autonomous optimization of reaction conditions. Reports of continuous-flow reactions using metal-free homogeneous catalysts remain very limited. Hopefully, more and more reactions will be reported and many high-yielding, low-cost, safe, scalable, and less wasteful continuous-flow processes using metal-free homogeneous catalysts will be developed in the near future.

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