C–C Bond Formation

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Asymmetric Carbon–Carbon Bond Formation under Continuous-Flow Conditions with Chiral Heterogeneous Catalysts

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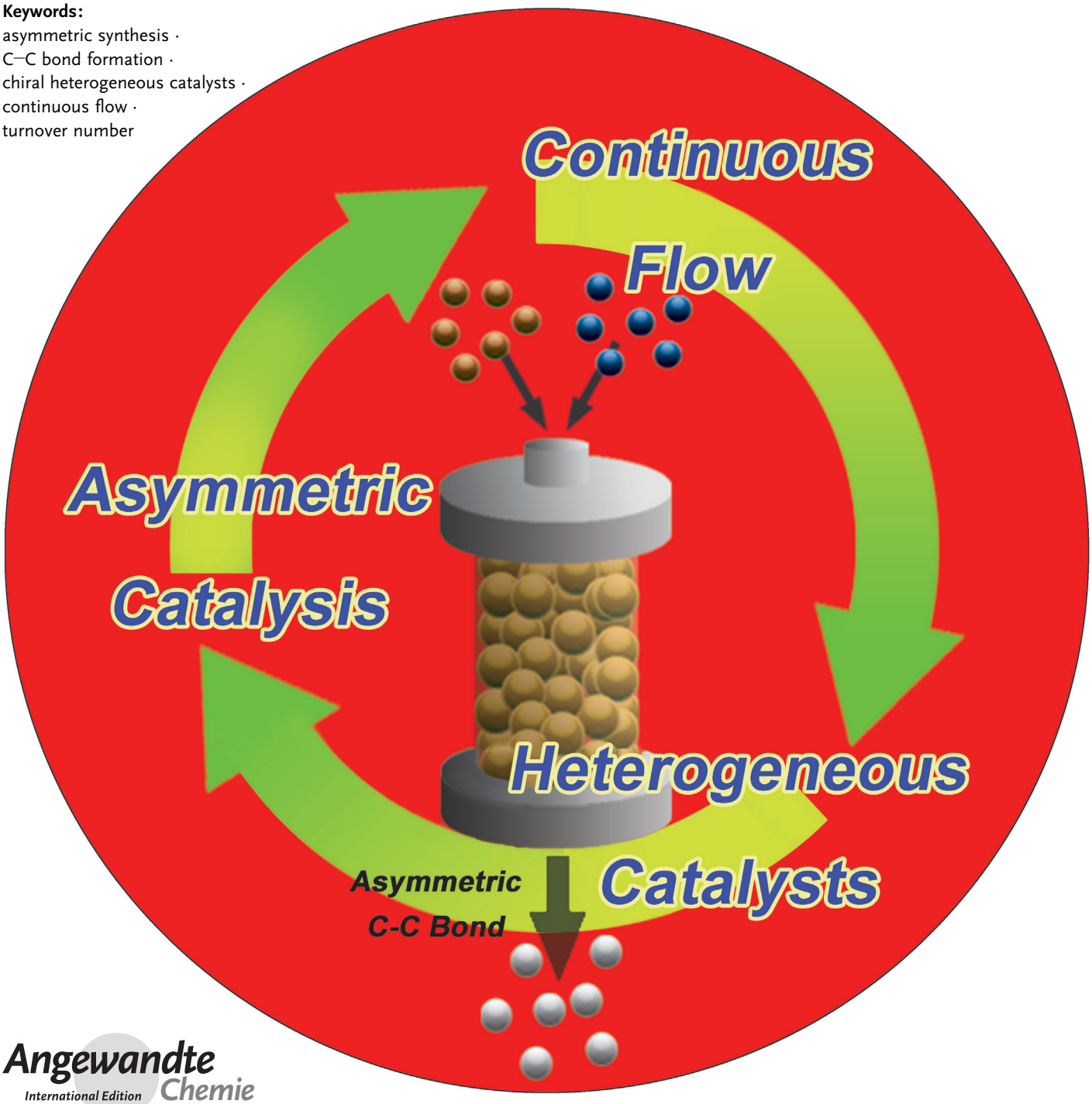
Keywords:
asymmetric synthesis · C–C bond formation · chiral heterogeneous catalysts · continuous flow · turnover number



Catalytic asymmetric carbon–carbon bond-forming reactions provide one of the most efficient ways to synthesize optically active compounds, and, accordingly, many chiral catalysts for these reactions have been developed in the past two decades. However, the efficiency of the catalysts in terms of turnover number (TON) is often lower than that of some other reactions, such as asymmetric hydrogenation, and this has been one of the obstacles for industrial applications. Although there are some difficulties in increasing the efficiency, the issues might be solved by using continuous flow in the presence of chiral heterogeneous catalysts. Indeed, continuous-flow systems have several advantages over conventional batch systems. Here we summarize the recent progress in asymmetric C–C bond-forming reactions under continuous-flow conditions with chiral heterogeneous catalysts.

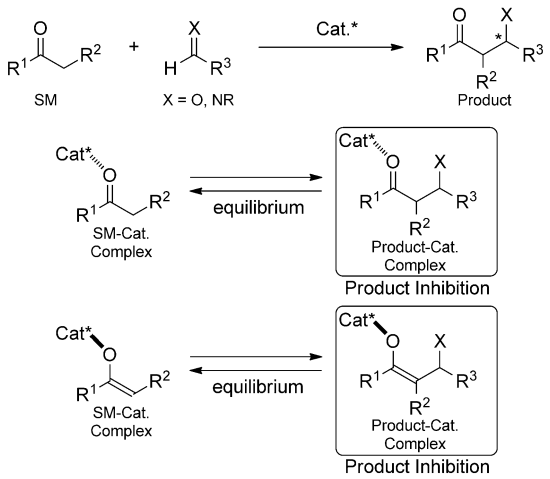
From the Contents

1. Introduction

Continuous-flow systems have several advantages over conventional batch systems.[1,2] Significant space, time, and energy are saved by using continuous-flow systems. Scale-up is also easy by increasing the column size or number of columns (numbering-up). Moreover, unique reactivities and selectivities are sometimes observed under continuous-flow conditions. As a result of the outflow of products, over-reactions are avoided, and pseudostoichiometric catalyst/substrate conditions in continuous-flow systems can increase the reactivity and selectivity. The separation of catalysts and products is very easy when heterogeneous catalysts are packed in continuous-flow columns.

Asymmetric catalysis is a major field in organic synthesis, and many enantioselective reactions based on chiral catalysts have been developed.[3–5] Among them, catalytic asymmetric carbon–carbon bond-forming reactions, which can construct basic carbon skeletons of target molecules, provide one of the most efficient ways to synthesize optically active compounds such as pharmaceuticals, liquid crystals, and agrochemicals. Through this catalytic process, the desired optically active compounds are obtained by using small amounts of chiral sources, and, accordingly, many chiral catalysts for asymmetric C–C bond-forming reactions have been developed over the past two decades.[3–5] However, the efficiency of the catalysts is often lower than that of some other reactions, such as asymmetric hydrogenation.[2c,6,7] For example, the turnover number (TON) is an index for evaluating the efficiency of catalysts, and the development of a catalyst with a high TON is a key factor for industrial applications. Although high TONs have been attained for some asymmetric hydrogenations,[6] the TONs of asymmetric C–C bond-forming reactions are generally lower.[8]

Fast catalytic cycles are required for the catalysts to be highly efficient.[9] Moreover, the issue of catalyst destruction must be addressed. Although many chiral catalysts have been developed, most catalysts are not stable in air and/or moisture, and hence most reactions must be carried out under strictly anhydrous conditions.[3–5] The development of robust catalysts that are tolerant to both water and oxygen is required so as to prevent destruction of the catalyst. Another issue to be addressed, and probably the most serious, in order to obtain high catalyst efficiency is product inhibition. Scheme 1 shows typical 1,2-additions of carbonyl compounds



Scheme 1. Possible product inhibition.

(aldol and Mannich reactions). The reactions are catalyzed by chiral metal/metalloid Lewis acids/bases or organocatalysts to afford optically active products. Ideally, in these reactions, the catalysts interact with the starting carbonyl compounds through covalent bonds or coordinate bonds. The problem is that the products also have carbonyl groups, which may interact with the chiral catalysts. The interactions depend on

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steric and electronic factors; however, these product inhibitions cannot be avoided in these systems. On the other hand, if the inhibition occurs under coordination equilibrium, the issue might be solved by using continuous flow with chiral heterogeneous catalysts, because the products are automatically separated from the chiral catalysts in continuous-flow systems.

This Review describes studies on asymmetric C–C bond formation under continuous-flow conditions in the presence of chiral heterogeneous catalysts (Figure 1).[10] Continuous flow with chiral homogeneous catalysts[11] will not be discussed.

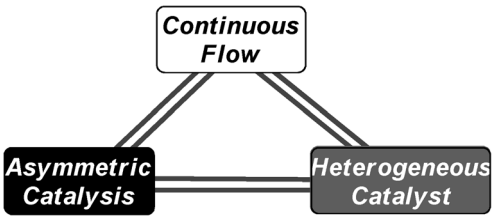
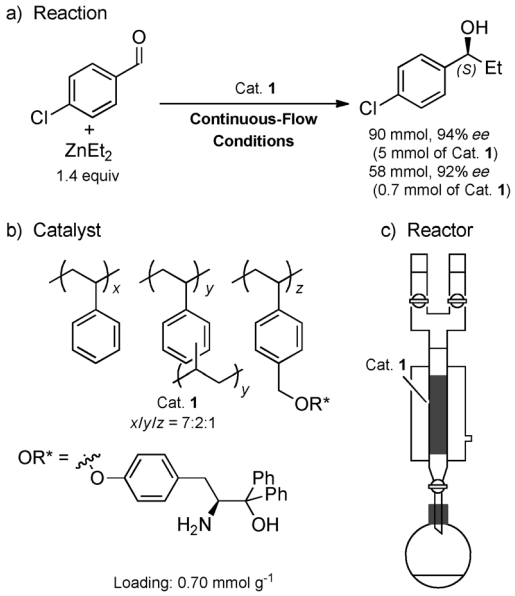


Figure 1. The "magic triangle" in asymmetric continuous-flow reactions.

2. Early Continuous-Flow Systems

Early studies on continuous-flow systems did not use pumps, such as peristaltic, syringe, or plunger pumps. The reactions were conducted under atmosphere pressure as a kind of gravity filtration. In this case, the system consisted of a column and a dropping funnel, so the systems were simple and easy to handle. However, these systems had disadvantages in terms of the temporal and spatial efficiencies of the system. The product amount per hour could not be increased. In addition, the solution eluted from the bottom of the column could not be recycled to the top of the column and reenter the column to allow any remaining starting substrates to react.

Itsuno et al.[12] reported the ethylation[13,14] of *p*-chlorobenzaldehyde to form an optically active alcohol by using a cross-linked, polystyrene-based, polymer-supported chiral amino alcohol catalyst **1** (Scheme 2b). In this ethylation,



Scheme 2. Ethylation of *p*-chlorobenzaldehyde in the presence of diethylzinc.

diethylzinc and *p*-chlorobenzaldehyde were added slowly to an ice-cooled, jacketed column containing insoluble polymer catalyst **1** (prepared by copolymerization) pretreated with *p*-chlorobenzaldehyde (Scheme 2c). A solution of the chiral product was eluted continuously into a flask at the bottom of the column. The TON was 83, and high enantioselectivities of up to 94% *ee* were achieved. Key to this reaction is the formation of an intermediate imine derived from an aldehyde and a polymer-supported chiral amino alcohol catalyst. Therefore, pretreatment of the aldehyde was required to overcome reproducibility problems and achieve high enantioselectivities.

The sequential synthesis of a chiral β-lactam starting from a carboxylic acid chloride and an iminoester under flow conditions was reported by Lectka and co-workers (Scheme 3).[15] In this system, the columns, which were filled with PS-supported organocatalysts, were connected sequentially. The carboxylic acid chloride and α-chloro glycinic esters were introduced into the parallel columns, the bottoms of which were connected to the next column, to afford the

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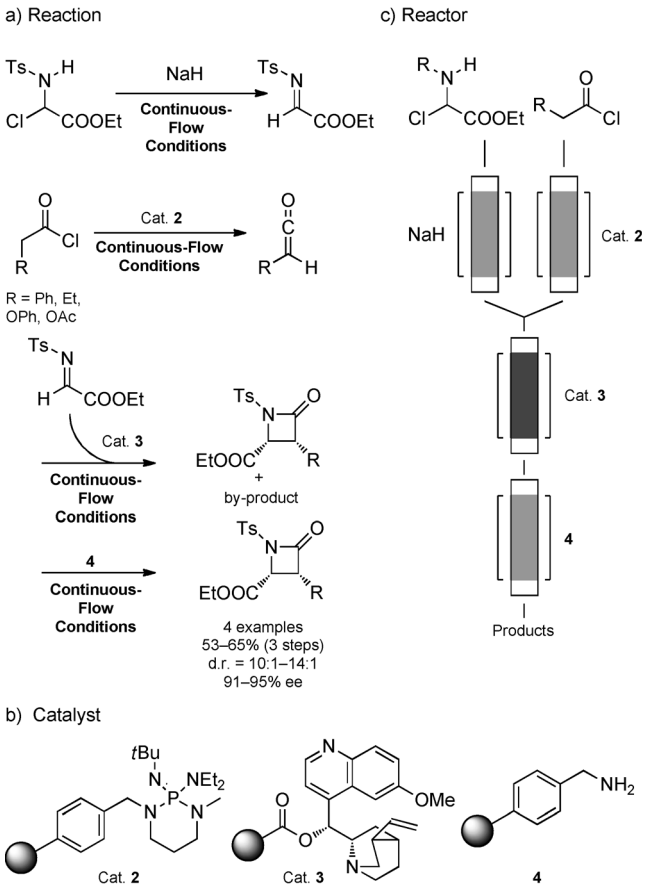
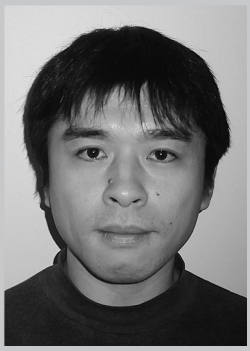
Tetsu Tsubogo studied chemistry at the Tokyo University of Science (BS in 2006; supervisor, Professor Takao Saito). He then joined Professor Shū Kobayashi's group at the University of Tokyo (MsD in 2008 and PhD in 2011). He is now assistant professor at The University of Tokyo. He was elected as a member of the Otsu Conference in 2011. His interests are asymmetric carbon—carbon bond-forming reactions with ubiquitous chiral metal catalysts.



Scheme 3. Sequential synthesis of chiral β-lactams starting from carboxylic acid chlorides and an iminoester.

desired chiral β-lactams[16] in good yields and with high diastereo- and enantioselectivity. The chiral catalyst **3** was prepared from Wang resin (100–200 mesh, 2.53 mmol g^{-1}) and quinine. Notably, an unstable ketene can be introduced into the second column directly, and it does not require isolation. Packed polymer-supported catalysts (catalysts **2** and **3**) can be recovered easily, simply by washing with an appropriate base solution, and the catalyst column was used 60 times without significant loss of yield or selectivity. Furthermore, purification steps can be simplified by using a scavenger column.



Takanori Ishiwata graduated from the Science University of Tokyo in 2000, received his MS in Chemistry from Saitama University in 2002, and then joined Tokyo Chemical Industry Co., Ltd. He is currently a visiting scientist at The University of Tokyo. His research involves the development of immobilized catalysts for asymmetric carbon–carbon bond formation and their applications to flow reactors.

3. Asymmetric 1,2-Addition Reactions in a Continuous-Flow System

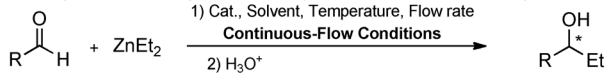
Asymmetric 1,2-addition reactions have been extensively studied and explored with homogeneous catalysts.[3] There are several types of asymmetric reactions, such as alkylation,[13,14] arylation,[17] aldol,[18] Mannich,[19] and cyanation[20] reactions. Alkylation, aldol, Mannich, and cyanation reactions have been reported in continuous-flow systems. Organocatalysts, such as proline derivatives, have also been employed in those reactions.

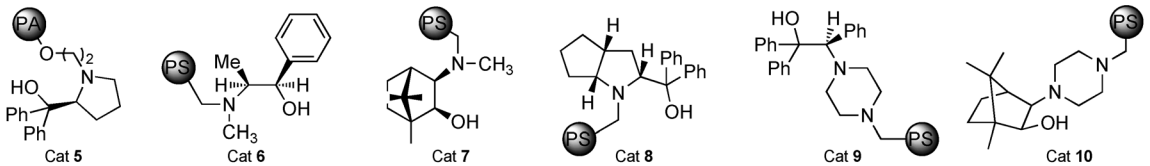
3.1. Asymmetric Addition of Organozinc Reagents to Aldehydes

Kragl and Dreisbach[21] reported a catalytic asymmetric addition[13,14] of diethylzinc to benzaldehyde in the presence of a cross-linked, polymethacrylate-based polymer containing a chiral amino alcohol (Table 1, entry 1; Figure 2). The authors reported a continuous asymmetric synthesis in a membrane reactor by using a soluble homogeneous catalyst (**5**). An advantage of this method is that fresh catalyst can be supplemented as required. A chiral ligand, an α,α-diphenyl-L-prolinol derivative, was coupled with a copolymer (Mw: ca. 96000 u; OH group: 0.75 mmol g^{-1}) derived from 2-hydroxyethyl methacrylate and octadecyl methacrylate and retained by an ultrafiltration membrane within the reaction vessel.[21] The solutions of benzaldehyde and diethylzinc in *n*-hexane were pumped separately into the reactor by means of two piston pumps. For the given concentrations of benzaldehyde (14 mM) and of diethylzinc (36 mM), the product, (*S*)-1-phenyl-propan-1-ol, was obtained in 50% *ee*. The maximum conversion was 30% at 0°C for a residence time of 2.5 h; the TON was 500.

Hodge and co-workers[23] reported the asymmetric reaction[13,14] of an aldehyde with diethylzinc catalyzed by PS-ephedrine **6** or PS-camphor derivatives **7** in toluene in benchtop flow systems (Table 1, entries 2 and 3; Figure 3). The immobilized catalysts were prepared from chloromethyl-functionalized polystyrene by using grafting methods.[24] This reaction was carried out by placing the PS catalyst (70–120 mesh), preswollen in toluene, in a round-bottomed tube (incubated at 20°C) and solutions of the aldehyde (0.2 M) and diethylzinc (0.5 M) in toluene were introduced into the bottom of the beads bed by peristaltic pumps. The product solution was collected at the top of the column and quenched with dilute hydrochloric acid. At the optimum flow rate (20 mL h^{-1}) with catalyst **6**, chiral 1-phenylpropan-1-ol was obtained in high yield (98%) and high enantioselectivity (98%). When the homogeneous catalyst (1*R*,2*S*)-*N*-benzylephedrin was used in the batch systems, the product was obtained with 80% *ee*. The increase in the *ee* value with the flow system may be explained by the relatively high concentrations of the substrates and removal of the product, which might interact negatively with diethylzinc to promote a racemic reaction under the conditions. The PS-camphor derivative **7** afforded the product in a high yield and a high enantioselectivity at the first stage of the reaction. After the catalyst had been used for 275 h, the yields dropped to 50–60% and

Table 1: Asymmetric ethylation of benzaldehyde with diethylzinc in the presence of alcohol catalysts under continuous flow.





Entry	Cat.	*T* [°C]	Flow rate [mL h^{-1}]			Conc [mM]		Yield [%][e]	*ee* [%][g]	Config.	Ref.
			RCHO[c]	Et_2Zn	total	RCHO[c]	Et_2Zn				
1[a]	**5**	0	–	–	–	14	36	30 (conv)	50	*S*	[21]
2	**6**	RT	10	10	20	200	500	98	98	*R*	[23]
3	**7**	RT	6	6	12	200	500	97	97	*S*	[23]
4[b]	**8**	RT	_[d]	_[d]	60	38	576	full conv[f]	99	*R*	[25]
5	**9**	10–20	21.6	21.6	43.2	1100	900	>99(conv)	93	*S*	[26]
6	**10**	0	7.2	7.2	14.4	440	880	>98(conv)	98	*S*	[29]

[a] *n*-Hexane was used. [b] A recirculation system was used. [c] Entries 1, 2, 4, 6: R = Ph—entry 3: R = Ph, 4-ClC_6H_4, 2-$MeOC_6H_4$, Cy—entry 5: R = Ph, 2-FC_6H_4, 4-FC_6H_4, 2-$CF_3C_6H_4$, 4-$CF_3C_6H_4$, 4-CNC_6H_4. [d] A mixture of PhCHO and Et_2Zn was used. [e] Maximum yield. [f] Chemoselectivity: 85%. [g] Maximum *ee*.

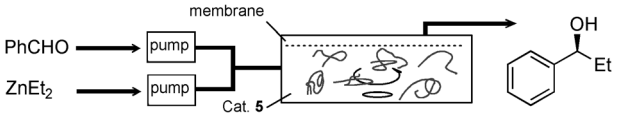


Figure 2. Flow reactor for the asymmetric ethylation of benzaldehyde with diethylzinc in the presence of a PS-prolinol derivative, as described by Kragl, Dreisbach, and co-workers.

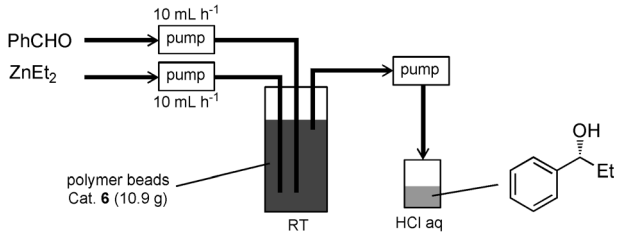


Figure 3. Flow reactor for the asymmetric ethylation of benzaldehyde with diethylzinc in the presence of PS-supported amino alcohols, as described by Hodge and co-workers.

the *ee* value to 81–84%. In this system, the residence time was about 5–6 h (12 m h^{-1}) and the TON was 3.

Luis, Martens, and co-workers[25] reported the catalytic asymmetric reaction[13,14] of diethylzinc with benzaldehyde in the presence of polymeric monoliths containing chiral amino alcohol **8** under flow conditions (Table 1, entry 4; Figure 4). Monoliths of the polymeric catalyst with the desired morphology and properties were obtained from a mixture containing monomers (10 mol% chiral alcohol/90 mol% DVB (divinylbenzene); no styrene was used) in toluene/1-dodecanol, which acted as a porogenic solvent. The monolithic column allowed the design of a flow system, in which the column was attached to a pump and the reaction mixture

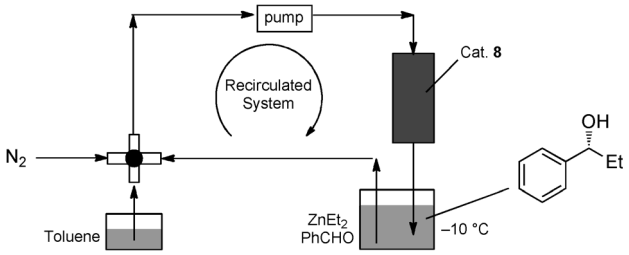


Figure 4. Flow reactor for the asymmetric ethylation of benzaldehyde with diethylzinc in the presence of PS-supported amino alcohol **8**, as described by Luis, Martens, and co-workers.

(diethylzinc and benzaldehyde) was cooled to −10°C. The mixture was recirculated through the catalyst column over 24 h at room temperature. After this period, the pump was stopped and the reaction was quenched. A quantitative conversion of the benzaldehyde was observed, and the desired product was obtained with 99% *ee* along with a lower amount of by-product. The monolithic column provided significantly better enantioselectivity than that obtained with homogeneous analogues and with polymers prepared by grafting. This improvement in the efficiency might be ascribed to the formation of more appropriate cavities during the polymerization process, or to the isolation of the catalytic sites through the high degree of cross-linking.

Pericàs et al.[26] reported the asymmetric reaction[13,14] of aldehydes with diethylzinc in toluene catalyzed by a PS-grafted amino alcohol **9**, derived from the reaction of (*R*)-2-(1-piperazinyl)-1,1,2-triphenylethanol with a Merrifield resin (2% DVB, Cl group: 0.91 mmol g^{-1})[27] in a continuous-flow system (Table 1, entry 5; Figure 5). The system consisted of a vertical, fitted, and jacketed glass column, which contained the supported catalyst. The catalyst resin was first swollen

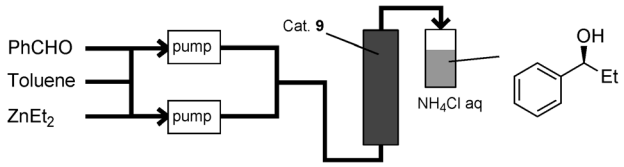
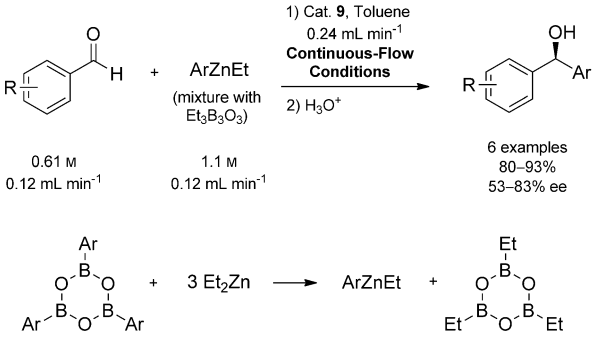


Figure 5. Flow reactor for the asymmetric ethylation of benzaldehydes with diethylzinc in the presence of PS-supported amino alcohol **9**, as described by Pericàs and co-workers.

with dry toluene for one hour. Next, the reactions were carried out by passing equal flows of a solution of benzaldehydes in toluene (0.9 M) and a solution of diethylzinc in toluene (1.1 M) through the column, using separate pumps to minimize background reactions. The crude mixture was collected from the upper end of the reactor, and quenched with saturated aqueous NH_4Cl. A complete conversion (> 99 %) was observed, and the desired chiral alcohol was obtained with 89 % *ee*. The flow rate could be increased up to 0.72 mL min^{-1} (residence time: 2.8 min) without any decrease in the yield or *ee* value. The TON was 60.

In the following year, the Pericàs research group[28] also reported the catalytic enantioselective arylation[17] of benzaldehydes with arylethylzinc (ArZnEt) generated in situ by using catalyst **9** in a continuous-flow system (Scheme 4). The



Scheme 4. Asymmetric arylation reactions of benzaldehydes with diethylzinc and triarylboroxin in the presence of PS-supported amino alcohol **9** under continuous flow.

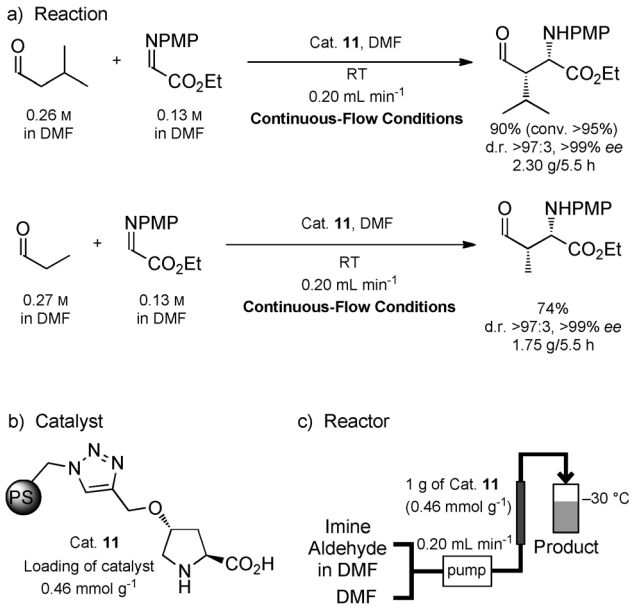
same system and catalyst as previously reported in the ethylation of benzaldehydes were used (Figure 5). The reactions were carried out by passing equal flows of a solution of benzaldehydes in toluene (0.61 M) and a solution of arylating agents in toluene (1.1 M), prepared from triarylboroxins and diethylzinc, through the column using separate pumps. The eluting product was collected in a flask containing a vigorously stirred aqueous solution of NH_4Cl to quench the reaction. The corresponding chiral diaryl methanol derivatives were obtained with excellent conversions (TON = 31) and moderate enantioselectivities (57–83 % *ee*).

A more robust PS-supported amino alcohol ligand **10** was developed for the ethylation reaction[13,14] by the same research group (Table 1, entry 6).[29] The previously reported catalyst **9** had a limited lifetime, and the operation of the continuous-flow devices over long periods of time was difficult. On the other hand, PS catalyst **10** was obtained by immobilization of 3-*exo*-piperidinoisoborneol[30] on Merrifield resin (1 % DVB, Cl group: 1.24 mmol g^{-1}). The experimental setup was similar to that of the previously described procedures (Figure 5). The reactions were carried out by passing equal flows of a solution of benzaldehydes in toluene (0.44 M) and a solution of diethylzinc in toluene (0.88 M) through the column charged with **10**. High conversion was obtained at a convenient combined flow rate (0.24 mL min^{-1}, residence time: 6 min), and the excellent robustness of the resin was shown in the system. The flow system could be used for 30 h, and a small decrease in the conversion was observed after 20 h. More remarkably, there was no deterioration in the enantioselectivity (98 % *ee*) over the whole process. In one single continuous-flow operation, 13.0 g of enantiopure 1-phenylpropanol were isolated, which represents a TON of 251 and a productivity of 6.4 mmol h^{-1} g (resin).

In the above alkylation and arylation reactions under continuous-flow conditions, the eluent should be quenched by acid to avoid overreactions. This means that additional treatment is required, which sometimes causes difficulty in operations.

3.2. Asymmetric Mannich Reactions

Pericàs and co-workers[31] reported highly stereoselective Mannich-type reactions[19] of aldehydes and ketones with *N*-(*p*-methoxyphenyl)ethyl glyoxylate imine catalyzed by polystyrene-supported (2*S*,4*R*)-hydroxyproline (**11**)[32] under continuous-flow conditions (Scheme 5). The experimental setup consisted of a jacketed Omnifit column, which was loaded with the grafted PS-proline derivative **11** (ca. 120 mesh) and connected to a pump used to feed the reactor with a solution of both reagents in *N*,*N*-dimethylformamide (DMF). The reagent mixture was pumped at 0.2 mL min^{-1} (residence time:



Scheme 5. Asymmetric Mannich-type reactions of aliphatic aldehydes with an imine catalyzed by a PS-proline derivative under continuous flow. PMP = *p*-methoxyphenyl.

6 min). After 5.5 h, the collected solution was diluted with water and extracted with diethyl ether. Enantiomerically and diastereomerically pure adduct (*syn*/*anti* > 97:3; > 99% *ee*) was obtained. At the end of the reaction, the conversion was almost complete (> 95%) and the TON was 17.

3.3. Asymmetric Aldol Reactions

Massi, Cavazzini et al.[33] reported the catalytic enantioselective aldol reaction[18] of *p*-nitrobenzaldehyde with cyclohexanone under flow conditions by using proline-functionalized silica packed-bed microreactors (Table 2, entry 1; Figure 6). The (2*S*,4*R*)-hydroxyproline derivative was immobilized on 3-mercaptopropyl-functionalized silica (particle size: ca. 50 μm, pore size: 60 Å, superficial area: 500 $m^2 g^{-1}$) by photoinduced thiol–ene coupling. The reactor was prepared using a stainless-steel column filled with immobilized catalyst **12**. A packed cartridge of triamine-functionalized silica gel was placed after the reactor to remove any remaining *p*-nitrobenzaldehyde selectively, thus facilitating the isolation of the aldol product. The reaction was carried out by pumping a solution of *p*-nitrobenzaldehyde (0.22 M) and cyclohexanone (0.66 M) in toluene at 5 μL min^{-1} (residence time: 32 min) through the column. The conversion was 82% (TON = 4.7), and the stereoselectivity was moderate (d.r. = 4:1, 78% *ee*) at 50 °C. A slight improvement in the stereoselectivity (d.r. = 5:1, 82% *ee*) accompanied by a marked decrease in conversion (38%) was observed at 0 °C. A further increase in the temperature to 70 °C resulted in rapid (ca. 2.5 h) degradation of the packed-bed material.

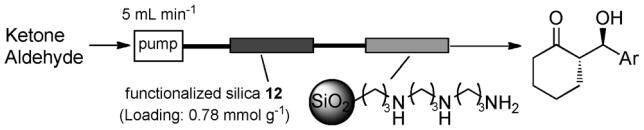


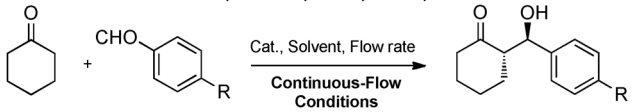
Figure 6. Flow reactor for the asymmetric aldol reactions of a ketone with an aldehyde catalyzed by a PS-proline derivative, as described by Massi, Cavazzini, and co-workers.

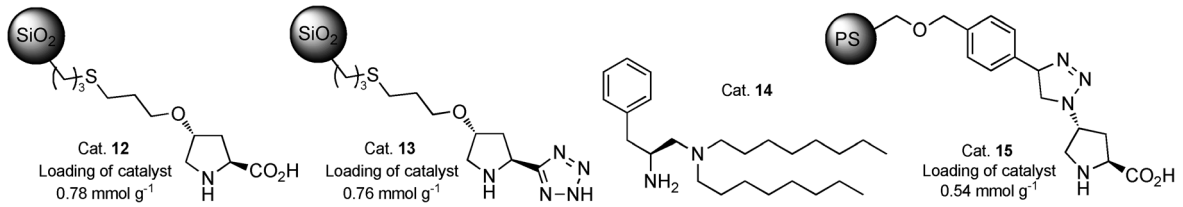
To prevent the degradation, another immobilized catalyst was developed. A 5-(pyrrolidin-2-yl)tetrazole derivative[34] was immobilized on 3-mercaptopropyl-functionalized silica (particle size: ca. 50 μm, pore size: 60 Å, superficial area: 500 $m^2 g^{-1}$) by photoinduced thiol–ene coupling.[35] The experimental setup was similar, and the reactor was prepared by filling the stainless-steel column with immobilized catalyst **13**. The reaction[18] was carried out by pumping a solution of *p*-nitrobenzaldehyde (0.1 M) and cyclohexanone (0.3 M) in toluene at 5 μL min^{-1} (residence time: 25 min) through the column (Table 2, entry 2; Figure 7). A high conversion (> 95%, TON = 1.0) was obtained with good selectivities (*anti*/*syn* = 2:1–3:1, 68–92% *ee*) at 50 °C. Remarkably, the packed silica **13** did not show any deactivation over 80 h at 50 °C. However, catalyst **13** was fully deactivated after 120 h at 50 °C (ca. 7 days on stream).

Figure 7. Flow reactor for the asymmetric aldol reactions of a ketone with an aldehyde catalyzed by a silica-supported proline derivative.

Sels and co-workers[36] reported the asymmetric aldol reaction[18] of 2-butanone with 4-(trifluoromethyl)benzaldehyde catalyzed by a noncovalently immobilized chiral diamine on a solid acid[37] under continuous-flow conditions (Table 2, entry 3; Figure 8). The experimental setup consisted

Table 2: Asymmetric aldol reactions of a ketone with an aldehyde catalyzed by a PS-proline derivative under continuous flow.





Entry	Cat.	R	*T* [°C]	Solvent	Conc [M] ketone	Conc [M] ArCHO	Flow rate [mL h^{-1}]	Conversion[f] [%]	*syn*/*anti*[i]	*ee* [%][j]
1	**12**	NO_2	0–50	tol	0.66	0.22	0.3	82[g] (38[h])	4:1[g] (5:1[h])	78[g] (82[h])
2[a]	**13**	EWG[d]	25–50	tol or iPr_2O	0.3	0.1	0.3	> 95	3:1	95
3[b]	**14**[c]	CF_3	45	–	–	0.125	1.0	–	3:1	97
4	**15**	EWG[e]	RT	DMF/H_2O (6:4)	ca. 4 equiv	0.79	1.5	86	97:3	98

[a] No deactivation of catalyst was observed within 80 h at 50 °C. [b] 2-Butanone was used. [c] With acid resin. [d] EWG = NO_2, CN, Br, Cl, 2-Cl. [e] EWG = CN, CO_2Me, NO_2, CF_3. [f] Maximum conversion. [g] 50 °C. [h] 0 °C. [i] Maximum d.r. [j] Maximum *ee*.

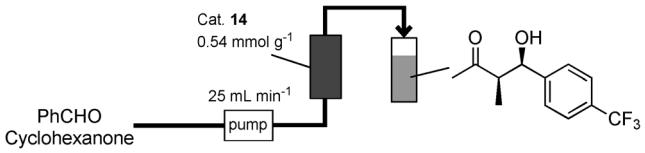


Figure 8. Flow reactor for the asymmetric aldol reactions of a ketone with an aldehyde catalyzed by a noncovalently immobilized chiral diamine, as described by Sels and co-workers.

of a glass column loaded with Nafion NR50 pellets (an immobilized acid, beads) preloaded with chiral diamine **14**[38] (molar ratio = 1:1.2). The column was connected to a syringe pump, and a mixture of both reagents was fed to the reactor. The reaction was carried out by passing preheated (45 °C) reagents (aldehyde in 2-butanone, 0.125 M) through the column at a rate of 1.0 mL h^{-1}. The initial diastereo- and enantioselectivity of the product were significantly improved compared with those of the corresponding batch reactions (*syn*/*anti* = 3:1, up to 97 % *ee*).

Pericàs and co-workers[39] reported the catalytic enantioselective aldol reaction[18] of benzaldehydes with cyclohexanone under flow conditions (Table 2, entry 4; Figure 9) by

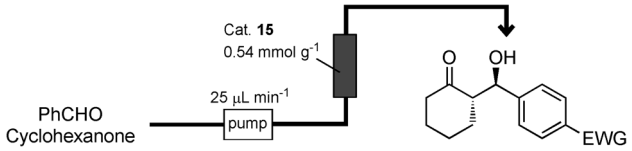
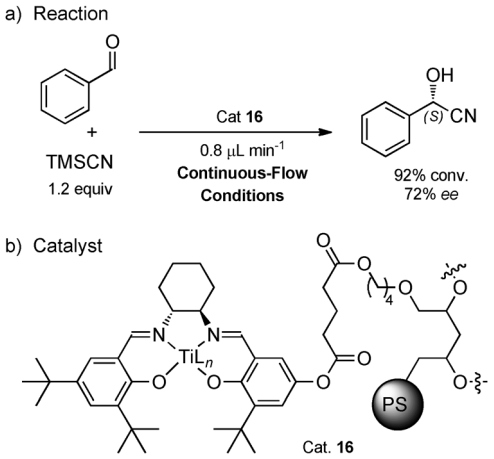


Figure 9. Flow reactor for the PS-proline-catalyzed asymmetric aldol reactions of a ketone with an aldehyde, as described by Pericàs and co-workers.

using a polystyrene-supported proline derivative **15**. The packed-bed reactor consisted of a vertically mounted Omnifit glass column, which was loaded with the PS-proline derivative **15** (prepared from home-made Merrifield resin; 8 % DVB), and was connected to a syringe pump. The reaction was carried out by passing the reagent solution (53.32 mmol *p*-nitrobenzaldehydes in DMF/H_2O/cyclohexanone = 1.5:1:1.7, 67.5 mL) through the column with **15**. The reagent mixture was pumped at 25 μL min^{-1} (residence time: 26 min), and after running the system for 45 h, the solvent was removed from the collected sample. The crude product was purified by flash column chromatography on silica gel to give the pure product (4.87 g, 19.54 mmol, d.r. = 96:4, 97 % *ee*, TON = 60).

3.4. Asymmetric Cyanation

The titanium(IV) complex of a polymer-supported chiral salen ligand was used by Moberg and co-workers for the enantioselctive cyanation of benzaldehyde with trimethylsilyl cyanide (TMSCN) or acetyl cyanide under continuous flow (Scheme 6).[40] To obtain the polymeric titanium–salen complex (Cat. **16**), they attached a modified salen ligand to hydroxy-functionalized divinylbenzene beads (particle size: 15 μm), which reacted with $TiCl_4$. Catalyst **16** was then loaded



Scheme 6. Asymmetric cyanation of an aldehyde with TMSCN catalyzed by a polymeric titanium–salen complex.

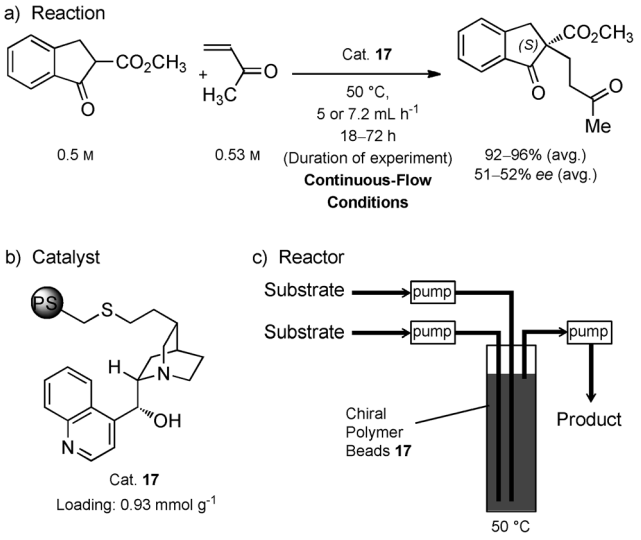
into a column and used for the asymmetric cyanation[20] of benzaldehyde. A flow rate of 0.8 μL min^{-1} afforded good results with TMSCN (92 % conv. 72 % *ee*). In the case of acetyl cyanide, a flow rate of 0.6 μL min^{-1} resulted in high enantioselectivity (70 % *ee*).

4. Asymmetric 1,4-Addition Reactions

Asymmetric 1,4-addition reactions (Michael reactions)[3] are very important for carbon–carbon bond formation. Although the reactions are well-established for homo- and heterogeneous conditions in batch systems, there are only four reports on the reaction under continuous-flow conditions. Catalysts based on the cinchona alkaloid, proline derivatives (poly-peptide), and Pybox-calcium chloride have been reported.

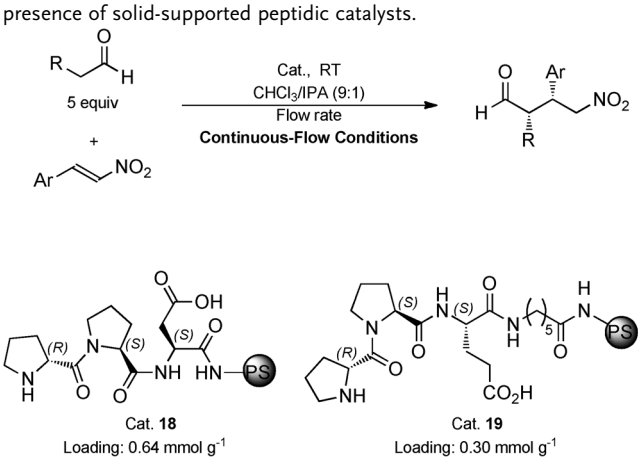
The first report of a 1,4-addition reaction[41,42] in continuous flow appeared from the Hodge research group.[43] They reported that polymer-supported cinchonidine **17** could catalyze a 1,4-addition reaction of a ketoester with methyl vinyl ketone under continuous-flow conditions (Scheme 7). Cinchonidine was attached to a polystyrene resin (starting polystyrene: 80–150 mm, 1 % DVB) containing a thiol group by a hydrothiolation reaction in the presence of 2,2′-azobis(2-methylpropionitrile) (AIBN) at 60 °C. The flow system is described in Scheme 7c. A ketoester and methyl vinyl ketone were individually delivered by two pumps to the flow tube, which contained the PS catalyst beads. The product solution was taken from the top of the bed by a third pump. At an optimum flow rate of 5.0 mL h^{-1} (residence time: ca. 6 h), the chiral 1,4-adduct was obtained in high yield with 51 % *ee*. The flow system functioned sufficiently for at least 72 h (TON = 12.3).

Fülöp and co-workers[44] demonstrated the 1,4-addition[45,46] of aldehydes to nitrostyrene by using solid-supported peptidic catalyst **18** in continuous flow (Table 3, entry 1; Figure 10). The peptide H-D-Pro-Pro-Asp-NH-resin (polystyrene resin with 4-methylbenzhydrolamine (MBHA)) was used as a catalyst for this reaction. They investigated flow



Scheme 7. 1,4-Addition of a ketoester with methyl vinyl ketone by using PS-cinchonidine catalyst **17**.

Table 3: 1,4-Additon reactions of aldehydes to nitroolefins in the presence of solid-supported peptidic catalysts.



Entry	Cat.	Flow rate [mL min^{-1}]	Yield[c] [%]	d.r.[d]	*ee*[e] [%]	Ref
1[a]	**18**	0.1	91	36:1	93	[44]
2[b]	**19**	0.12	quant	50:1	97	[47]

[a] 60 bar. R = Me, Et, *n*Pr, *n*Bu, Bn, *i*Pr, Ar = Ph. [b] R = Me, Et, Ar = Ph, *p*-BrC_6H_4, *p*-ClC_6H_4. [c] Maximum yield. [d] Maximum d.r. [e] Maximum *ee*.

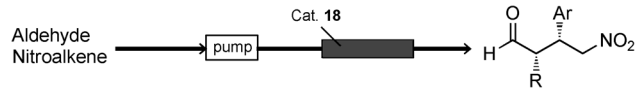


Figure 10. Flow reactor for the 1,4-addition reactions of aldehydes with nitroolefins in the presence of solid-support peptidic catalyst **18**.

rates at 0.01–0.5 mL min^{-1}, and it was found that an acceptable yield, diastereo-, and enantioselectivity were obtained at a flow rate of 0.1 mL min^{-1} (residence time: 7 min). When the flow rate was decreased, the diastereoselectivity decreased because of epimerization of the product by the peptide catalyst in the column. The authors also varied the pressure and found that the yield was increased at 60 bar (1 bar = 10^5 Pa). This catalyst could be used at least five times, and even after the 10th run, the product was obtained in nearly 70% yield. Finally, they expanded the substrate generality, and showed that several α-alkyl-substituted aldehydes reacted with β-nitrostyrene in low to high yields and high diastereo- and enantioselectivity.

Wennemers and co-workers[47] applied the immobilized peptide catalysts **19** (aminomethylated polystyrene resin substrate: 0.41 mmol g^{-1} (NH_2 group), 100–200 mesh), which was originally developed in their research group,[45,46] to continuous-flow systems (Table 3, entry 2; Figure 11). The flow rate was about 0.23 mL min^{-1} (residence time: < 60 min). In their system, a total TON of over 600 (219 TON/round) was achieved and over 100 g of product was obtained.

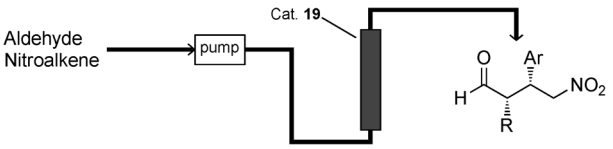
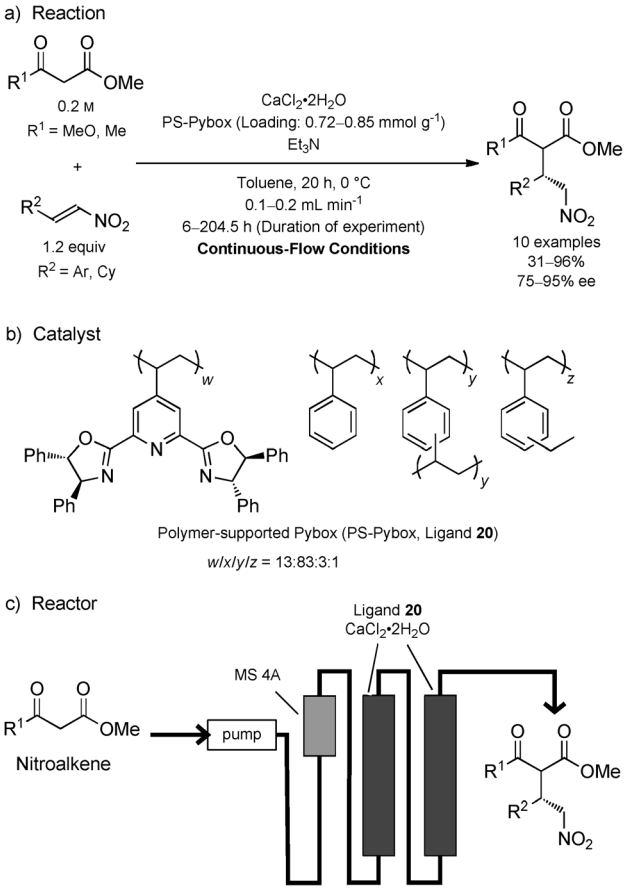


Figure 11. Flow reactor for the 1,4-addition reactions of aldehydes with nitroolefins in the presence of solid-support peptidic catalyst **19**.

Kobayashi et al.[48] reported robust chiral calcium chloride catalyzed asymmetric 1,4-addition reactions of a 1,3-dicarbonyl compound with nitroalkenes (Scheme 8).[49] In general, chiral calcium catalysts such as Box-Ca, Pybox-Ca, and binol-Ca, are unstable under air because of hydrolysis.[50] On the other hand, $CaCl_2$ is stable under air, is abundant, inexpensive, and is harmless compared with other main-group and transition metals. More robust chiral catalysts were developed based on $CaCl_2$. The chiral $CaCl_2$ complex prepared from $CaCl_2$ and Pybox catalyzed 1,4-addition reactions of 1,3-dicarbonyl compounds, especially malonate, with nitroalkenes, and the reactions worked very well under air. The first trial in a batch system gave the desired product in 92% yield and 94% *ee* by using Pybox-$CaCl_2$, which was then immobilized on cross-linked polystyrene (PS-Pybox **20**) by co-polymerization. Complex **20** was first tested in a batch system, and was then applied to a continuous-flow system (Scheme 8c). The system could be used continuously for at least 8.5 days (216.5 h) at 0.1 mL min^{-1} (6.0 mL h^{-1}). The product could even be obtained in high yield and high enantioselectivity at 0.2 mL min^{-1} (12.0 mL h^{-1}). The TON reached 228, and the catalyst was still functional. The wide substrate scope of this continuous-flow system was also shown.

5. Asymmetric Cyclization Reactions

Luis and co-workers[51] reported the use of a continuous-flow reactor for an asymmetric cyclopropanation reaction[52,53] in the presence of a monolithic PS-Pybox-Ru catalyst (Table 4, entries 1–3; Figure 12). They chose polystyrene-based Pybox and applied it to the cyclopropanation reaction of styrene with ethyl diazoacetate under continuous-flow conditions in CH_2Cl_2, without solvent, and in supercritical



Scheme 8. Robust (PS-Pybox)-$CaCl_2$-catalyzed asymmetric 1,4-addition reactions of 1,3-dicarbonyl compounds with nitroalkenes, as described by Kobayashi and co-workers.

carbon dioxide ($scCO_2$)[54]. For the preparation of the catalyst-containing column, they treated PS-Pybox with an excess amount of the dichloro(*p*-cymene)ruthenium(II) dimer in CH_2Cl_2. In this system, the reaction proceeded to the same level in the CH_2Cl_2, solvent-free, and $scCO_2$ conditions (entries 1–3). Under the CH_2Cl_2 and solvent-free conditions, the flow rate was 0.02 mL min^{-1}, while under $scCO_2$ conditions, the reaction was conducted at a flow rate of 0.165 mL min^{-1} (residence time: ca. 4 min). The catalyst was stable under these reaction conditions, with only minimal degeneration of the performance over a period of 5 h. The TONs were 6 (CH_2Cl_2), 35 (neat), and 46 ($scCO_2$). Analysis of the product steam by ICP-MS showed that the total metal leaching was < 1 ppm.

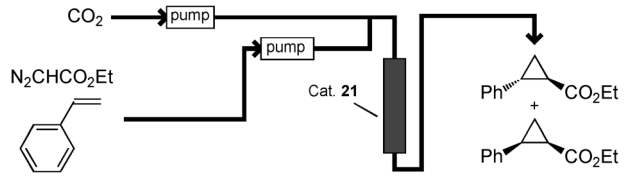
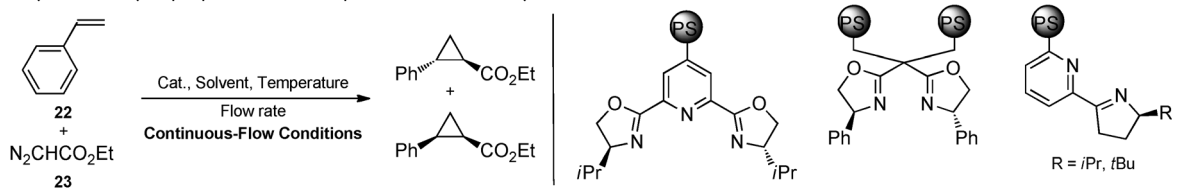


Figure 12. Flow reactor for an asymmetric cyclopropanation in the presence of the (PS-Pybox)-Ru catalyst, as described by Luis and co-workers.

García-Verdugo, Luis, and co-workers[55] also reported the same reaction[52,53] with a different catalyst, monolithic (PS-Box)-Cu (**24**), under continuous-flow conditions (Table 4, entries 4–6). The reaction was conducted under CH_2Cl_2, solvent-free, and $scCO_2$ conditions (entries 4–6). The desired product was obtained with moderate enantioselectivity in all cases. When $scCO_2$ was used as the solvent, the flow rate was increased to 1.1 mL min^{-1} (residence time: 0.64 min). The best TON was 19.5 under solvent-free conditions. No noticeable changes were observed in the product yield or enantioselectivity after about 5 h of continuous use under the conditions assayed (CH_2Cl_2, solvent-free, and $scCO_2$). Anal-

Table 4: Asymmetric cyclopropanation in the presence of PS catalysts.



Entry	Cat.	Solvent	Substrate ratio	Flow rate [mL min^{-1}]	*T* [°C]	Yield [%]	*trans*/*cis*	*ee* [%] *trans*	*ee* [%] *cis*	Ref.
1	**21**	CH_2Cl_2	**22**/**23** = 6:1	0.02	RT	20–53	80:20–85:15	76–82	39–48	[51]
2	**21**	–	**22**/**23** = 7:1	0.02	RT	48–72	82;18–83:17	76–78	41–43	[51]
3[a]	**21**	$scCO_2$	1.73 M (in **22**)	0.165	40	63	87:13	77	47	[51]
4	**24**	CH_2Cl_2	**21**/**22** = 4:1	0.002	RT	61	–	71	55	[55]
5	**24**	–	1.78 M (in **22**)	0.02	RT	44	–	57	51	[55]
6[a]	**24**	$scCO_2$	1.73 M (in **22**)	1.1	40	63	53:47	59	44	[55]
7	**25**	CH_2Cl_2	**22**/**23** = 3:1	0.02–0.03	RT	44–57	–	44–57	39–60	[56]
8[a]	**25**	$scCO_2$	**22**/**23** = 3:1	0.55	40	28–47	–	37–55	37–57	[56]

[a] 8 MPa.

ysis of the solution by ICP-MS showed that the total metal leaching was < 1 ppm.

Martinez-Merino and co-workers[56] also reported a cyclopropanation reaction catalyzed by monolithic PS-supported copper (**25**).[52,53] They developed a new type of PS-Pyox polymer and applied it to a continuous-flow system. In this reaction, both CH_2Cl_2 and $scCO_2$ could be used and the desired products were obtained with the same selectivity (Table 4, entries 7 and 8). The use of $scCO_2$ resulted in better productivity than CH_2Cl_2.

Hashimoto and co-workers[57] reported enantioselective carbonyl ylide cycloadditions[58] of diazodiketoester with styrene or phenylacetylene in the presence of a polymer-supported dirhodium (II) catalyst (**27**) in a continuous-flow reactor (Scheme 9, Table 5). Firstly, they investigated the PS-dirhodium(II) catalysts. In these reactions, the swelling volumes of the catalysts are important for improving the yields. That is, when the swelling volumes were increased, the yields of the desired products were improved (in batch reactions). To increase the swelling volumes, they introduced the trifluoromethyl group to the polystyrene backbones. After investigating immobilized Rh catalysts, they conducted enantioselective carbonyl ylide cycloaddition reactions under continuous-flow conditions. Both styrene and phenylacetylene reacted well under flow conditions. When styrene was used as a substrate, the reaction proceeded smoothly to afford the desired product in good yield and excellent enantioselectivity with 0.1 mol% of the catalyst at 0.5 mL h^{-1}; this system could be used for at least 60 h (TON = 780). The reaction products contained only 2.1 ppm Rh, which corresponds to 0.013% of the initial catalyst charge (ICP-MS analysis). They then employed phenylacetylene in this reaction. The desired cyclized product was obtained in high yield and excellent enantioselectivity at a flow rate of 30 mL h^{-1}. They also attempted to reduce the catalyst loading, and they finally succeeded in decreasing the catalyst loading to 0.0067 mol%. In this case, a TON of 11700 was reached.

Table 5: Detailed conditions of carbonyl ylide cycloaddition reactions.

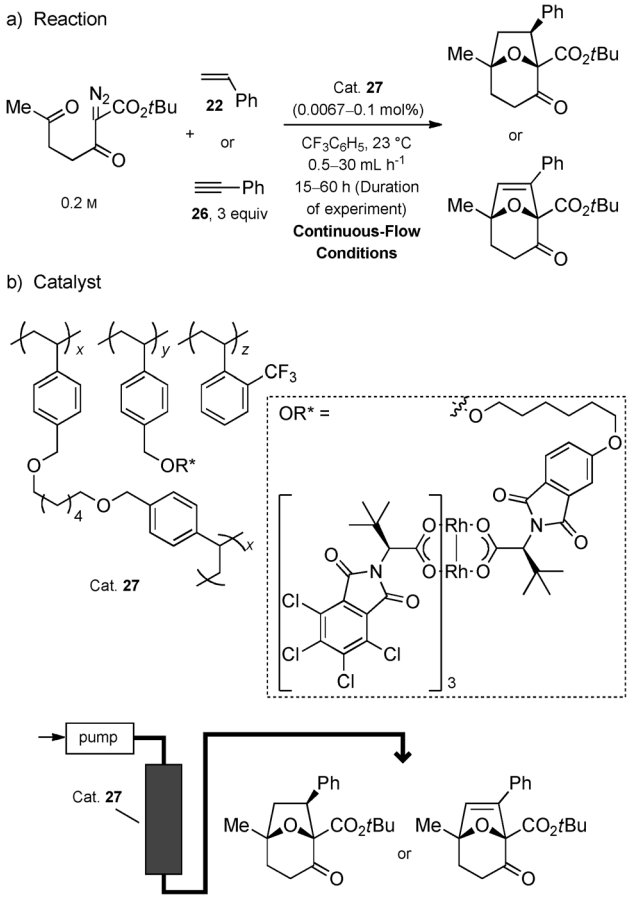
Entry	Substrate	Catalyst loading [mol%]	Flow rate [mL h^{-1}]	Yield [%]	*ee* [%]
1[a]	**22**	0.1	0.5	78	99
2[b]	**26**	0.0067	30	78	97

[a] Duration of experiment: 60 h. [b] Duration of experiment: 15 h.

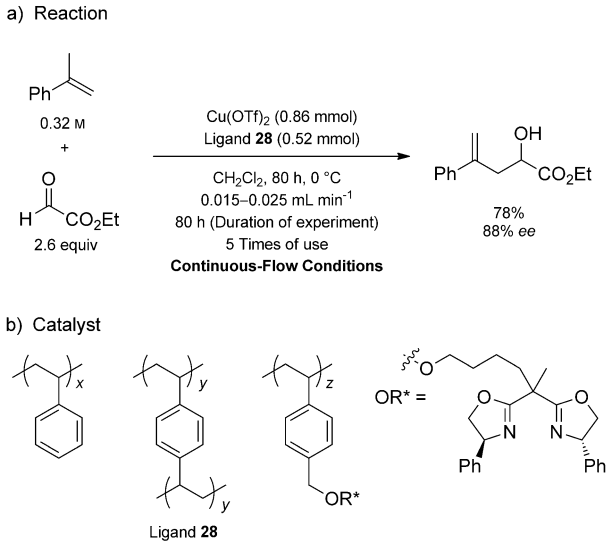
6. Miscellaneous Reactions

Other examples of continuous-flow asymmetric carbon–carbon bond-forming reactions, such as ene,[59,60] Diels—Alder,[61,62] and domino Michael–Knoevenagel reactions,[63] have been reported.

Salvadori and co-workers[64] reported the glyoxylate–ene reaction[59,60] of α-methylstyrene with a (PS-Box)-Cu catalyst (Scheme 10). Firstly, they developed insoluble Box ligand **28** (superficial area in dry state: < 5 m^2 g^{-1}), and applied it to an ene reaction under batch conditions. The desired products were obtained in high yield and high enantioselectivity. A solution of α-methylstyrene and glyoxylate in CH_2Cl_2 was run through the column. The product was obtained in 78% yield



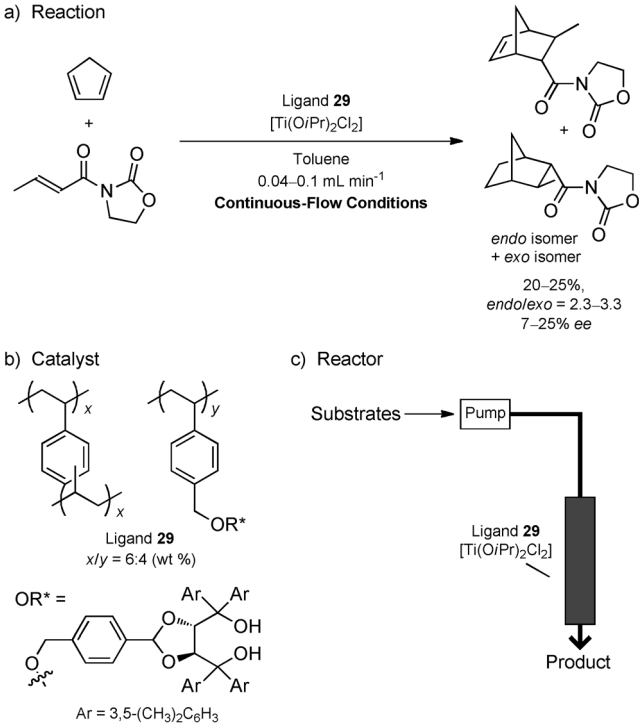
Scheme 9. Enantioselective carbonyl ylide cycloaddition reactions of a diazodiketoester with styrene or phenylacetylene with a PS-dirhodium(II) catalyst.



Scheme 10. A glyoxylate–ene reaction of α-methylstyrene in the presence of a (PS-Box)-Cu catalyst.

and 88% *ee* at 0.015–0.025 mL min^{-1} (residence time: ca. 6 h). By this procedure, 23 mmol of the product was efficiently created over 80 h, and the enantioselectivities between the five runs were unchanged. The total TON was 51.

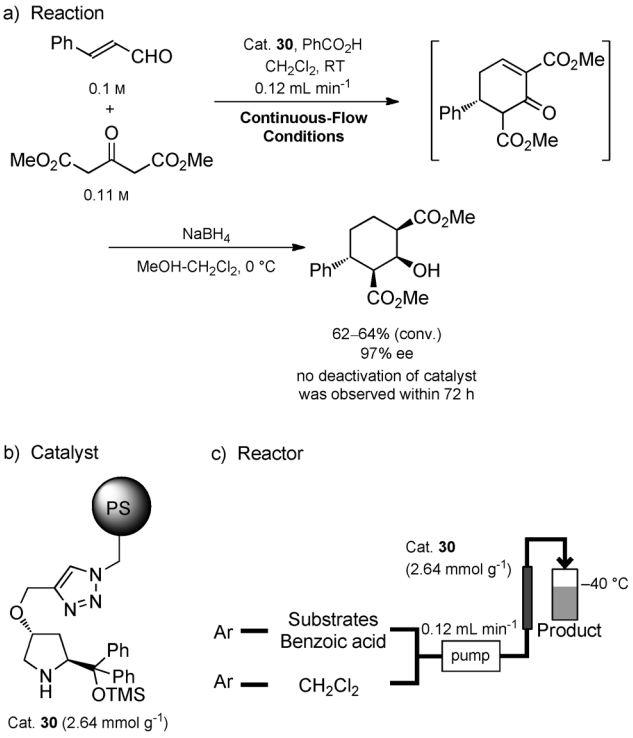
Altava, Burguete, Luis et al.[65] developed monolithic polymer-supported titanium catalysts with taddol ligands (**29**) and applied them to the asymmetric Diels–Alder reaction[61,62] between cyclopentadiene and crotonoamide under flow conditions (Scheme 11). They investigated the



Scheme 11. Asymmetric Diels–Alder reaction of cyclopentadiene with crotonoamide in the presence of taddolate **29**.

morphological properties of monolithic columns to change the composition of the porogenic mixture. In general, the medium pore diameter $D_{p,med}$ considered appropriate for this kind of materials range from 1000 to 2000 nm. From these experiments, they found about 10% of toluene in weight of the initial mixture obtained suitable monoliths with the expected porosity and without "wall effects" (i.e. the eluent is not flowing through cracks in the monolith or between the wall of the mold and the polymer). Then, they applied those optimized monolithic polymers to an asymmetric reaction. In this reaction, the desired product was obtained in higher yields when the flow rate was increased. This polymer-supported taddolate (copolymerized in a mold, and then treated with $[TiCl_2(OiPr)_2]$ in toluene) showed an extraordinary long-term stability; it was reported to be active for at least one year. However, the yield and the diastereo- and enantioselectivity were not sufficient. The authors also applied this catalyst to the alkylation reaction[13,14] of benzaldehyde with diethylzinc.

Pericàs and co-workers[66] reported the enantioselective domino Michael–Knoevenagel reaction[63] of dimethyl 3-oxoglutarate with 3-substituted acrolein derivatives catalyzed by immobilized diphenylprolinol trimethylsilyl ether **30** under continuous-flow conditions (Scheme 12). The diphenylprolinol trimethylsilyl ether was supported on a Merrifield resin



Scheme 12. An enantioselective domino Michael–Knoevenagel reaction in the presence of PS-prolinol derivative **30**.

(1% DVB) by Huisgen cycloaddition. The experimental setup consisted of a glass column loaded with the PS catalyst **30** and connected to a pump, which was used to feed the reactor with a solution of all the reagents in CH_2Cl_2; the outlet of the column was connected to a receiving flask. The reaction was carried out by passing the reagent solution (0.1M, *trans*-3-(4-methoxyphenyl)acrolein, 0.11M dimethyl 3-oxoglutarate, 0.1M benzoic acid in CH_2Cl_2) at 0.12 mL min^{-1} (residence time: 10 min) through the column charged with **30**. The eluted solution was kept in a receiving flask at −40 °C during the operation for 72 h. Workup involving borohydride reduction of the cyclohexenone product allowed isolation of the cyclohexanol product. After continuous operation for 72 h, 8.7 g (TON = 66) of the pure cyclohexanol products were isolated.

7. Conclusions and Perspective

In conclusion, we have summarized here recent progress in asymmetric C–C bond-forming reactions under continuous-flow conditions in the presence of chiral heterogeneous catalysts. The survey is comprehensive, but the reactions are limited: asymmetric 1,2-addition (ethylation, arylations, aldol, Mannich, and cyanation reactions), 1,4-addition, cyclization, ene, Diels–Alder, and domino Michael–Knoevenagel reactions. In the ethylation reactions with diethylzinc, PS-

supported amino alcohol derivatives were employed as the chiral catalysts, and some of them showed high enantioselectivities and good substrate compatability. To extend the arylation of aldehydes, triarylboroxins were used as the arylation reagents, and the desired diaryl alcohols were obtained with moderate to high enantioselectivities. PS-proline derivatives were applied to asymmetric Mannich reactions. Enantiomerically and diastereomerically pure adducts were obtained in the reaction of aliphatic aldehydes with glyoxylate imine. Immobilized proline derivatives were mainly used as catalysts in the asymmetric aldol reaction. Some of them showed high diastereo- and enantioselectivities. Immobilized cinchona alkaloid, polypeptide, and Pybox-$CaCl_2$ catalysts were developed for asymmetric 1,4-addition reactions. Immobilized polypeptide and Pybox-$CaCl_2$ catalysts showed good results in terms of faster flow rates, relatively large production, and broader substrate scope. The effective lifetime of the chiral calcium catalyst exceeded one week (8.5 days). Box-Cu and Rh catalysts were used for the asymmetric cyclization of diazo compounds with styrene. In this system, the reactions were conducted under solvent-free or $scCO_2$ conditions. While the efficiency of some reactions were improved, the yields as well as chemo- and enantioselectivities were still low to moderate. Moreover, in the enantioselective carbonyl ylide cycloaddition reactions of a diazodiketoester with styrene and phenylacetylene, the immobilized Rh catalyst showed excellent activity, and the desired products were obtained in high yield and high enantioselectivity. In addition, the catalyst loading was reduced, and the flow rate could be increased. In a glyoxylate–ene reaction of α-methylstyrene in the presence of a (PS-Box)-Cu catalyst, the desired product was obtained in high yield and high enantioselectivity. The domino Michael–Knoevenagel reaction was also conducted under continuous-flow conditions, and the desired product was obtained in good yield with high enantioselectivity.

In these reactions, except of a very few examples, most reports showed only one example under continuous-flow conditions. Researchers have developed chiral heterogeneous catalysts; their activity was evaluated in a conventional batch system, and then continuous-flow conditions were tested. From this aspect, more investigations of continuous-flow conditions, especially in terms of substrate scope, are necessary. In addition to substrate scope, faster flow rates ($>0.1\ mL\,min^{-1}$), longer catalyst lifetimes (over days), and high yield ($>80\,\%$) as well as high chemo-, diastereo-, and enantioselectivity (>80–$90\,\%$ selectivity in each case) are required.

Finally, TONs are also very important in continuous-flow systems. TONs in continuous-flow systems are somehow related to the catalyst lifetime. As a consequence of the efficiency in separating and isolating products from catalysts as well as the high TONs and long catalyst lifetimes, relatively lower TOFs (turnover frequencies) in continuous-flow systems compared with those for batch systems may be acceptable. The avoidance of product inhibition theoretically supports the advantage of continuous-flow systems. The development of more efficient chiral heterogeneous catalysts is crucial for greater efficiency.

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