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Recent Advances in Asymmetric Catalysis in Flow

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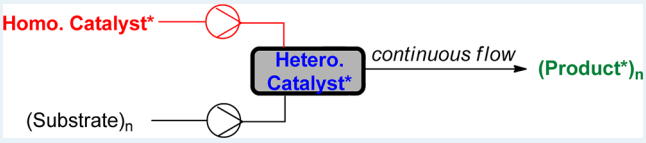
ABSTRACT: Asymmetric catalysis in flow has been attracting much attention very recently because of the potential advantages over its batchwise counterpart, such as high-throughput screening and synthesis, easy automation with the integration of on-demand reaction analysis, little or no reaction workup, and potential long-term use of the catalysts in the case of heterogeneous catalysis. Homogeneous asymmetric catalysis performed in a microreactor has demonstrated successful examples in fast catalyst screening, integrated inline/onlineanalysis, microflow photocatalysis, multistep transformation with unstable intermediates, and potential for lower catalyst loading or homogeneous catalyst recylcing. Since heterogeneous asymmetric catalysis serves as a better way than its homogeneous analogue for catalyst separation and recycling, this Review Article summarizes recent development via different catalyst immobilization methods, such as covalent support, a self-supported method, an adsorption method, and H-bonding, electrostatic or ionic interaction, and nonconventional media, as well. In addition, biocatalysis, including enzyme-catalyzed kinetic resolution and transformation, in flow will be discussed either in homogeneous or heterogeneous mode.



KEYWORDS: *asymmetric catalysis, homogeneous, heterogeneous, continuous flow chemistry, microreaction technology, solid-supported catalyst, biocatalysis*

1. INTRODUCTION

Along with the increasing demand on the application of a single enantiomer of chiral compounds, the development of efficient methods for the synthesis of enantiomerically enriched building blocks and intermediates continues to be of great interest to both academia and industry.[1,2] Asymmetric catalysis[3,4] is, in particular, one of the most general and appealing strategies to generate chiral compounds with high economy and efficiency, whereby achiral starting materials are transformed directly into enantioenriched products using only minute amounts of a renewable chiral component. Over the past few decades, intense research in this field has greatly expanded the scope of catalytic reactions that can be performed with high enantioselectivity and efficiency in either a homogeneous or heterogeneous way. Despite the remarkable success, however, only a few examples of asymmetric catalysis have been developed into industrial processes.

The major technical concerns for this situation are the need for (1) fast process optimization (particularly screening of suitable catalyst systems), (2) high potential of automatic operation (e.g., process, monitoring, and scale-up), and (3) reusable chiral catalyst development (mainly means heterogeneous chiral catalyst) for industrial implementation. As for the first two concerns, both homogeneous and heterogeneous asymmetric catalysis[5,6] would significantly benefit from continuous processing with conveniently scalable flow devices. Continuous flow technology[7−33] has excellent potential for the integration of a high level of automation and for the incorporation of on-demand reaction analysis. This can be advantageous for applications such as high-throughput screening and synthesis as well as for the continuous production of significant quantities of compound at higher efficiency and lower costs. However, in terms of the third concern mentioned above, heterogeneous asymmetric catalysis (either immobilization of homogeneous catalyst or chiral modification of heterogeneous metal catalyst) serves as a better way than its homogeneous counterpart for catalyst separation and recycling, which is also very important for large-scale production. Moreover, a heterogeneous catalyst could circumvent product contamination (metal leaching in the case of a homogeneous metal catalyst), particularly in pharmaceutical and fine chemicals production. Of course, in terms of activity, productivity, enantioselectivity, stability, ease of recovery, reusability, and so on, catalyst immobilization is still quite challenging to keep comparable or superior to its homogeneous counterpart.

In the past decade, there have been two major types of significant developments in parallel for continuous flow chemistry: namely, solid-supported catalyst/reagent/scavenger "column" (e.g., packed-bed reactor) for flow synthesis and microreactor technology (MRT), mainly for fluid process, respectively. The applications in the former case have been pioneered by the Itsuno group[21] and further extended by Hodge,[23] Lectka,[22] and Ley[24−26] groups. Among those,

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heterogeneous catalysis is supposed to combine both reaction and separation when performed in a continuous-flow mode,[27−29] with the advantages of easy automation, little or no reaction workup, and potential long-term use of the catalysts, whereas in the latter case, MRT has witnessed explosive development as enabling technology[7−20] and demonstrated many advantages, such as improved heat and mass transfer as well as mixing, and also easier scale-up and reproducibility due to the precise control over reaction conditions in these devices. Although the topic of asymmetric reactions in MRT or in flow has been summarized in a couple of related review articles or book chapters,[30−33] "pure" asymmetric catalysis in a flow reactor, as a narrower concept, is still waiting for an overview on its fast development in the past years.

This Review will focus on very recent research results of asymmetric catalysis in a continuous-flow mode. The context is divided to three major categories of reactions: (1) homogeneous asymmetric catalysis, especially in a microreactor, featuring fast catalyst screening, lower catalyst loading, higher temperature, integrated inline/online analysis, microflow photocatalysis, and multistep transformation with unstable intermediates; (2) heterogeneous asymmetric catalysis with different immobilization methodologies, such as covalent support, self-supported method, adsorption method and H-bonding, electrostatic or ionic interaction, and nonconventional media as well for catalyst recycling; and (3) biocatalysis in flow, such as enzyme-catalyzed kinetic resolution and other transformations. Because of length limitation, some earlier examples of asymmetric catalysis in flow would be mentioned once or only cited in the reference and therein. And soluble polymer-supported catalytic system[34] or continuously stirred tank reactor[35] is also beyond the scope of this article.

Generally speaking, continuous flow reactors can roughly be divided into microscale, mesoscale, and large scale. Although mesoscale (normally 1−10 mm channel size) and even large scale could be conveniently achieved via equaling-up, microscale is mainly focused here for the fundamental R&D of asymmetric catalysis in flow, that is, 50−1000 μm channel size for chip or coil type reactors and 1−20 mm tube diameter for packed-bed reactors.[18,36] It is also well-known that the continuous flow process often leads to a substantial increase in the productivity compared with a batch process;[19] however, the productivity difference was not highlighted in some examples reviewed because of varied research interests and limited information in those references. For a better understanding of the microflow devices applied to asymmetric catalysis, an illustration of different types of flow reactors in this context is summarized in Figure 1. In addition to the micro(channel) reactor without catalyst immobilization (abbreviated as MRT for homogeneous catalysis), other catalytic flow reactors for heterogeneous catalysis, such as the packed-bed reactor, monolith (parallel-plate reactor), and fluid-bed reactor, are also demonstrated in the following context by using different catalyst immobilization methods. In addition, a reverse-flow reactor for recycling of homogeneous catalysts will be discussed in Section 3.3 (Adsorption Method and H Bonding).

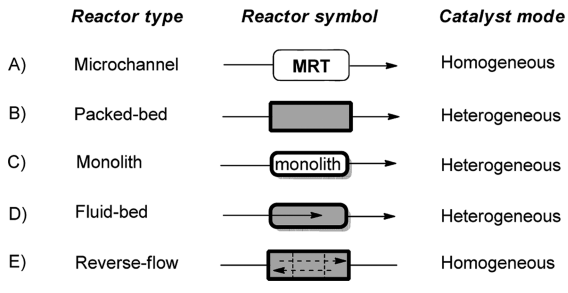


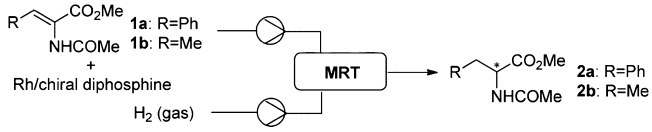
Figure 1. Illustration of reactors with different immobilization methods in this context.

2. HOMOGENEOUS ASYMMETRIC CATALYSIS IN FLOW

Despite the rapid development of continuous process in organic synthesis and catalysis in the past decade, asymmetric catalysis under continuous flow conditions with good levels of enantioselectivity is falling far behind. One reason might be that reactions in flow are usually conducted at elevated temperatures to decrease residence time, whereas most asymmetric catalytic methods are conducted at low temperatures toward high enantioselectivity.[37] Only a few examples of homogeneous asymmetric catalysis in continuous flow have been reported, usually performed in microreactors, that is, microfluidic flow systems consisting of microscale channels. As demonstrated in the following context, asymmetric catalysis could benefit from the use of MRT, especially for fast catalyst/ligand screening with lower catalyst loading, higher temperature with maintained enantioselectivity, integrated inline/online analysis, microflow photocatalysis and multistep transformation with unstable intermediates.

2.1. Fast Catalyst Screening and Lower Catalyst Loading. One of the earliest and most important asymmetric catalyses investigated in a microreactor is the well-known gas−liquid asymmetric hydrogenation, which has been a continuous topic in the de Bellefon group since 2000.[38−42] High-throughput screening of catalysts/ligands with low catalyst loading was the main target of this research. A combination of an (pulse) injection system and a micromachined device, such as a mesh microreacor and a falling-film microreactor, could afford dynamic sequential operations for kinetic studies, as shown in Scheme 1. In case of a rhodium/(*S*,*S*-BDPPTS)-

Scheme 1. High-Throughput Screening of Rhodium Catalysts for Homogeneous Asymmetric Hydrogenation



catalyst in an aqueous phase, up to 214 tests were performed with methyl (*Z*)-(−)-acetamidocinamate **1a** as substrate in a short time and with an average inventory of Rh/test as low as 14 μg.[39] Among up to 20 rhodium-chiral diphosphine catalysts, a very active catalyst such as the Rh/Diop complex could also be tested in the mesh microreactor with a short residence time (1 min). The residence time was further extended to 3 min (for methanol) in a helicoidal single-channel falling-film microreactor for this type of reaction at microliter scale.[41] With this device, even very low catalyst loadings (an average inventory of 0.1 μg Rh catalyst) could lead to reliably reproducible results.

Very recently, Ley and co-workers reported the homogeneous asymmetric hydrogenation of a number of trisubstituted olefins **3** utilizing a tube-in-tube gas−liquid flow reactor.[43] As

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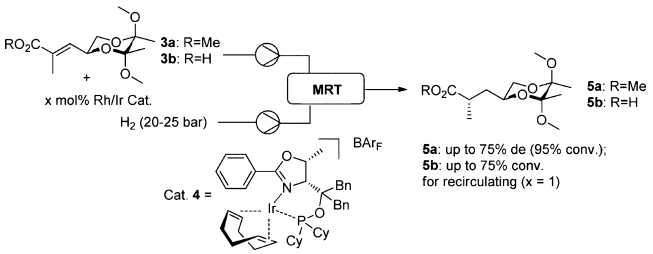
shown in Scheme 2, multiple parameters, such as pressure, solvent, temperature, and catalyst loading, could be rapidly

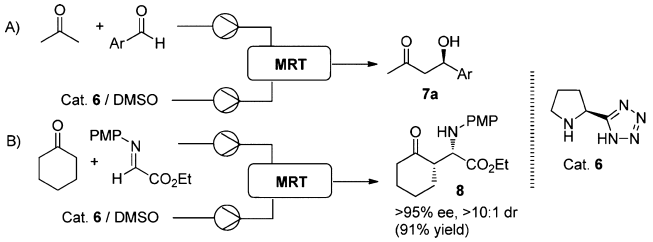
Scheme 2. Homogeneous Asymmetric Hydrogenation in Flow Using a Tube-in-Tube Reactor



screened and optimized for a number of chiral iridium- and rhodium-based catalysts, and scale-up could also be conveniently realized by using flow setup. It was found that catalyst (*R*,*R*)-**4** exhibited the highest activity and selectivity for hydrogenation of methyl ester **3a**, resulting in product **5a** with up to 75%diastereomeric excess (de) at 95% conversion. In the case of a less reactive acid substrate **3b**, the setup was further modified through a recycling process,[44] which greatly prolonged catalytic activity and afforded up to 75% conversion at a lower catalyst loading (1 mol %).

As the first organocatalytic asymmetric aldol reaction in a microreactor, another successful example of lower catalyst loading with a continuous-flow reactor rather than a batchwise one was reported by Seeberger and co-workers.[45] Organocatalytic condensation of various aromatic aldehydes with acetone catalyzed by 5-(pyrrolidin-2-yl)tetrazole (catalyst **6**) could be dramatically accelerated under reduced catalyst loading (5 mol %, 20 min) and higher temperature (60 °C), affording slightly higher yields and selectivities of aldol adduct **7a** (Scheme 3A). The scope of this organocatalysis was further

Scheme 3. Acceleration and lower catalyst loading for homogeneous asymmetric aldol/mannich reactions

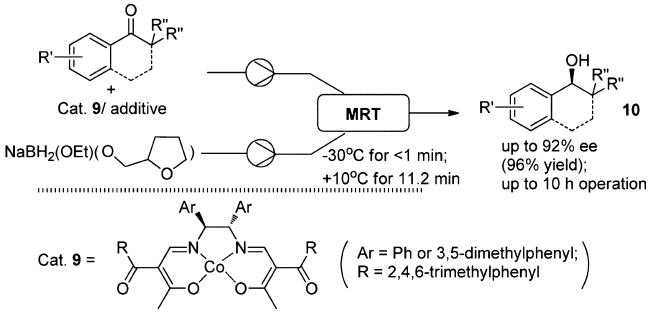


extended to Mannich reactions using an α-iminoglyoxylate as an acceptor and cyclohexanone as a donor, giving β-amino ketone **8** with >95% ee and >10:1 diastereomeric ratio (Scheme 3B).

It is noteworthy to mention that McQuade and co-workers recently demonstrated a different strategy in which a homogeneous catalyst is prepared continuously using a packed bed of a catalyst precursor,[46] namely, a continuous proline-catalyzed α-aminoxylations via leaching of solid L-proline. For a long-term flow test over 4 h, the target product on a 10 g scale was obtained in an average yield of 78% and 98% ee with a 20 min residence time; the consumed proline catalyst was calculated to be ∼12 mol % (5 mol % proline for 2 h in batch process).

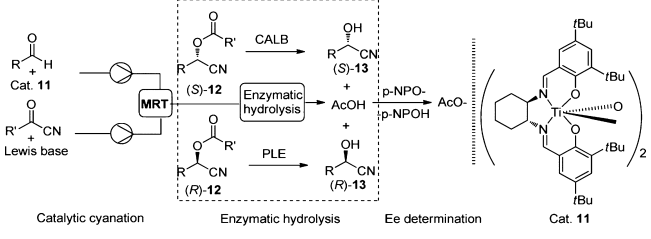
2.2. Higher Temperature with Maintained Enantioselectivity. Highly enantioselective homogeneous catalysis with precise control under continuous-flow conditions was established recently by Yamada and co-workers for the cobalt-catalyzed borohydride reduction of tetralone derivatives.[47] A microreactor allowed a higher reaction temperature with the residence time of 12 min than the corresponding batch system to maintain enantioselectivity as well as reactivity (Scheme 4). Moreover, the present system of cobalt catalyst **9** was directly applied to gram-scale synthesis (10 h operation) and afforded the reduced products **10** with up to 92% ee.

Scheme 4. Homogeneous Asymmetric Catalytic Reduction by Co-Salen Complexes in a Microreactor



2.3. Integrated Online/Inline Analysis. As mentioned above, one merit of a flow device is the convenience of incorporating (high throughput) online/inline analysis tools[48] into the whole system; for instance, enantiomeric exess or yield determination as online analysis, and ramon, FT-infrared monitoring or mass spectrometric measurement as inline analysis. An earlier example for this purpose was reported by Moberg[49] and Hult in 2007,[50] demonstrating the combination of high-throughput synthesis through homogeneous enantioselective Ti-salen-catalyzed (catalyst **11**) cyanation and the following online analysis via enzymetic hydrolysis of acylated cyanohydrins **12**. The yields and enantiomeric excesses of O-acylated cyanohydrins **12** obtained from chiral Lewis acid/Lewis base-catalyzed additions of α-ketonitriles to prochiral aldehydes in a microreactor could be accurately determined by an enzymatic method for efficient catalyst optimization (Scheme 5). The amount of remaining aldehyde was

Scheme 5. Homogeneous Asymmetric Cyanation Followed by Inline Enzymetic Analysis Method



determined by spectrometric measurement after its enzyme-catalyzed reduction (NADH/HLADH) to an alcohol, and the two product enantiomers were analyzed after subsequent hydrolysis first by the *S*-selective *Candida antarctica* lipase B (CAL-B) and then by the unselective pig liver esterase. Since close to linear relationships were observed between values determined by the enzymatic method and by GC, this

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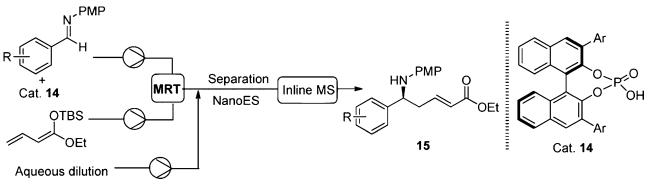
downscaling online analysis was successfully applied to 18 cyanohydrin products, providing an efficient method for initial screening of yields and enantioselectivities without any purification of the reaction mixture.

A second fully integrated microfluidic system for asymmetric organocatalysis and analysis was developed by Belder and co-workers recently for the vinylogous Mannich reaction,[51] including enantioselective organocatalysis, enantiomer separation, and mass spectrometric detection by nanoelectrospray (nanoES) ionization on a single microchip.[52] As shown in Scheme 6, Brønsted acid catalysts **14** were conveniently

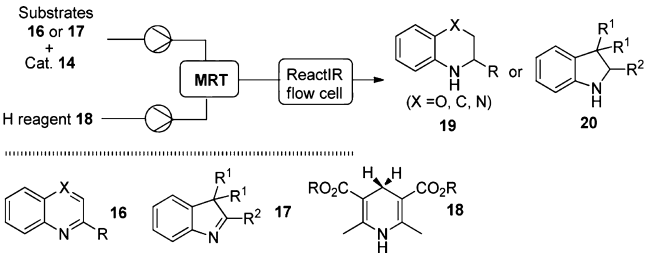
Scheme 6. Homogeneous Asymmetric Organocatalytic Vinylogous Mannich Reaction and Inline Analysis on a Single Microfluidic Nanospray Chip



screened to give Mannich products **15** with up to 66 ± 4% ee. It is worth mentioning that this microchip setup also exhibited great potential for mechanism investigation by inline detection and identification of reaction intermediates.

In addition to mass spectrometric analysis described herein, FTIR serves as one option of analytical tools to be integrated with a microreactor system. For example, Rueping and co-workers reported continuous-flow catalytic asymmetric transfer hydrogenations of benzoxazines, quinolines, quinoxalines, and 3*H*-indoles by integrating an inline ReactIR flow cell,[53] which allows fast and convenient optimization of reaction parameters. The corresponding products **19** and **20** were obtained in good yields and with excellent enantioselectivities (up to 99% ee) following a real-time continuous-flow optimization (Scheme 7).

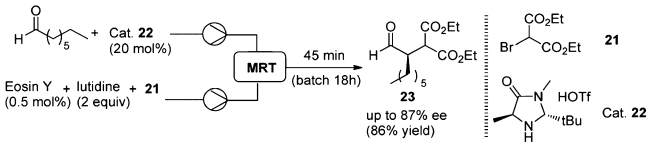
Scheme 7. Homogeneous Asymmetric Organocatalytic Transfer Hydrogenation Integrated with Inline FTIR



2.4. Microflow Photocatalysis. Continuous photocatalytic transformations[54] have been regaining increasing attention as an interesting synthetic methodology in the context of green chemistry and as a result of their potential for developing new chemical reactions. Compared with conventional batch reactors, continuous microflow methods present a valuable alternative approach to circumvent known drawbacks, such as low productivity and energy transfer efficiency. The high surface-to-volume ratio (small channel depth) not only ensures improved sample irradiation but also contributes to high spatial illumination homogeneity, resulting in greatly enhanced heat and mass transfer as compared with common batch systems. Shortened reaction times and, hence, prevention of undesired side reactions may contribute to higher selectivity and product purity. Although well established for UV photochemistry,[55,56] microreactors have until now found only limited applications for visible-light photocatalytic transformations.[57] Likewise, there are only a few reports on (homogeneous) enantioselective catalysis in microflow systems.[58−60] For example, Ichimura and co-workers have reported an asymmetric photosensitized addition of methanol to (*R*)-(+)-(*Z*)-limonene[58] in a microreactor. The increase in the quantum yield and slight de increase of the photoadducts (*cis*- and *trans*-4-isopropenyl-1-methoxy-1-methylcyclohexane) over that obtained in a batch reaction system resulted from the shortened residence time and, therefore, the suppression of the sequential side reaction processes.

A recent successful development of flow conditions to both enhance productivity of (enantioselective) photocatalytic reactions and facilitate challenging transformations involving unstable intermediates was reported by Zeitler and co-workers.[60] Operationally simple microreactor and FEP (fluorinated ethylene propylene copolymer) tube reactor systems enabled a significant rate acceleration of a synergistic enantioselective α-alkylation of aldehyde via organocatalyst **22**, together with photoredox catalyst Eosin Y. As shown in Scheme 8, this approach could increase the productivity of the target

Scheme 8. Asymmetric Visible Light Photoredox Catalysis under Microflow Conditions



product **23** by 2 orders of magnitude with up to 87% ee. Other transformations involving the conversion of unstable intermediates, such as visible light photoredox Aza-Henry reactions, could also be improved via the same photocatalytic device.

2.5. Multistep Transformation with Unstable Intermediates. Recently, multistep synthesis in continuous flow[36,61−65] has emerged as a powerful alternative to traditional procedures because it often allows one to circumvent time-consuming and labor-intensive isolation of intermediates. Despite recent advances, multistep synthesis under flow conditions remains challenging because of its increased complexity as compared with single-step flow processes. Solvent or catalyst compatibility,[66] flow rate synergy, as well as the effect of byproducts and impurities from upstream reactions on the downstream ones must be considered. However, when the telescoping[61,62] of a multistep flow synthesis is possible, there would be the great benefit that intermediates are not isolated but are directly transferred into the next flow reactor, especially in the case of unstable intermediates generated from fast and exothermic reaction steps.

Yoshida and co-workers have reported in 2011 a flow microreactor system for the generation of a configurationally unstable chiral organolithium intermediate **25**, which was trapped with an electrophile before it epimerizes.[67] As shown in Scheme 9, the catalytic enantioselective carbolithiation of conjugated enynes **24** by sparteine ligand **27** followed by the reaction with electrophiles was accomplished to obtain enantioenriched chiral allenes **26** with up to 92% ee. On the

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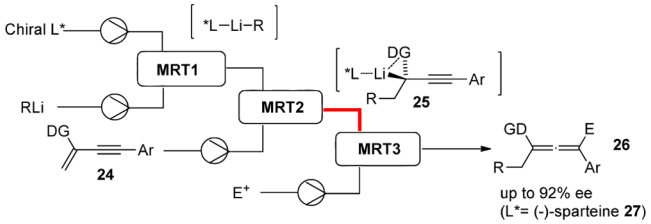
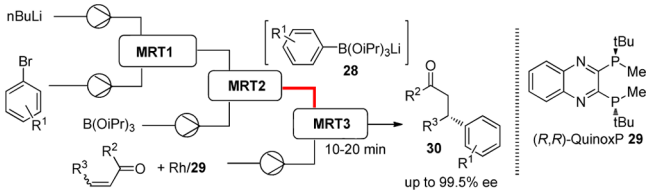
Scheme 9. Enantioselective Carbolithiation Followed by Trapping with Electrophiles



basis of this method, a high-resolution control of the residence time using a flow microreactor was realized, which would add a new dimension to asymmetric multistep synthesis.

Very recently, Buchwald and co-workers reported an enantioselective β-arylation of ketones enabled by lithiation/borylation/1,4-addition sequence under flow conditions.[68] The use of a flow process allowed for the rapid, safe, and efficient lithiation of aryl bromides at room temperature, their conversion into aryl triisopropylborates **28**, and subsequent utilization in rhodium-catalyzed asymmetric 1,4-addition to give final products **30** with up to 99.5% ee (Scheme 10). In this

Scheme 10. An Efficient Three-Step Synthesis of Enantiopure β-Arylated Ketones in Continuous Flow



protocol, readily available aryl bromides were used as starting material instead of arylboron reagents and no isolation or purification of arylboron species was needed. Moreover, lithiation at mild temperature afforded a short residence time (within minutes), demonstrating a high potential for scale-up. It is worth noting that this process was enabled by the efficient handling of solids under acoustic irradiation conditions.

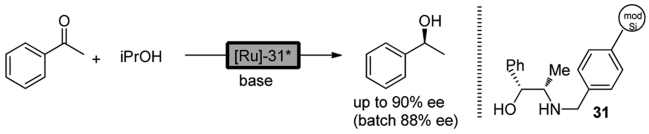
3. HETEROGENEOUS ASYMMETRIC CATALYSIS IN FLOW

As mentioned above, heterogenizing homogeneous catalysts on a (solid) support represents a future trend of industrial application toward the increase of the efficiency of enantioselective synthetic techniques, due to difficult recycling and possible contamination of usually expensive (homogeneous) chiral catalysts or ligands. In conjunction with continuous flow, the reaction and separation of supported catalysts can be performed simultaneously, which would further broaden the scope of the chemical processes involved. Furthermore, no mechanical stirring or agitation in a flow mode would avoid the mechanical degradation of the support material, which might lead to significantly shortened lifetimes of supported catalysts/reagents. In principle, the use of immobilized catalysts in flow would afford more economically and environmentally friendly processes, with a high potential of longer term usage and usually higher overall productivity. However, one of the main difficulties of asymmetric catalysis using solid-supported catalysts is the development of an immobilization strategy that maintains both good stereoselectivity and catalyst activity. Selectivities obtained using homogeneous catalysts that work well in solution phase can often be significantly reduced when the catalysts are heterogenized[69,70] This following section will summarize some recent developments in heterogeneous asymmetric catalysis in flow, with the emphasis on different immobilization methods: namely, covalent polymer support, a self-supported method, an adsorption method and H-bonding, electrostatic or ionic interaction, and a nonconventional media method. Each of these immobilization strategies has advantages and limitations with respect to the others, and some of them are further classified by reaction or catalyst (metal-complex, organocatalyst, and enzyme) type in the following context.

3.1. Covalent Polymer Support. Covalent bonding linkage is by far the most frequently used strategy and is generally assumed to furnish the strongest binding between the homogeneous part and a support. However, it is synthetically demanding, since generally, some special functionalization of the ligand is required, either for grafting to a preformed support (for example, polystyrene or inorganic nanoparticle support) or for forming an organic polymer by copolymerization with suitable monomers (monolith type). The application of a covalent polymer support in heterogeneous asymmetric catalysis will be discussed below on the basis of different types of reactions.

3.1.1. Transfer Hydrogenation. Reek and Leeuwen have reported a continuous asymmetric transfer hydrogenation by using a silica-supported ruthenium catalyst.[71] As shown in Scheme 11, the ruthenium complex of NH-benzyl-(1*R*,2*S*)-

Scheme 11. Continuous Asymmetric Transfer Hydrogenation Reaction by Using Heterogeneous Ruthenium Catalysts on Silica



(−)-norephedrine (**31**) covalently tethered to silica showed high activity and enantioselectivity in the continuous reduction of acetophenone, providing up to 90% ee (slightly higher than batch 88% ee) at a conversion of 95% (Scheme 11). This catalyst also showed a very constant catalytic activity in the flow mode, and no catalyst deactivation occurred over a period of 1 week, which was ascribed to effective site isolation by suitable covalent immobilization.

3.1.2. Organozinc Reagent Addition. An asymmetric catalysis other than hydrogenation that has been examined extensively in continuous flow using supported catalysts is the enantioselective addition of diethylzinc (or extended to arylzinc) to benzaldehydes.[23] In 1990, Itsuno and co-workers reported their pioneering work of continuous asymmetric ethylation of aldehydes using polymeric chiral α-amino alcohols.[21] In an upscaled test, 90 mmol of (*S*)-1-(*p*-chlorophenyl)propanol could be produced with 94% ee through a column containing 5 mmol of a polymeric catalyst. Following this strategy, polymer-supported camphor derivative **32** (Scheme 12) was applied by the Hodge group[72] in a flow system to catalyze the reaction of benzaldehyde with diethylzinc to give 1-phenylpropanol **36a** in >95% yield and >94% ee. However, in this case, both yield and ee were significantly deteriorated after processing for 275 h, which was

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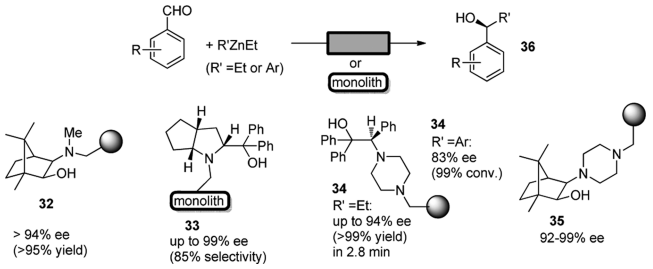
Scheme 12. Heterogeneous Asymmetric Addition of Zinc Reagent to Aldehyde in Flow[a]



[a]Default R′ = Et.

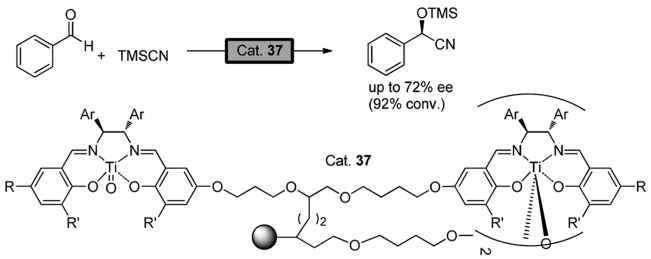
attributed to the gradual chemical degradation of the catalyst sites. Different from a packed-bed reactor, a monolithic column usually could avoid possible diffusional problems for highly cross-linked resins with a superior performance of flow distribution.[73] For example, monolith catalyst **33** could afford almost enantiopure products **36** in 85% chemoselectivity,[74] which demonstrated better asymmetric induction than both its homogeneous analogues and the polymer-supported catalyst by grafting.

Since 2008, Pericàs and co-workers have begun their research on this topic to extend the scope of zinc reagents and to develop more efficient heterogeneous catalytic systems, as well, for this continuous asymmetric transformation. For example, a functional polymer **34**, obtained by reaction of (*R*)-2-(1-piperazinyl)-1,1,2-triphenylethanol with a Merrifield resin, has been loaded in a packed-bed reactor and used as the catalyst for the continuous enantioselective production of 1-arylpropanols through a single-pass operation.[75] The high catalytic activity depicted by **34** allows complete conversion of the substrates toward up to 94% ee of target products within unprecedently short residence times (2.8 min). By using this method, the authors also reported the uninterrupted synthesis of a small library of enantiopure 1-arylpropanols by the sequential operation of the flow system. Furthermore, this group extended the scope of zinc reagents to ArZnEt by using triarylboroxins as the ultimate source of aryl groups in the presence of the same catalyst, **34**.[76] As the first single-pass, continuous flow enantioselective arylation of aldehyde, this flow arylation of aldehydes could be conveniently optimized by using arylboroxins as an atom-economical, inexpensive and readily available aryl group source. The target diarylmethanols could be prepared in large scale with up to 83% ee at 99% conversion, which enabled this flow process to be an efficient alternative for the multigram production of carbinol compounds (Scheme 12).

Very recently, Pericàs group also developed a new polystyrene-supported (2*S*)-(−)-3-exopiperazinoisoborneol (**35**), which was successfully applied as a ligand in the continuous flow asymmetric alkylation of aldehydes with Et_2Zn.[77] A broad scope of aldehyde substrates (R = aryl, alkyl, and alkenyl) could be efficiently transferred to the corresponding alcohols with up to 99% ee. Moreover, the supported ligand turned out to be highly chemically stable due to only a marginal decrease in conversion after 30 h of single-pass operation (Scheme 12).

3.1.3. Cyanation. As mentioned in Section 2.3, homogeneous enantioselective silyl-cyanation of benzaldehydes has been already applied in a flow reactor by using either La-pybox[49] or Ti-salen[50] complexes as catalyst. Correspondingly, the Moberg group also developed its heterogeneous analogue by grafting chiral Ti-salen catalyst to macroporous monosized polystyrene-divinylbenzene beads (Scheme 13).[78] The enantio-

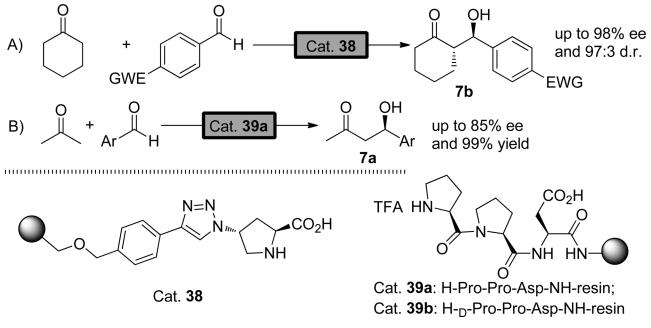
Scheme 13. Heterogeneous Asymmetric Cyanation



selectivities (up to 72%) observed from this newly developed catalyst, **37**, are comparable to those obtained in batch reactions, which shows the high potential for high-throughput screening of catalytic performance.

3.1.4. Aldol Reaction. The catalytic asymmetric aldol reaction is one of the most important C−C bond forming methodologies, which was extensively investigated especially by using many kinds of organocatalysts in the past decade.[79] Following the first organocatalytic asymmetric aldol reaction in microreactor developed in 2009,[45] the Pericàs group described the application of polystyrene-immobilized proline-based catalysts in packed-bed reactors for the continuous-flow enantioselective α-aminoxylation of aldehydes.[80] This system allowed the easy and fast preparation (about 5 min residence times) of a series of β-aminoxy alcohols with up to 96% ee and high productivity of 32.7 (mmol product/mmol catalyst) by using about 2.5 mol % catalyst, which was a 4-fold reduction compared to the corresponding batch process. Very recently, the same group reported another novel solid-supported organocatalyst 4-(1-triazolyl)proline, **38** (on 8% DVB-PS), for continuous-flow enantioselective aldol reactions.[81] High activity (TON up to 61) depicted by the supported catalyst **38** and its chemical/mechanical stability have allowed its application in packed-bed reactors for continuous flow processing (Scheme 14A). Almost enantiomerically pure (98% ee) adducts with a

Scheme 14. Asymmetric Aldol Reaction Catalyzed by Heterogeneous Organocatalysts



diastereomeric ratio of 97:3 could be produced in gram amounts under continuous flow conditions with a residence time of 26 min. Furthermore, the effective catalyst loading could be reduced to 1.6%, which was a 6-fold reduction of catalyst loading compared with the corresponding batch process. However, nonactivated aldehydes were remaining targets for this continuous-flow asymmetric catalysis.

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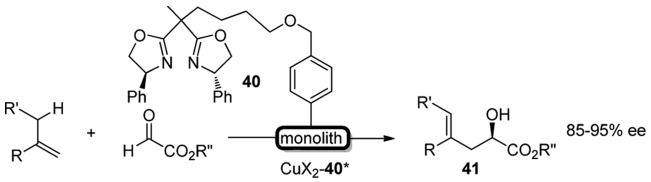
Another recent successful example of asymmetric aldol reaction in a continuous-flow reactor was reported by Fülöp and co-workers with a highly reusable heterogeneous peptide, **39a**, which was readily synthesized and immobilized by solid-phase peptide synthesis (SPPS) on a swellable polymer support in one single step.[82] After thorough optimization of the reaction conditions, β-hydroxyketone products **7a** were obtained in high yields and stereoselectivities (85% ee) comparable with literature batch results (Scheme 14B). The lack of peptide cleavage from the resin means no workup, no purification, and no product loss. Moreover, the residence time on the catalyst bed was as low as 6 min and, thus, suggested a very promisingly high productivity.

3.1.5. Ene Reaction. The heterogeneous asymmetric catalytic glyoxylate−ene reaction in a flow system has been reported by Salvadori and co-workers by using an insoluble polymer-bound bis(oxazoline)−copper complex (**40**).[83] As shown in Scheme 15, good activity and ee values in the

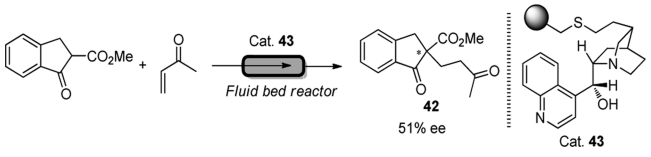
Scheme 15. Enantioselective Glyoxylate−Ene Reaction with Heterogeneous Cu-Box Complex



range 85−95% have been obtained during five to seven recycles without noting any degradation of the enantioselectivity, either under flow conditions or in batch mode. Moreover, most of the recycles were carried out without the need of any additional $Cu(OTf)_2$, demonstrating that this type of box ligands served as effective and easily recoverable catalyst precursors.

3.1.6. Michael and Michael−Knoevenagel Reactions. In 2006, Hodge and co-workers reported a continuous Michael reaction between methyl 1-oxoindan-2-carboxylate and methyl vinyl ketone by passing solutions of the reactants through a fluid bed of polymer-supported tertiary amine at 50 °C.[84] The Michael product **42** was obtained in high yield and 51% ee in the case of polymer-supported cinchonidine **43**, demonstrating results comparable to cinchonidine itself (Scheme 16). In

Scheme 16. Asymmetric Michael Reactions Catalyzed by Polymer-Supported Cinchonidine in a Bench-Top Flow System



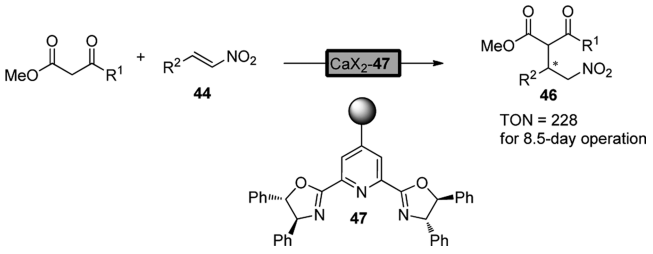
addition, the use of a fluid bed reactor was attractive because it allows gel-type beads to be used satisfactorily in a flow system. Another very recent example was developed by Fülöp and co-workers for the first continuous-flow asymmetric organocatalytic conjugate addition of aldehydes to nitroolefins **44a**.[85] A solid-supported peptide **39b** (see also Scheme 14) has been utilized as catalyst, which was readily synthesized and immobilized in one single step. As outlined in Scheme 17, synthetically useful chiral γ-nitroaldehydes **45** could be

Scheme 17. Michael Reaction of Aldehydes to Nitroolefins by Solid-Supported Peptide Catalysts

generated in excellent yields and stereoselectivities within short reaction times, and catalyst reusability, the ease of product isolation, and facile scale-up could enhance the efficiency of this flow chemistry.

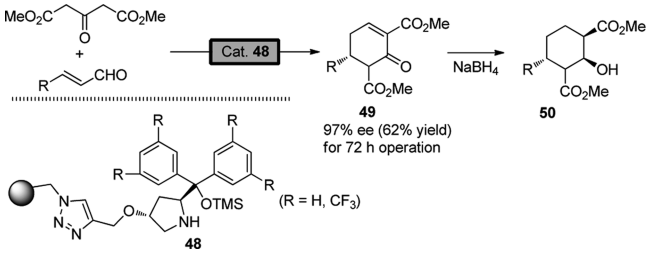
In addition to supported organocatalysts, a chiral heterogeneous Ca-pybox catalyst, **47**, was reported recently by Kobayashi and co-workers to be highly efficient in an asymmetric Michael addition of 1,3-dicarbonyl compounds to nitroalkenes **44** in a flow system.[86] As shown in Scheme 18, the

Scheme 18. Michael Addition with Heterogeneous Calcium-Pybox Catalyst



synthetically useful γ-nitro carbonyl compounds **46** could be generated from a wide substrate scope in high yields and high enantioselectivities, and the catalyst could afford a high TON of 228 without loss of activity after 8.5 days of continuous operation. In addition, a continuous enantioselective domino Michael−Knoevenagel reaction[87] of dimethyl 3-oxoglutarate and 3-substituted acrolein derivatives was successfully developed by Pericàs and co-workers recently using immobilized diarylprolinol silyl ether catalyst **48** (Scheme 19). This

Scheme 19. Synthesis of Enantiomerically Enriched Cyclohexane Derivatives with Polymer-Supported Diarylprolinol Silyl Ether Catalysts



polystyrene-supported organocatalyst exhibited a remarkable robustness, which allows its use for three consecutive days without any appreciable deterioration of its performance to give target adducts **49** in up to 97% ee (62% yield). This domino catalysis, followed by a simple reduction, could provide a straightforward and efficient methodology for the preparation of highly functionalized cyclohexane derivatives **50**.

3.1.7. Kinetic Resolution of Epoxide and Diol. In 2007, Kirschning and co-workers developed a novel continuous-flow reactor device (PASSflow) for a dynamic kinetic resolution of terminal epoxides using immobilized chiral cobalt−salen

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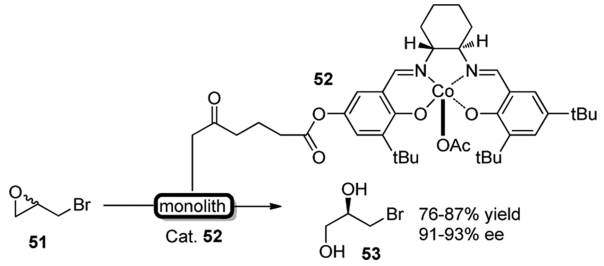
complexes.[88] Among different types of covalently immobilized Jacobsen's cobalt–salen complexes (for example, polymer grafting, composite raschig ring, and monolith PASSflow reactor), the monolithic megaporous glass/polymer **52** in Scheme 20 showed the best activity and enantioselectivity and

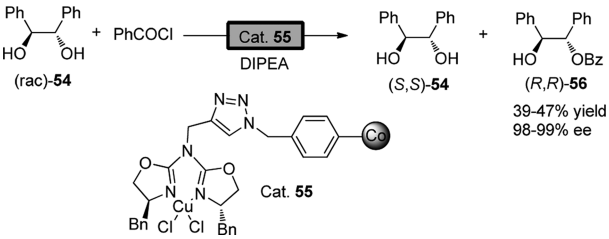
Scheme 20. Dynamic Kinetic Resolution of Epibromohydrin Using a PASSflow Microreactor



could be used repeatedly after a simple reactivation protocol. The enantioselective ring-opening of epibromohydrins **51** with water or phenols was successfully applied in continuous-flow mode to give target products **53** in up to 93% ee.

Magnetic nanoparticles exhibiting a core/shell structure have recently attracted a lot of attention as scaffolds for the grafting of homogeneous compounds, since they can be readily dispersed in solvents and recycled by applying an external magnetic field as "heterogenized" catalysts.[90] Although superparamagnetic iron oxide nanoparticles (SPION; e.g., magnetite particles) could serve as a versatile support with a suitable coating for the metaloxide core, its low saturation magnetization compared with the bulk material could not afford the effective recycling of the supported catalyst.[90] Because of the advantage of extraordinary high magnetization, carbon-coated cobalt nanoparticles were recently utilized as magnetically recyclable supports for azabis(oxazoline)–copper(II) complexes through a copper(I)-catalyzed azide/alkyne cycloaddition reaction,[89] and the efficiency of the resulting nanomagnetic catalyst **55** was tested in the continuous-flow kinetic resolution of racemic 1,2-diphenylethane-1,2-diol **54** via asymmetric monobenzoylation (Scheme 21). This first

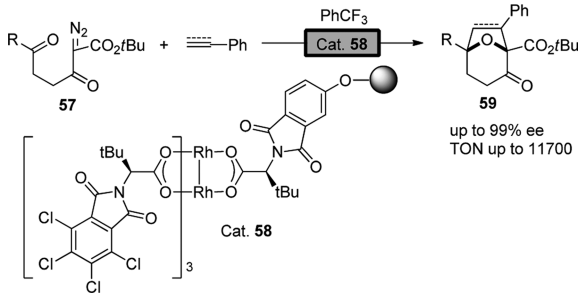
Scheme 21. Kinetic Resolution of Racemic 1,2-Diol Catalyzed by Magnetic Co/C Nanoparticles-Immobilized Copper(II) Complex



transition-metal complex immobilized on carbon-coated cobalt nanoparticles proved to be a promising and versatile alternative to well-established SPION particles, giving the target product **56** in 98–99% ees at 39–47% yields.

3.1.8. Cycloaddition. The first example of a continuous flow system with immobilized dirhodium(II) complexes was reported recently by Hashimoto and co-workers, demonstrating a successful tandem carbonyl ylide formation–cycloaddition intermolecular reaction.[91] The immobilization of [Rh_2(S-PTTL)(S-TCPTTL)$_3$] (PTTL = *N*-phthaloyl-*tert*-leucinate, TCPTTL = *N*-tetrachlorophthaloyl-*tert*-leucinate) has been accomplished by copolymerization of the Rh(II)-complex-containing monomer with 2-(trifluoromethyl)styrene and a flexible cross-linker. Under continuous flow conditions, high yields as well as high levels of enantioselectivity (up to 99% ee) and turnover number could be achieved (Scheme 22). The

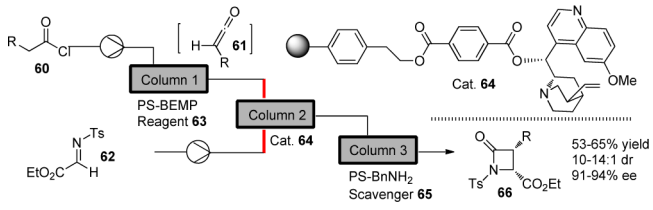
Scheme 22. Enantioselective Carbonyl Ylide Cycloaddition with a Polymer-Supported Dirhodium(II) Catalyst



robust nature of this monolith Rh catalyst **58** was demonstrated by the retention of full activity and enantioselectivity for a number of hours (up to 60 h) with a low leaching level (2.1 ppm). Moreover, this flow system exhibited exceptionally high turnover numbers (up to 11 700) relative to the homogeneous catalyst system.

3.1.9. β-Lactam Synthesis and α-Chlorination. As mentioned before, a "flush and flow" column concept has been developed by the Lectka group for asymmetric catalysis, with solid phase reagents, catalysts, and scavengers packed in a series of "reaction columns".[22] One example is a Wang-resin-supported quinine derivative, which was applied in the reaction of imino esters with ketenes, leading to the stereoselective synthesis of β-lactams.[92,93] As shown in Scheme 23, unstable

Scheme 23. Continuous-Flow Enantioselective Synthesis of β-Lactam with Immobilized Quinine Derivative



intermediate ketene **61** was generated from the corresponding acid chloride with polymer-supported BEMP reagent **63** (column 1) and then reacted with an imino ester in a reaction catalyzed by the resin-supported quinine catalyst **64** (column 2) with a long and rigid linker. Finally, nucleophilic scavenger **65** (column 3) was used to remove excess reagents and byproducts. This three-step sequence was carried out in a single process using an assembly of jacketed glass columns with gravity-driven flow-through over the course of 2 h, providing target β-lactams **66** in both high diastereoselectivity (up to 14:1) and enantioselectivity (up to 94% ee). Moreover, the catalyst column was reused 60 times without any observed decrease in activity or enantioselectivity.

As an extension of this concept, the same group also reported a continuous-flow asymmetric α-chlorination of acid halides by using the same organocatalyst **64** (Scheme 24).[94] Highly

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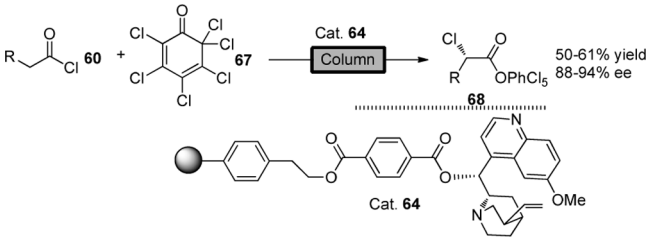
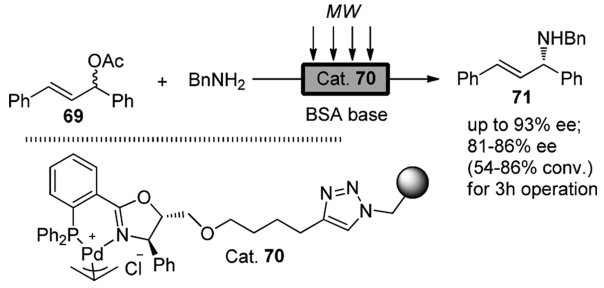
Scheme 24. Asymmetric α-Chlorination of Acid Chlorides with Immobilized Quinine Derivative



optically active α-chloroesters **68** in high enantiomeric excess (up to 94% ee) and good yields could be generated, and this methodology was further extended to a diastereoselective synthesis of the metalloproteinase inhibitor BMS-275291.[95] This cinchona alkaloid derivative served the dual purpose of dehydrohalogenation and asymmetric induction and was found to be reusable at least up to 100 times after regeneration each time by flushing with a solution of *i*-PrNEt$_2$ in THF.

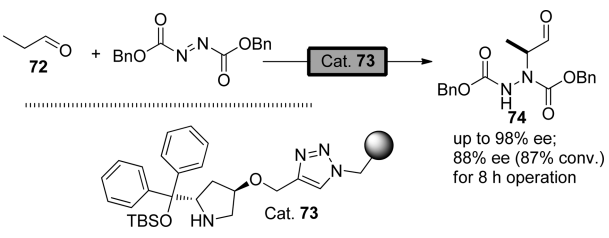
3.1.10. Allylic Amination and α-Amination. Pericàs and co-workers have reported a continuous-flow, highly enantioselective allylic amination with an immobilized Pd−phox complex (Scheme 25).[96] The optimal azidomethyl polystyrene-

Scheme 25. Enantioselective Allylic Amination with Immobilized Pd-Phox Complex



supported catalyst **70**, generated via click chemistry, could afford very high catalytic activity and enantioselectivity (93% ee) for broad scope applicability, especially under microwave-promoted continuous flow conditions. In addition, microwave irradiation other than conventional heating was found to account for the acceleration of this heterogeneously catalyzed reaction. Following this allylic amination, the same group also developed an efficient polystyrene (PS)-supported diphenylprolinol silyl ether organocatalyst **73** for continuous enantioselective α-amination of α,β-unsubstituted aldehydes (Scheme 26).[97] High conversions and enantioselectivities (up to 98%) could be achieved in very short reaction times at low (1−2 mol %) catalyst loading. Moreover, a simple solution to the catalyst

Scheme 26. Continuous Asymmetric α-Amination of Aldehydes Catalyzed by PS-Diphenylprolinol Silyl Ethers

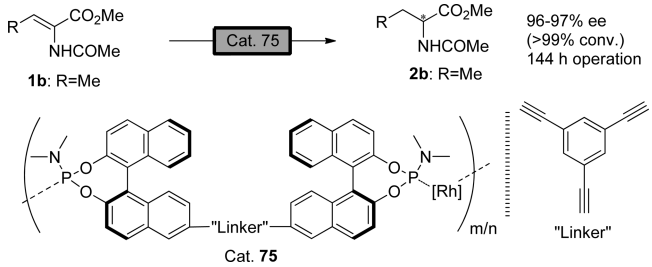


deactivation problem has allowed repeated recycling and reuse (10 cycles; accumulated TON of 480) and long-standing continuous flow operation (8 h) with short residence time (6 min).

3.2. Self-Supported Method. Construction of self-assembled metal−organic frameworks using well-designed multitopic ligands and reactive metal centers comprises a simple and efficient means of chiral catalyst immobilization, which has been pioneered and extensively investigated by the Ding group.[98−102] The resulting self-supported catalysts are stable and well behaved under catalytic conditions, demonstrating outstanding reactivity and selectivity, comparable to or even better than their analogous homogeneous counterparts.

In 2009, Ding and co-workers developed a type of recyclable, self-supported Rh-MonoPhos catalyst by simple mixing of multitopic MonoPhos-based ligands with [Rh(cod)$_2$]BF$_4$ (cod = cycloocta-1,5-diene), which was used for continuous flow asymmetric hydrogenation as the stationary-phase material (Scheme 27).[103] Without the use of extra added support, the

Scheme 27. Continuous-Flow System for Asymmetric Hydrogenation Using Self-Supported Chiral Rh-MonoPhos Catalysts



resulting self-supported catalysts showed outstanding catalytic performance for the asymmetric hydrogenation of a broad substrate scope, giving up to 98% ee. The linker moiety in those supported Rh-MonoPhos catalysts influenced the reactivity significantly, albeit with slight impact on the enantioselectivity. A continuous flow reaction system using an activated C/**75** mixture as stationary-phase catalyst for the asymmetric hydrogenation of **1b** was developed and run continuously for a total of 144 h with >99% conversion and 96−97% enantioselectivity. It is worth mentioning that the total Rh leaching in the product solution is 1.7% of that in the original catalyst **75**.

Following the same strategy, a robust heterogeneous self-supported chiral titanium cluster (SCTC) catalyst and its application in the continuous enantioselective imine-cyanation/Strecker reaction was recently reported by Seayad and Ramalingam.[104] Before this research, only few efficient and reusable heterogeneous catalysts could be applied in this asymmetric catalysis at room temperature. By controlling the hydrolysis of a preformed chiral titanium alkoxide complex, the isolated SCTC catalysts **76** were remarkably stable and showed up to 98% enantioselectivity (ee) with complete conversion of a wide variety of imines within 2 h at room temperature (Scheme 28). Moreover, the heterogeneous catalysts were recyclable more than 10 times without any loss in activity or selectivity, which allows them to be integrated in a packed-bed reactor for continuous flow cyanation. In the case of benzhydryl imine, up to 97% ee and quantitative conversion with a throughput of 45 mg/h were achieved under optimized flow conditions at room

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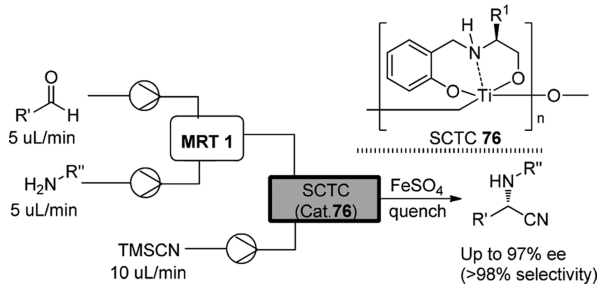
Scheme 28. Asymmetric Cyanation of Imines with Self-Supported Chiral Titanium Cluster (SCTC)



temperature. Finally, a continuous flow three-component Strecker reaction was performed by using the corresponding aldehydes and amines instead of the preformed imines, providing the corresponding amino nitriles with up to 98% ee.

3.3. Adsorption Method and H Bonding. Adsorption[105] represents a very facile immobilization method because a simple impregnation procedure can be sufficient to furnish the heterogenized catalyst. Because only weak van de Waals interactions are present, immobilization of catalyst via an adsorption method tends to be nonstable and often diminished by competing interactions with solvents, substrates, or both, resulting in extensive catalyst leaching. However, the combination of adsorption and desorption steps was reported to be a fast and convenient method for catalyst screening and homogeneous catalyst recycling, as well. The asymmetric catalytic system is generally composed of a traditional metal catalyst and a chiral inductor that adsorbs on the metal surface, leading to chiral catalytic sites. The desorption of chiral inductors and cleaning of metal catalysts after adsorption and reaction steps will close the cycle, which could be repeated for the screening of several inductors under different operating conditions. An earlier example was reported by de Bellefon and co-workers in 2007, with a focus on microstructured reactors as a tool for chiral modifier/inductor screening in gas−liquid−solid asymmetric hydrogenations.[42] In the case of ethylpyruvate substrate, a continuous microstructured reactor equipped with a perforated (5 mm) membrane was used for a series of Pt/γ-Al_2O_3 catalysts modified with chiral inductors under high hydrogen pressure (45 bar). Among the eight chiral inductors investigated, cinchonidine gave the best enantioselectivity (63% ee), and the very low reaction volume (100 μL) also offered a short operating time.

To further extend the application of the adsorption/desorption combination, Reek and co-workers recently reported a reverse-flow adsorption (RFA) for process-integrated recycling of homogeneous transition-metal catalysts used both in hydrogenation and hydrosilylation (Figure 2).[44] The substrate is pumped into the reactor through path A and desorbs the catalyst from bed I until bed II is saturated. Then the flow is reversed, and substrate is pumped in through route B. The RFA technology for process-integrated recycling of homogeneous catalysts using these tailor-made phosphine ligands (guest) and silica-supported (host) materials resulted in a stable, semicontinuous catalytic system. Supermolecular interactions were considered as "linkers", either between the urea groups on host and guest (H-bonding) or an amino group on host and a carboxyl group on the guest (ionic interaction). Homogeneous rhodium catalysts **79** applied in asymmetric hydrogenation of methyl acetamidoacrylate **77** and asymmetric

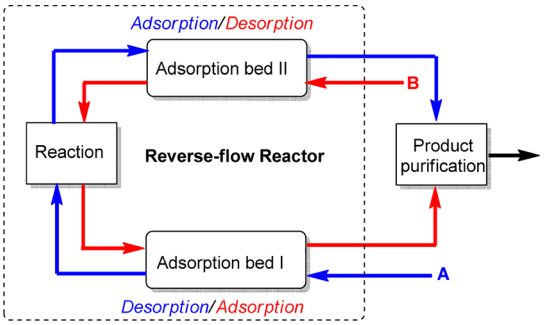
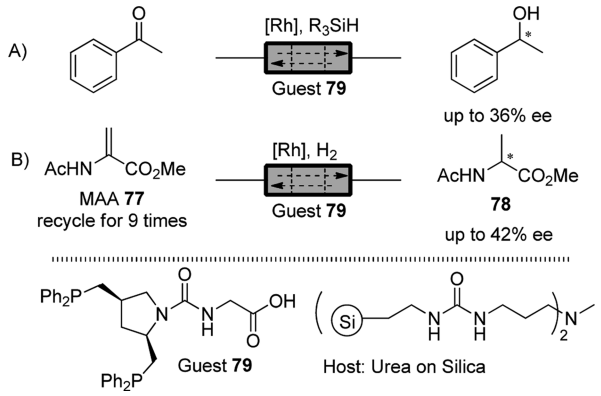


Figure 2. Reverse-flow adsorption for homogeneous catalyst recycling.

hydrosilylation of acetophenone (Scheme 29) could be recycled several times without significant loss in conversion

Scheme 29. Reverse-Flow Adsorption for Homogeneous Catalysts Recycling in Hydrogenation and Hydrosilylation



under optimized RFA flow conditions. It is worth noting that the desorbed catalyst was still active and not decomposed, and this advantage enabled the RFA technique to be a promising concept for recovery and recycling of homogeneous transition-metal catalysts.

3.4. Eelectrostatic/Ionic Interaction. In addition to the adsorption method and H-bonding, electrostatic or ionic interaction[106] serves as another common and conceptually simple noncovalent support method by catalyst adhesion, which is applicable to heterogenization of ionic catalytic species. The catalyst of concern can be adhered by ion-pairing onto either an anionic or a cationic solid support, which includes organic or inorganic ion-exchange resins, and inorganic clays and zeolites. Although the catalyst instability and leaching would be problematic because of competition with ionic species in solution, this immobilization strategy has already demonstrated a couple of successful examples for continuous-flow heterogeneous asymmetric catalysis.

In 2011, Bakos and co-workers reported a continuous-flow system for heterogeneous asymmetric hydrogenation using supported chiral Rh-MonoPhos catalyst for the hydrogenation of methyl 2-acetamidoacrylate 77 by using an H-Cube hydrogenation reactor.[107,108]"In situ"-generated [Rh(COD)-((*S*)-MonoPhos)$_2$]BF_4 complex was immobilized on commercially available Al_2O_3 and mesoporous Al_2O_3 by means of phosphotungstic acid (PTA).[106] The optimum reaction conditions were determined and studied at different temperature, pressure, and flow rate values. Furthermore, the effect of the substrate concentration, microstructure of the support, and

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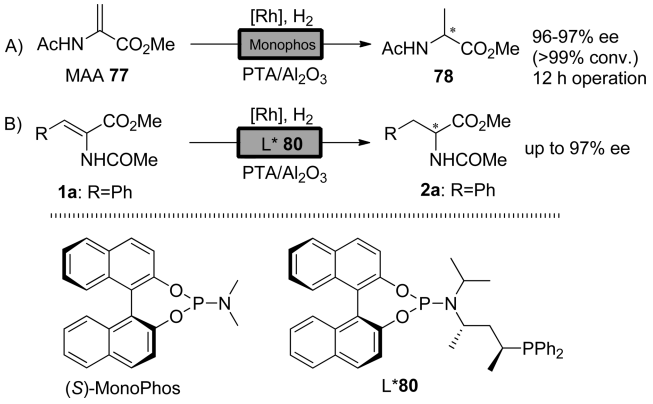
the stability of the complex were investigated in the flow system, resulting in a continuous operation for 12 h toward product **78** in >99% conversion and 96−97% ee (Scheme 30A).

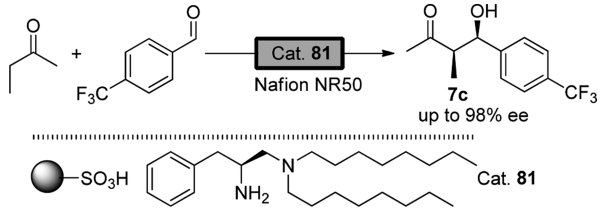
Scheme 30. Heterogeneous Asymmetric Hydrogenations with Immobilized Rodium Catalyst by Ionic Interaction



Later on, the same group also developed a heterogeneous rhodium catalyst modified by a new phosphine−phosphoramidite, **80**, on Al_2O_3/PTA, which was successfully used in the continuous hydrogenation of (*Z*)-α-acetamidocinnamic acid methyl ester, **1a**, over 12 h to give an average of 97% ee of **2a** (Scheme 30B).[109] The screening of this heterogenized catalyst [Rh(COD)(**80**)]/PTA/Al_2O_3 was also performed in an H-Cube reactor by filling the catalyst in CatCart cartridges.

Another example of ionic interaction as noncovalent immobilization method for continuous flow asymmetric catalysis was reported by Sels and co-workers.[110] As shown in Scheme 31, chiral primary amino acid-derived diamines **81**

Scheme 31. Solid Acids As Heterogeneous Support for Diamines in Asymmetric Aldol Reactions

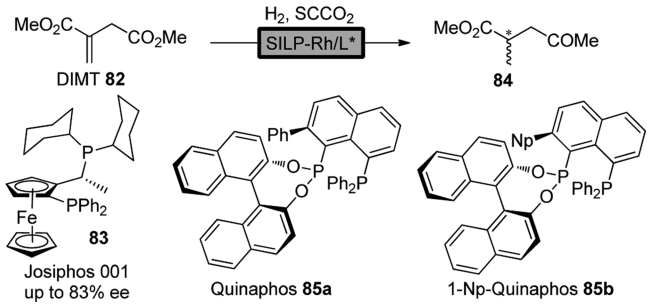


were immobilized on organic and inorganic sulfonated solid acids (commercial sulfonated fluoropolymer nafion NR50) through acid−base interaction and then applied in the direct asymmetric aldol reactions of linear ketones and aromatic aldehydes. In this approach, the solid acid has a dual function: acting as anchor for immobilization and governing the activity and selectivity of the chiral catalyst. Under optimized conditions, aldol products were obtained in high yields and with excellent enantioselectivity, for instance, the *syn* product **7c** with up to 98% ee. Furthermore, catalysis with the supported diamine was demonstrated to occur truly heterogeneously, and the loaded Nafion NR50 beads could serve as a stationary phase for the flow reactor system.

3.5. Nonconventional Media. Changing the reaction media from conventional volatile organic solvents to a form of nonconventional media, with or without chemical manipulation on the catalyst, represents another type of general strategy used to recover and reuse a (chiral) catalyst system.[111] Most frequently, ionic liquids,[28] supercritical fluids (usually supercritical carbon dioxide, $SCCO_2$),[28,29] perfluorinated liquids,[112] and even water were utilized as the "green" supplants for those environmentally hazardous organic solvents. Another advantage of the catalysis in such a medium was considered as the easy catalyst separation and recovery under either monophasic or biphasic conditions, with a variable degree of solvent effects on catalytic reactivity and selectivity. Moreover, a concept of supported ionic liquid phase (SILP) catalysis has attracted increasing interest recently[28,29] because it describes a molecular catalyst that is dissolved in a small amount of an immobilized ionic liquid (IL) on the surface of a solid support, typically a porous oxidic material, such as silica or alumina. The infinitesimal solubility of ILs in $SCCO_2$ allowed for retention of the SILP while organic products were continuously extracted. So far, the combination of SILP catalysis with $SCCO_2$ flow has been successfully applied in organic synthesis[113−123] and lipase-catalyzed transformations (also see section 4.2.2), affording high activity together with excellent stability. In the following context, some examples of the applications of nonconventional media in continuous asymmetric catalysis will be discussed, including hydrogenation,[113−117] cyclopropanation,[118−120] and hydroformylation.[123]

3.5.1. Hydrogenation. On the basis of the previous result,[113] the Poliakoff group continued their research on the application of $SCCO_2$ in continuous flow asymmetric hydrogenation by using a composite catalyst immobilization system modified with several different types of asymmetric bisphosphine ligands. Among those ligands tested, Josiphos 001 (**83**) from Solvias AG (Scheme 32) proved to be the best to obtain target product

Scheme 32. Continuous Asymmetric Hydrogenation in $SCCO_2$ Using an Immobilized Homogeneous Catalyst



84 with >80% ee in the asymmetric hydrogenation[115,116] of dimethyl itaconate (DMIT, **82**), which is higher than that reported for the same reaction via batchwise process with a homogeneous catalyst in $SCCO_2$. However, the majority of other ligands were unsuccessful, demonstrating the fact that immobilizing an asymmetric catalyst and retaining high enantioselectivity is by no means a trivial task, especially when the catalyst is to be used in a solvent as unusual as $SCCO_2$.

Recently, Leitner and co-workers[115] have developed the first example of a continuous enantioselective hydrogenation for which a SILP catalyst based on a chiral transition-metal complex and $SCCO_2$ as the mobile phase are used. In the case of dimethyl itaconate substrate **82**, this prototypical reaction could generate the target product with >99% ee with high turnover frequencies (TOFs) up to 10 500 h^{-1} when the Rh complex of commercial (*Sa*,*Rc*)-1-naphthyl-QUINAPHOS **85b** was used as the catalyst in the biphasic system [EMIM][NTf_2]/

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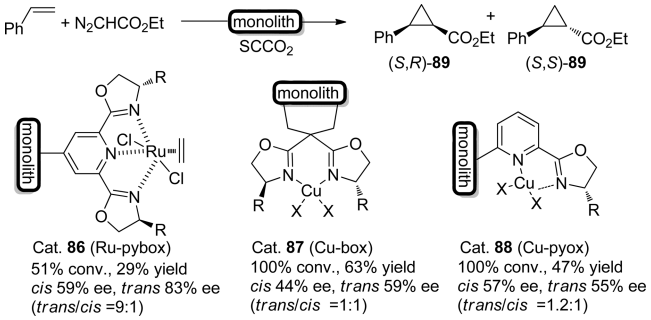
$SCCO_2$ at 40 °C and 120 bar total pressure (20 bar H_2 included).

Very recently, the same group continued their research in this field, and a versatile lab to pilot scale continuous reaction system for supercritical fluid processing was developed.[117] The completely automated setup facilitated a computerized control and optimization of all parameters and also afforded direct insight into catalyst performance by integrating an inline view cell and supercritical fluid chromatography (SFC), as well, which permits high process control at both minimum flow rates for research and development in early-on testing and kilogram quantity production. For example, the amounts of precious catalyst could be minimized to <1 g of SILP material supporting 1.4 μmol of Rh-QUINAPHOS **85** in 0.20 mL of ionic liquid, affording turnover numbers of 70×10^3 (108 kg product per gram Rh) at enantioselectivity of more than 98%. It is noteworthy that this process could be up-scaled by 1 order of magnitude to produce 1.3 kg of product per week without further optimization.

3.5.2. Cyclopropanation. Luis group has investigated the asymmetric cyclopropanation (CP) reaction of styrene in flow with a series of chiral monolithic catalysts Ru-pybox **86**,[118] Cu-box **87**,[119] and Cu-pyox **88**,[120] as well, shown in Scheme 33.

Scheme 33. Asymmetric Cyclopropanation Reaction with Monolithic Miniflow Reactors in $SCCO_2$



Cat. **86** (Ru-pybox)
51% conv., 29% yield
cis 59% ee, *trans* 83% ee
(*trans*/*cis* =9:1)

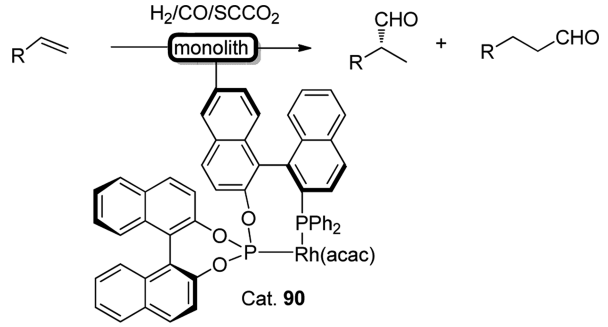
Cat. **87** (Cu-box)
100% conv., 63% yield
cis 44% ee, *trans* 59% ee
(*trans*/*cis* =1:1)

Cat. **88** (Cu-pyox)
100% conv., 47% yield
cis 57% ee, *trans* 55% ee
(*trans*/*cis* =1.2:1)

One of the main outcomes obtained was the results obtained was the observation of a significant improvement in the productivity when going from conventional to supercritical conditions within the same reactor. Thus, for instance, macroporous ruthenium catalysts **86** showed a more environmentally friendly reaction between styrene and ethyl diazoacetate (EDA) to prepare CP products, affording a 7.7-fold increase in productivity (TON($SCCO_2$) 46 mol CP/mol pybox vs TON (dichloromethane) 6 mol CP/mol pybox) for 8 h of operation. Another advantage of the work under flow and supercritical conditions is the easy and fast optimization of the system via precise control of reaction parameters, such as pressure, temperature, and flow rate. More interestingly, in all cases, the conversion, chemoselectivity, and enantioselectivity were comparable or slightly superior to those under batch conditions with the same catalysts.

3.5.3. Hydroformylation. The asymmetric hydroformylation reaction is another successful example in which the application of $SCCO_2$ could improve the catalytic process through easy separation of catalyst and extension of olefin substrate scope (less volatile olefins) under a flow system. Nozaki and co-workers recently reported a covalently PS-anchored (*R*,*S*)-BINAPHOS-Rh(I) catalyst, **90**, for asymmetric hydroformylation of olefins in the presence of $SCCO_2$ (Scheme 34).[123] In

Scheme 34. Asymmetric Olefin Hydroformylation with Supported (*R*,*S*)-BINAPHOS-Rh(I) Complex in $SCCO_2$



Cat. **90**

addition to the inherent merits by using continuous flow $SCCO_2$, other advantages of this cross-linked heterogeneous catalysts over its homogeneous counterparts included collision of substrates with the active center of the catalyst, higher loading of the catalyst, avoidance of undesirable dimeric species formation, and a positive steric effect on the selectivities. By using this $SCCO_2$-flow column reactor, less volatile olefins, such as styrene, vinyl acetate, 1-alkenes, and fluorinated alkenes, were successfully converted into the corresponding isoaldehydes with high ee values.

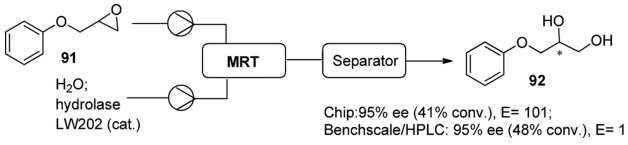
4. ASYMMETRIC BIOCATALYSIS IN FLOW

As a clean and efficient method for chemical transformations, enzyme-driven asymmetric catalysis has been applied to a number of industrial processes, including some in continuous flow.[124,125] In addition to the application as miniaturized total analysis systems (μ-TAS),[126] microflow devices have demonstrated many advantages for enzyme-catalyzed kinetic resolution and other transformations in flow,[17,20,28,29] including biocatalytic reactions in $SCCO_2$ and multistep chemo-(enzymatic) reactions.

4.1. Enzyme-Catalyzed Kinetic Resolution. Numerous applications involving the enzymatic resolution of racemic substrates have been developed recently in a flow mode either by hodrolysis, acylation, or (trans)esterification.

4.1.1. Resolution by Hydrolysis. In 2006, Belder and Reetz reported the first example of a novel integrated chip device with a combination of a microfluidic reactor and analysis unit, which was successfully utilized in the epoxide hydrolase catalyzed hydrolytic kinetic resolution of glycidyl phenyl ether **90**.[52] Integration of chemical reaction and analysis on a chip resulted in reduced reagent consumption and, thus, allowed a highly accelerated screening with results comparable to those using a conventional bench-scale/HPLC method for the different enzymes investigated. For example, 95% ee of product **92** could be detected on-chip at a conversion of 41% (E = 101) and 95% ee at 48% conversion (E = 115) for the bench-scale/HPLC method (Scheme 35).

Scheme 35. Enantioselective Epoxide Hydrolysis and Following Analysis on a Chip



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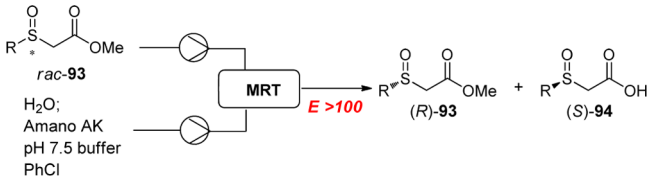
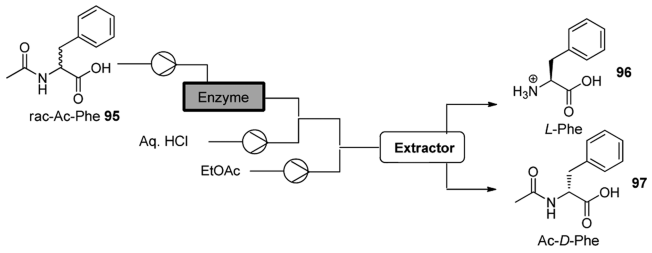
Burgess and co-workers recently developed a continuous flow biocatalytic resolution of methyl sulfinyl acetates, **93**, by integrating a subsequent extraction unit of the sulfinyl carboxylate products, **94**.[127] Product inhibition was encountered for some substrates in the resolution of methyl sulfinylacetates mediated by lipase Amano AK, which would cause an inefficient kinetic resolution in terms of both conversion and enantiomeric excess. By continuously removing the target carboxylatic product from the enzyme and substrate via aqueous−organic solvent extraction, product inhibition could be avoided and, thus, afforded an effective resolution of sulfinyl acetates with an *E* value as high as >100 (Scheme 36).

Scheme 36. Biocatalytic Resolutions of Methyl Sulfinylacetates



4.1.2. Resolution by Acylation. Maeda and co-workers reported an integrated microreaction system for optical resolution of racemic amino acid **95**, including a cross-linked polymeric acylase aggregate-immobilized microreactor and the subsequent microextractor (Scheme 37).[128] Use of the enzyme

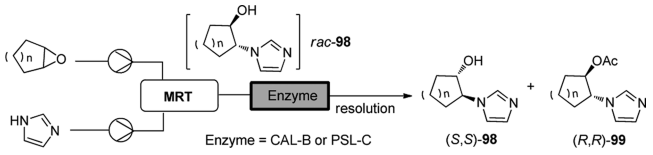
Scheme 37. Integrated Microreaction System for Kinetic Resolution of Racemic Amino Acids



microreactor, which was prepared by membrane formation on the microchannel surface, enabled a highly enantioselective reaction for a racemic amino acid derivative. In addition, the microextractor provided a laminar flow of two immiscible solutions, which enabled selective extraction of the product. For example, almost 100% of L-Phe **96** (99% ee) remained in the aqueous phase, whereas up to 84−92% of the acetyl D-amino acid **97** was extracted into the organic phase. By using this integrated system, an efficient continuous production of optically pure unnatural amino acids could be realized.

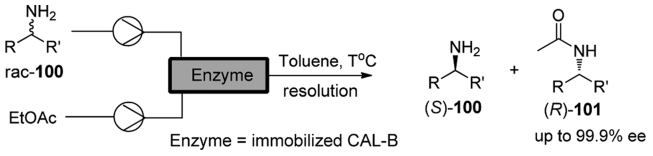
Another example of enzymatic resolution by acylation in continuous flow mode was recently reported by Luis and co-workers to give enantiopure 1-(2-hydroxycycloalkyl)-imidazoles.[129] For the first step of the ring-opening reaction, the continuous flow system gave obviously improved productivity compared with microwave batch processes, although similar conversions were obtained in both cases. In addition, for the second step of the lipase-catalyzed kinetic resolution of the racemic 2-(1*H*- imidazol-yl)cycloalkanols **98**, the continuous flow reactor demonstrated much higher efficiency than the corresponding batch processes, with either immobilized CAL-B or PSL-C catalysts (Scheme 38). The continuous flow biotransformations facilitated the scale-up of the production of these chiral imidazoles toward the synthesis of chiral ionic liquids.

Scheme 38. Multistep Synthesis of Chiral Enantiopure 1-(2-Hydroxycycloalkyl)imidazoles via Enzymetic Resolution



Very recently, Poppe and co-workers studied the effect of the temperature on enantiomeric ratio (*E*) and the specific reaction rate in the continuous flow kinetic resolution of racemic amines **100** via acetylation by variously immobilized *Candida antarctica* lipase B (CAL-B) biocatalysts in the 0−70 °C range (Scheme 39).[130] In most cases, almost enantiopure products **101** could

Scheme 39. CAL-B Immobilization Affects the Continuous-Flow Kinetic Resolution of Racemic Amines at Various Temperatures



be produced by using ethyl acetate as the acylation reagent. Alteration of *E* in the kinetic resolutions of three differently flexible amines as a function of the temperature was rationalized by the various flexibilities of the lipase in its different forms. The results indicated that the character of the temperature effect depended significantly both on the nature of the substrate and on the mode of immobilization.

In addition, few examples about continuous flow dynamic kinetic resolutions (DKR) have been reported so far, mainly because of problematic coupling between racemization and the resolution step. For instance, Livingston and Taylor developed the DKR of 1-phenylethylamine using membrane reactors[131] with a combination of commercial CAL-B (Novozyme 435) and Shvo complex, leading to 91% conversion and 99% ee after 72 h.

4.1.3. Resolution by (Trans)esterification. Kinetic resolution of varied racemic acids via (trans)esterification in flow, such as ibuprofen derivatives, has been another interesting topic. Yuryev and co-workers recently reported their work on the kinetic resolution of 2-chloro-3,3,3-trifluoropropionic acid (CTFPA) substrates in flow mode.[132] By screening 30 commercially available lipases and esterases for the hydrolysis or transesterification of the desired substrate, the transesterification of racemic CTFPA methyl ester **102** in flow proved to give the best result in a 10-mL packed-bed reactor containing the cross-linked enzyme aggregate of *Candida rugosa* lipase (CRL). As shown in Scheme 40, the mixture of (*S*)-**102** and (*R*)-**103** with 82% and 90% ee, respectively, could be produced at 4.0 g/L/h space-time yield; however, the productivity decreased to 1.0 g/L/h after 4 repetitive batches, although the enantioselectivity remained intact.

4.2. Enzyme-Catalyzed Transformation. In addition to the enzyme-catalyzed kinetic resolution mentioned above, there

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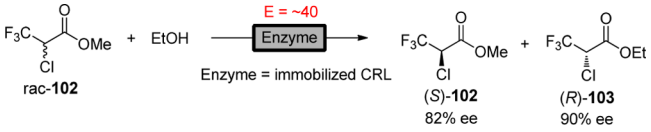
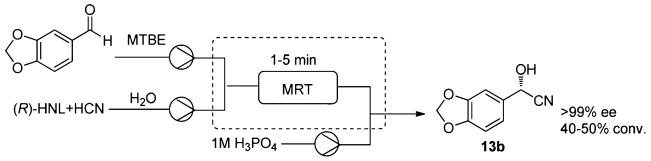
Scheme 40. Kinetic Resolution of Racemic Ibuprofen via (Trans)esterification in Flow



are many interesting applications of asymmetric biocatalysis in other transformations. Some examples for cyanation, reaction in $SCCO_2$, and multistep reaction via coupled biocatalysis, as well, will be discussed in the following section.

4.2.1. Enantioselective Cyanation. As mentioned above in sections 2.3, 3.1.3, and 3.2, asymmetric cyanation could be performed in flow either by homogeneous or heterogeneous transition metal complexes for useful C−C formation.[49,50,78,104] In the case of enzymatic catalyst, Rutjes and co-workers have reported one example using a borosilicate microreactor chip for the enantioselective formation of cyanohydrins **13** from aldehydes using hydroxynitrile lyase (HNL)-containing crude cell lysates.[133] As shown in Scheme 41, the flow device

Scheme 41. Enzymatic Enantioselective Cyanation Reaction

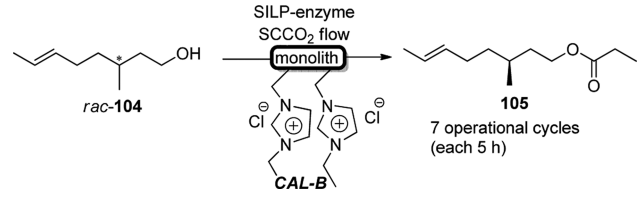


consisted of three inlets: one for the aqueous phase delivering the cell lysate, KCN, and citric acid (in situ HCN generation); one for the organic phase containing the aldehyde substrate; and a third one at the end of the reactor channel as a quenching inlet for deactivation of the enzyme. By using this chip reactor, up to 58 reactions were performed serially within 4 h, requiring a total of only 150 μL of cell lysate. Values of >95% ee were obtained with aromatic substrates and 85% ee for an aliphatic substrate, results fully consistent with those obtained from the larger batchwise process in which a stable emulsion was formed.

4.2.2. Biocatalytic Enantioselective Reaction in $SCCO_2$. As mentioned before in section 3.5, nonconventional media including $SCCO_2$, has been applied in continuous flow asymmetric catalysis toward more efficient separation and recycle of the catalysts. In the case of enzymatic catalysis,[20,28,29,134] some earlier examples have already been reported, including (dynamic) kinetic resolution of secondary alcohol[135,136] and biocatalytic reduction of ketone[137] with immobilized lipase in continuous $SCCO_2$ flow reactors.

In 2007, Luis and co-workers reported a polymeric monolith reactor with covalently supported ionic liquid phases (SILP) for continuous asymmetric transesterification in $SCCO_2$.[138] On the basis of styrene−divinylbenzene or 2-hydroxyethyl methacrylate−ethylene dimethacrylate, those bioreactors were prepared with imidazolium unit loadings ranging from 54.7 to 39.8 wt % IL per gram of polymer. The SILPs were able to absorb *C. antarctica* lipase B (CAL-B), leading to highly efficient and robust heterogeneous biocatalysts (Scheme 42). The catalytic activity of the monolith mini-flow bioreactors (M-SILP-CAL-Bs) remained practically unchanged for seven operational cycles of 5 h each under different supercritical conditions. The best results, with a total turnover number (TON) of 35.8×10^4 mol citronellyl propionate **105**/mol enzyme, were obtained when

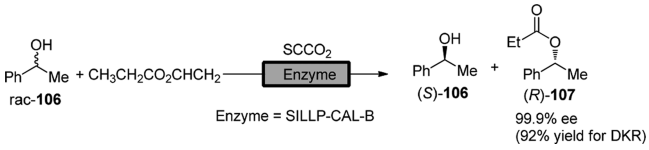
Scheme 42. Bioreactors Based on Monolith-Supported Ionic Liquid Phase for Enzyme Catalysis in $SCCO_2$



the most hydrophobic monolith was assayed at 80 °C and 10 MPa. It is worth mentioning that the results substantially exceeded those obtained for packed-bed reactors with supported silica-CAL-B catalyst under the same experimental conditions.

Lozano et al. recently investigated the immobilization of CAL-B onto supported ionic liquid-like phases (SILLPs) for the kinetic resolution of *rac*-1-phenylethanol **106** to develop an environmentally friendly process, namely, the maximum activity, selectivity, and stability of the resulting supported biocatalyst by flow processes using $SCCO_2$.[139] This case involved the use of hydrophilic SILLPs (chloride anion) with high loadings of IL moieties and CAL-B. Moreover, the combination of the immobilized biocatalyst with an acidic zeolite could afford the DKR process of this secondary alcohol. As shown in Scheme 43, the target product **107** with high

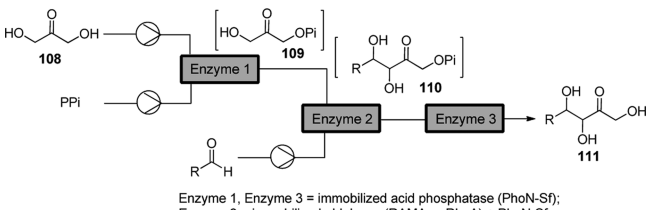
Scheme 43. Continuous (Dynamic) Kinetic Resolution of Racemic Secondary Alcohol in SILLP−$SCCO_2$ Systems



productivity (92% yield) and enantioselectivity (>99.9% ee) could be obtained by using a "one-pot" reactor containing a mixture of both catalyst particles under $SCCO_2$ flow conditions (50 °C, 10 MPa).

4.2.3. Multistep Synthesis via Coupled Biocatalysis. Along with the development of biotransformation or biocatalysis, coupled chemo(enzymatic) reactions in continuous-flow systems[17] represent a future trend and are considered as a powerful tool for multistep organic synthesis. For example, Wever and co-workers recently reported a new flow process with coupled immobilized enzymes to synthesize complex chiral carbohydrate analogues from achiral inexpensive building blocks (dihydroxyacetone, pyrophosphate, and different aldehydes) in a three-step cascade reaction.[140] As shown in Scheme 44, the first reactor contained immobilized acid

Scheme 44. Multistep Synthesis of Carbohydrates via Cascade Flow Reactors with Coupled Enzymes



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phosphatase, which phosphorylated dihydroxyacetone **108** to dihydroxyacetone phosphate **109** using pyrophosphate as the phosphate donor. The second flow reactor contained acid phosphatase and immobilized fructose-1,6-diphosphate aldolase or rhamnulose-1-phosphate aldolase, which was supposed to couple the formed intermediates **109** to aldehydes, resulting in phosphorylated carbohydrates **110**. Finally, the target product **111** would be generated via dephosphorylation after the third reactor containing acid phosphatase. By using different immobilized aldolases, varied stereoisomers of carbohydrate analogues could be conveniently achieved. Moreover, different aldehydes could be used to synthesize the corresponding carbohydrates on a gram scale, such as the D-fagomine precursor.

5. SUMMARY AND OUTLOOK

Recent progress of asymmetric catalysis in flow is summarized. A flow reactor, especially a microreactor, has been proved to be a powerful tool, mainly for homogeneous asymmetric catalysis, with respect to fast catalyst screening, lower catalyst loading, integrated inline/online analysis, and multistep transformation with unstable intermediates. Catalyst immobilization of a homogeneous catalyst would lead to a heterogeneous catalyst through covalent support, a self-supported method, an adsorption method and H-bonding, electrostatic or ionic interaction, and nonconventional media, as well. Significant improvement has been demonstrated toward easy automation, little or no reaction workup, and potential long-term use of the catalysts. In addition, biocatalysis with emphasis on enzyme catalysts was separately summarized in either homogeneous or heterogeneous mode. Recent progress in enantioselective multistep flow synthesis, in particular with in situ-generated unstable intermediates or multiple catalyst systems, is noteworthy not only from the viewpoint of discovery of new catalysis based on mechanistic design, but also as a result of their potential for practical synthesis of valuable chiral compounds via cascade asymmetric catalysis. In addition, innovation on the chiral catalyst immobilization strategy is highly desirable for further development of reusable catalyst systems. We also believe that R&D on novel flow equipment will facilitate the application of those asymmetric catalyses, which are not efficient on the basis of currently available facilities.

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Notes

The authors declare no competing financial interest.

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