ACES Asian Chemical Editorial Society

DOI: 10.1002/ajoc.202100165

ASIAN JOURNAL OF ORGANIC CHEMISTRY
Minireview

Special Collection

Recyclable Organocatalysts in Asymmetric Synthesis

Zeynep Dilşad Susam and Cihangir Tanyeli*[a]

This paper is dedicated to the memory of Professor Idris Mecidoglu Akhmedov, who was the pioneer scientist in asymmetric synthesis.



© 2021 Wiley-VCH GmbH

Abstract: Chiral organocatalysts are extensively in demand over the past 30 years for the synthesis of asymmetric compounds with remarkable stereoselectivities in high yields. In addition to these great facilities, they are eco-friendly, non-toxic, highly stable, and inexpensive structures so that a tremendous amount of studies has been developing. Besides, recyclable organocatalyst studies are of great interest to develop their environmental-friendly feature lately. Increasing the usage of these catalysts by saving the asymmetric results could become the most desirable characteristic in near future. This survey summarizes the following studies that have been done so far to enlight this subject and our headlights cover-up silica supported organocatalysts, polymer supported organocatalysts, magnetic nanoparticle supported organocatalysts, gold nanoparticle supported organocatalysts, ionic liquids organocatalysts and fluorous supported organocatalysts.

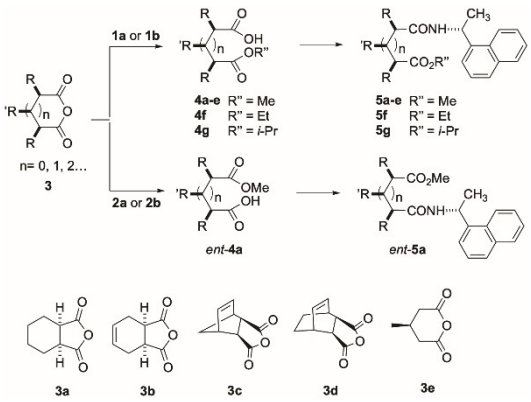
1. Introduction

Among the asymmetric synthesis methods, organocatalysis have been used as a powerful tool for the last couple of decades, preferably due to its cheap, non-toxic, robust, metal-free, environmental-friendly, inert, easily available nature. Besides that, they are also simple in terms of handling and storage. A great interest has been arised to enhance these precious chiral structures to achieve remarkable results in asymmetric synthesis.[1–5] Countless studies have been done in many different types of reactions such as Michael,[5–9] aldol,[10–16] Diels-Alder,[17–21] Henry,[22–27] aza-Henry,[28–33] Friedel-Crafts,[34–38] Povarov,[39–42] decarboxylative Doebner-Knoevenagel[43,44] reactions and many others. Although asymmetric organocatalysis can be considered as the most successful and easy way to synthesize enantioenriched compounds,[45] one of the most debated drawbacks is the possibility of agglomeration and aggregation due to high catalyst loading in the reactions. In some cases, up to 20–30 mol% catalyst loading[46,47] is required, so that it draws an attention to the recyclization of the catalyst for many researchers in addition to developing new catalysts for stereoselective synthesis. For this purpose, immobilized and reusable catalyst studies have been pursued to recycle these significant structures. By using a solid support, alongside the promoted activity and selectivity, the recovery and recycling was achieved in many applications with either cheap and easily accessible organocatalysts like L-proline or relatively expensive and synthetic complex organocatalysts. In principle, an insoluble support causes a heterogeneous catalyst, which is easy to recover from the reaction medium by simple filtration; however slower reaction rate can occur. On the contrary, a soluble support like polymer supports needs an additional step to be recovered (precipitation by an addition of a solvent) may fasten the reaction rate. In addition to the aforementioned advancements, the reusable immobilized organocatalysts can be adopted to flow chemistry.[48,49] Although there are some reviews on supported organocatalysts, we would like to combine and survey the studies on different types of anchored materials such as, silica, magnetic, gold, ionic resin, fluorous and polymer supports for immobilized organocatalysts in asymmetric transformations in this review.

2. Silica Supported Organocatalysts

In the early stages of organocatalysis, the studies of heterogeneous catalysis have been initiated as well. In 2004, Han et al. designed silica supported organocatalysts and evaluated them in the asymmetric desymmetrization of *meso*-cyclic anhydrides with methanol.[50,51] 1,4-Bis(quinidinyl)anthraquinone based doubly anchored organocatalysts (**1a**, **2a**) and the more flexible versions, which were tethered to the support from one end (**1b**, **2b**), were synthesized (Figure 1 and Scheme 1).

The optimization of the solvent was performed with catalyst **1a** and the best enantioselectivity (88% ee) was achieved with 5 mol% **1a**, 0.05:1 mixture of methanol and toluene/CCl_4 (1:1) at −30 °C with 78% conversion in 72 h. These results were consistent with the literature examples.[52–54] Other trials show that the more rigid system of quinuclidine analogues (**1a**, **2a**) gave higher enantioselectivities with respect to more flexible ones (**1b**, **2b**). The highest enantioselectivity (92% ee) was obtained with **1a** (20 mol%) in 72 h with 73% conversion in one-pot synthesis at −10 °C with *meso*cyclic anhydride **3b**.



Scheme 1. Desymmetrization of *meso*-cyclic anhydrides.

[a] *Z. D. Susam, Prof. Dr. C. Tanyeli*
Department of Chemistry
Middle East Technical University
Dumlupınar Bulvarı, No. 1, 06800, Çankaya, Ankara (Turkey)
E-mail: tanyeli@metu.edu.tr

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ajoc.202100165

This manuscript is part of a special collection on Organocatalysis Click here to see the Table of Contents of the special collection.

© 2021 Wiley-VCH GmbH

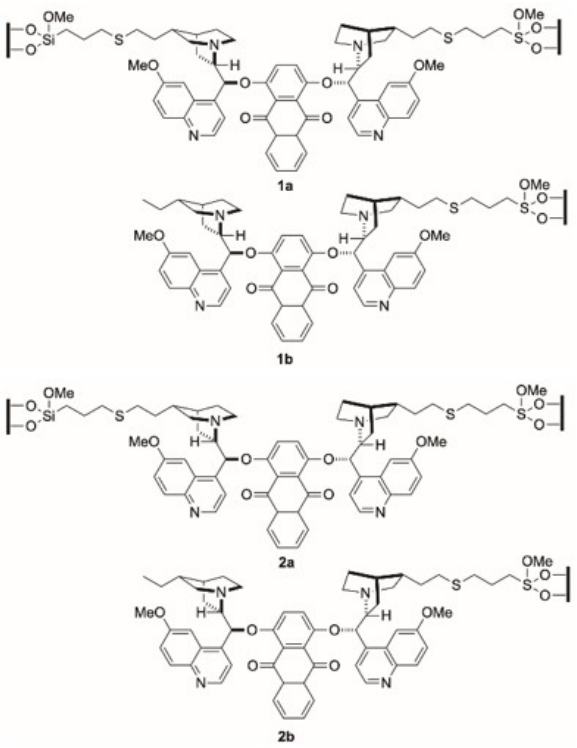


Figure 1. 1,4-Bis(quinidinyl)anthraquinone based organocatalysts.





Zeynep Dilşad Susam was born in Kocaeli (Turkey) in 1989. She received her BSc in 2012 from Middle East Technical University. She obtained her MSc under the supervision of Prof. Dr. Cihangir Tanyeli, studying organocatalytic aza-Henry reactions. Currently, she is pursuing her PhD in Prof. Tanyeli's research group. Her research focuses on the development of new catalysts and one-pot domino reactions.

Cihangir Tanyeli obtained his PhD degree in 1988 from Middle East Technical University, Department of Chemistry, Ankara-Turkey. He worked as a postdoctoral researcher at the Ruprecht Karls Universitat Heidelberg supported by NATO and DAAD. He started as a faculty member in 1990 at METU and continues as a full professor since 1997. His main research interests include the development of bifunctional organocatalysts and organocatalytic asymmetric reactions. He is Humboldtians supported by Alexander von Humboldt foundation in 1997 at RWTH Aachen. Since 2017, he is the member of the science academy, Turkey.

Additionally, the recyclability of **1a** was investigated by separating it from the reaction mixture by simple filtration, then reusing it for 5 more runs. There was no significant change in the enantioselectivity (92–89% ee) or catalytic activity (70–73% conversion).

In 2008, Ma and co-workers chose cyclohexanone addition to *trans*-β-nitrostyrenes as model reaction to test their silica supported heterogeneous organocatalyst **6** which was synthesized from 3-aminopropyl functionalized silica and Boc-(*S*)-proline (Figure 2, Scheme 2).[55]

The catalytic activity studies started with solvent screening in the presence of 10 mol% catalyst **6** at room temperature. The best conversion and highest stereoselectivity were achieved under neat condition (97% conversion and 91% ee for the major diastereomer, 96:4 dr). With the optimized condition in hand, the derivatization study was performed with a wide variety of nitroalkenes and ketones. All nitrostyrene derivatives with cyclohexanone gave good results in terms of both chemical yield and enantioselectivity (96–98% yields, 84–91% ee, respectively). However, the outcomes for different ketones ranged between 40–77% ee.

The recyclability study was also done after quenching the reaction by filtration and washing with ethyl acetate. The supported catalyst exhibited good catalytic activity with high diastereo- and enantioselectivity which were maintained up to four cycles shown in Table 1.

In the same year, Wang and co-workers also studied the same reaction by using a silica gel supported pyrrolidine-based chiral ionic liquid as a recyclable organocatalyst, which was prepared from (*S*)-Boc-L-proline (Figure 3).[56] Majority of the trials with solvents afforded excellent stereoselectivities (96 to 99% ee, 99:1 dr); however, the major drawback of using solvents caused low chemical yields. To overcome the chemical yield issue, they carried out the reaction under neat condition using 10 mol% of catalyst **7a** with 91% isolated yield at room temperature for 36 h (Scheme 3).

In their further derivatization studies; a variety of nitroolefins with different substituents were investigated and all of them gave excellent enantio- and diastereoselectivities in good yields. Besides nitroolefins, some different ketones were also used. Although, tetrahydrothiopyran-4-one and tetrahydro-4H-pyran-4-one were also suitable substrates as Michael donors and gave great results (88% yield, 95% ee, 95:5 dr and 85% yield, 93% ee, 96:4 dr, respectively), whereas acetone and cyclopentanone served as efficient Michael donor with excellent yields, but moderate enantioselectivities (92% yield, 52% ee and 87% yield and 41% ee, respectively). To recover the supported catalyst **7a**, a simple filtration was applied and the catalyst was washed with EtOAc and DCM. Then it was reused six more times and gave excellent results once again as it did before (Table 2).

Generation of supported organocatalysts with hybrid silica, provides many advantages such as high surface area, chemical inertness, in addition to the thermal & mechanical stability and easy recyclability thanks to the properties of the organic materials.

© 2021 Wiley-VCH GmbH

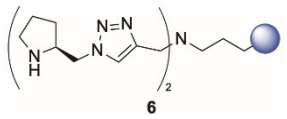
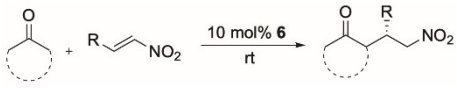


Figure 2. 3-Aminopropyl functionalized silica and Boc-(*S*)-proline.



Scheme 2. Ketone addition to β-nitrostyrenes with catalyst **6**.

Table 1. Recycling studies of silica-supported catalyst **6** in the Michael reaction of cyclohexanone to β-nitrostyrene.

Cycle	1	2	3	4
Yield[a] (%)	97	96	93	95
dr (*syn*/*anti*)[b]	96:4	97:3	95:5	94:6
ee[c]	91	90	90	91

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis (Chiralpak AD-H).

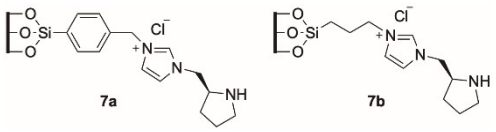
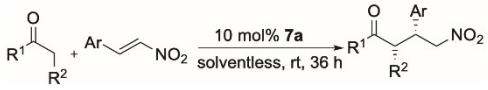


Figure 3. Silica gel supported pyrrolidine-based chiral ionic liquid.



Scheme 3. Michael additions of ketones and aldehydes to β-nitrostyrenes with catalyst **7 a**.

Table 2. Recycling studies of silica-supported catalyst **7 a**[a] in the Michael reaction of cyclohexanone to β-nitrostyrene.

Cycle	Yield[b] [%]	ee[c]	dr[d]
1	91	98	98:2
2	89	98	98:2
3	90	97	98:2
4	88	98	98:2
5	81	98	98:2
6	85	98	97:3

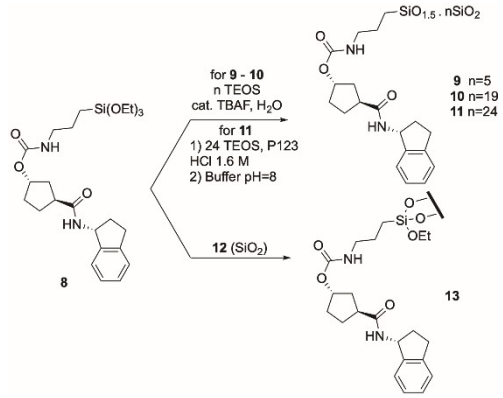
[a] Nitrostyrene (0.5 mmol), cyclohexanone (0.4 mL), and reused **7 a** (contains 0.05 mmol of active loading) under solvent-free reaction conditions at room temperature (25 °C) for 36 h [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AD-H). [d] Diastereomeric ratio, dr (*syn*/*anti*) determined by ^{1}H NMR.

The surfactant-assisted sol-gel synthesis and grafting methods are common ways to prepare the silica-supported catalysts. Since they are built with strong C–Si covalent bond, they provide a chemically stable and also controlled active fragment loading.[57]

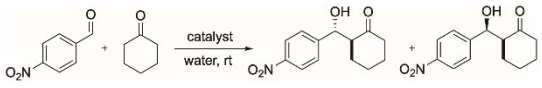
The activities of these silica supported organocatalysts **9**–**11** and **13** (Scheme 4) were tested on the direct asymmetric aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone in water at room temperature by Pleixats and co-workers (Scheme 5). Catalyst loadings ranging between 1–20 mol% were screened and also *p*-nitrobenzoic acid was tried as an additive in some of the screenings. Excellent conversion (99%) with 88% ee of the major diastereomer and 86:14 diastereomeric ratio was obtained without any additive. These results were also compared with the homogeneous analogues; Najéra's prolinamides (Figure 4). However, their enantiomeric excess values were lower than the supported ones, although they have similar conversions.

After having these encouraging results with the activity and selectivity, they tested the reusability of the catalysts. The stereoselectivities remained same even up to 5 runs recycling. Another interesting outcome from the recycling was that they observed a decrease in the reaction rate of the 5 mol% catalyst loading, on the contrary, the reactions were faster with 10 mol% loading even after 5 runs.

Mesoporous silica supports are stable in terms of both covalent and electrostatic immobilization due to their pore apertures and pendant silanol groups that help functionalization and manipulation. They are also economically friendly and



Scheme 4. Silica gel supported organocatalysts of Pleixats.



Scheme 5. Direct asymmetric aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone.

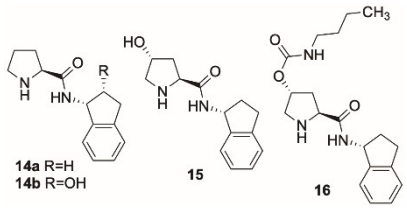


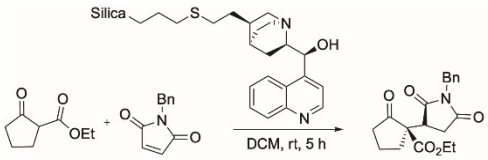
Figure 4. Najera's prolinamides **14 a-b** and homogeneous nonsilylated prolinamide analogues **15** and **16**.

© 2021 Wiley-VCH GmbH

sustainable accordingly these systems can be used in many studies. Raja and co-workers claimed that, immersing cinchonine organocatalyst to the inner walls of mesoporous silica with 60 Å diameter is wiser, because they showed enhanced turnovers and modest enantioselectivities, which are higher than homogeneous analogues.[58]

To control the catalyst performance, hydrophobic environment was created by the methylation of the pendant silanol groups. It showed that, this type of heterogeneous catalysts increased the turnover numbers, and it was also proven that the active site is much more accessible. However, enantioselectivities and conversions are less than previous case (74% to 56% ee) more likely from the sterical restriction in the Michael addition of ethyl-2-oxocylcopentanecarboxylate to *N*-benzylmaleimide (Scheme 6).

In 2016, Pleixats and co-workers used two different monosilylated proline sulphonamide **17** and **18** precursors in the synthesis of 6 different types of sol-gel organocatalysts **19**–**23** by sol-gel cogelification and grafting methods. The efficiency of them was tested in terms of their activity and recyclability in the same asymmetric direct aldol reaction as they used in their previous study.[59]



Scheme 6. Michael addition of *N*-benzylmaleimide to ethyl-2-oxocylcopentanecarboxylate.

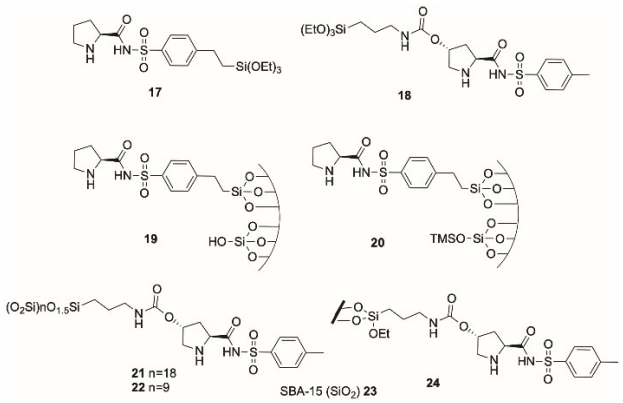
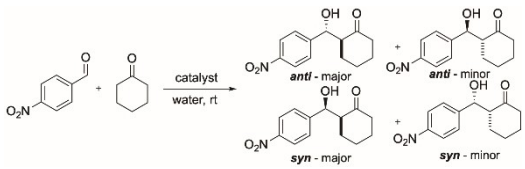


Figure 5. Monosilylated proline sulphonamides and silica supported catalysts.



Scheme 7. Cyclohexanone addition to *p*-nitrobenzaldehyde.

Catalyst **19** was obtained by sol-gel co-condensation from **17**, and **20** is the trimethyl silylated derivative of **19**. The rest of the catalysts was synthesized from precursor **18**. Sol-gel method was used in the synthesis of **21** and **22**. Mesostructured silica of SBA-15 type was also synthesized as **23** and finally, with grafting method, **24** was prepared from **23** (Figure 5).

The direct asymmetric aldol reaction between *p*-nitro benzaldehyde and cyclohexanone was chosen to test the activity of these catalysts (Scheme 7). Without in the absence of any co-catalyst, the reaction was carried out with 10–20 mol% catalyst loadings in water. Good conversions and moderate to good enantioselectivities were achieved (dr and ee up to 90/10 and 94%, respectively). In order to compare the results, the homogeneous proline sulphonamide was also tested under the same reaction conditions and gave a slight better result in terms of dr ratio, 99:1 and enantioselectivity as 96% (Table 3, entry 11).

Comparing 6 different silica supported organocatalysts in terms of the nature, length of the linker, characteristic of the matrix, and the derivatization site on the catalytic organic moiety, clearly indicates that **21**, **22** and **24** showed better activity and selectivity in this particular reaction.

Over the years, many silica supported heterogeneous organocatalysts have been designed and evaluated in different types of reaction.[60–64] However, we would like to give the last example to this category done by Pleixats and co-workers to show the improvements in this field.[65]

In this study, they synthesized the recyclable mesoporous organosilica nanoparticles derived from proline-valinol amides and tested the efficiency on the direct aldol addition of *p*-nitrobenzaldehyde and cyclohexanone once again. Six different supported catalysts **26**–**31** were prepared and used in the optimization studies (Figure 6). Among them, **26**, **28** and **30** gave better results in terms of both stereoselectivity and chemical yields.

Table 3. Optimization study of Pleixats' work.

Entry[a]	Cat [mol%]/Cycle	t [h]/[%][b]	$dr_{anti/syn}$[c]	er_{anti}[d]
1	21 (10)/1	96/>99	84/16	90/10
2	21 (10)/2	96/>99	75/25	95/5
3	21 (10)/3	144/>99	85/15	96/4
4	21 (10)/4	168/>99	84/16	90/10
5	21 (20)/1	96/>99	79/21	97/3
6	21 (20)/2	96/>99	79/21	88/12
7	22 (10)/1	144/85	90/10	84/16
8	22 (10)/2	144/>99	83/17	96/4
9	22 (10)/3	144/83	88/12	87/13
10	22 (10)/4	168/>99	84/16	87/13
11	22 (20)/1	144/98	87/13	98/2
12	22 (20)/2	144/>99	80/20	90/10
13	24 (10)/1	96/>99	90/10	94/6
14	24 (10)/2	96/>99	88/12	97/3
15	24 (10)/3	144/>99	92/8	90/10
16	24 (10)/4	168/>99	90/10	89/11

[a] Reaction conditions: aldehyde (1 equiv.), cyclohexanone (5 equiv.), water (0.5 mL/mmol aldehyde) and the indicated amount of the corresponding catalyst at rt. [b] Yield of the diastereomeric mixture determined by ^{1}H NMR spectroscopy. [c] Diastereomeric *anti/syn* ratio determined by ^{1}H NMR spectroscopy. [d] Enantiomeric ratio of the *anti*-diastereomer determined by chiral HPLC (Daicel Chiralpak ADH column).

© 2021 Wiley-VCH GmbH

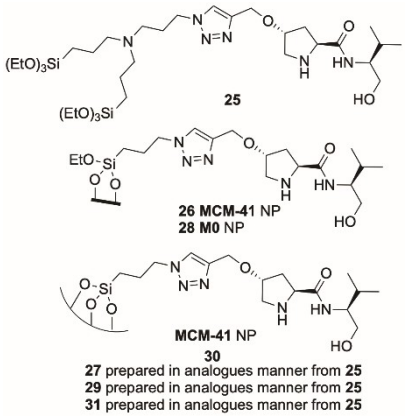


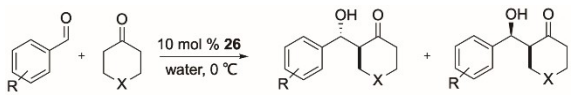
Figure 6. Preparation of Mesoporous Organosilica Nanoparticles **26**–**31**.

During the optimization studies, they figured out that the use of nanoparticles of silica helps to reduce some issues arising from the diffusion and the low reaction rates resulted from the use of bulk organosilica. The best condition was found with catalyst **26** (10 mol%) in water at 0 °C for 8 h (full conversion, 89:11 dr and 82% ee) in Scheme 8. The scope of the reaction was extended with different aldehydes and ketones. Almost nearly excellent yields, good enantio- (74–90% ee) and diastereoselectivies (81:19–90:10 dr) were obtained.

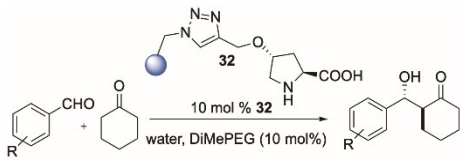
The reproducibility of the catalytic performance is also investigated by using the same reaction. For recycling the catalyst, it was washed with ethyl acetate, centrifugated and decantated. They found out that the activity and diastereo- and enantioselectivities were preserved up to five consecutive cycles.

3. Polymer Supported Organocatalysts

In asymmetric aldol reactions, the use of water as solvent is favorable in terms of recovery and recycling of nonpolar catalysts. Therefore, employing immobilized catalysts with highly hydrophobic polymer chains in aqueous medium is advantageous.



Scheme 8. Cyclohexanone addition to *p*-nitrobenzaldehyde with catalyst **26**.



Scheme 9. Cyclohexanone addition to aldehydes with catalyst **32**.

In 2006, Pericàs and co-workers chose 3-hydroxyproline as the monomeric catalyst and via 1,3-dipolar cycloaddition reactions of an azide-substituted Merrifield resin, the heterogeneous catalyst **32** was accomplished.[66] This catalyst was tested in the direct aldol reaction of cyclohexanone with benzaldehyde. 10 mol% catalyst loading was applied for the solvent screening and addition of DiMePEG screenings (Scheme 9). Hence, 10 mol% of **32**, 10 mol% of DiMePEG was determined as the optimal condition in water at room temperature in 60 h (75% yield, 96:4 dr, 96% ee).

To check the catalyst activity and stereoselectivity, the optimal condition was applied to the same reaction with monomeric catalyst, and anti/syn ratio was reduced to 63:37 and the major enantiomer's ee was found as 83%, which were quite lower than the polymer catalyst. With the optimized condition, a set of aldehydes and ketones were screened. Aromatic aldehydes gave good results similar to benzaldehyde; however, the use of different ketones decreased the stereoselectivity and chemical yield. Among the ketones, the best result was obtained with cyclopentanone with 97% yield, 83:17 dr and 87% ee of *anti*-product in 60 h. Recyclability was also tested by quenching the catalyst via filtration and washing with EtOAc. No decrease in stereoselectivity or activity was observed until 3 more runs.

Another polymer supported organocatalyst was applied in the aldol reaction of cyclohexanone to *o*-nitrobenzaldehyde by Tao and co-workers in 2007.[67] Two L-Proline based linear polystyrene supported catalysts **33a** and **33b** (Mw = ca. 5000) with flexible spacers were synthesized (Figure 7). Initial studies were conducted with 5 mol% catalyst in different DMF-water mixtures. The best result was achieved with 15:1/DMF:Water ratio as 95:5 diastereomeric ratio with 95% ee and 73% chemical yield in 24 h. With this optimized condition, cyclohexanone was tested with different aldehydes. Similar selectivities and reactivities were observed in the range of 83:17 to 95:5 dr, 84–96% ee and 46–91% yield, respectively. Moreover, this polymer supported organocatalyst can also be recovered and reused as well, giving unchanged stereoselectivity, although slowly diminishing yields were obtained up to 4 cycles.

A polystyrene-immobilized pyrrolidine catalyst **34** was synthesized by Wang et al. in 2008 (Figure 8).[68] It was prepared from Merrifield resin (2% DBV, loading 2.0 mmol/g active Cl from Sigma Aldrich) and then a click reaction took place.

This catalyst was evaluated in the Michael addition of cyclohexanone to nitroolefins. With the addition of 2.5 mol% TFA, reaction was performed under neat condition at 10 °C in 3 days and excellent enantioselectivity (> 99% ee), diastereose-

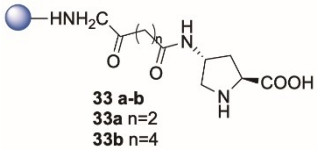


Figure 7. L-Proline based linear polystyrene supported catalysts **33a** and **33b**.

© 2021 Wiley-VCH GmbH

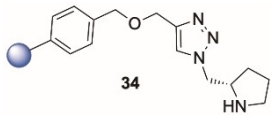


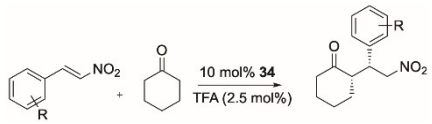
Figure 8. Polystyrene-immobilized pyrrolidine catalyst **34**.

lectivity (>99:1 dr) and isolated yield (97%) were achieved (Scheme 10).

A variety of nitroolefins were used and high isolated yields were obtained with all of them. *para*-Substituents gave rise to excellent results (99% ee and 99:1 dr) in most cases. The *ortho*- and *meta*- positions also led to good yields with good enantio- and diastereoselectivities (88-90% ee, 97:3-98:2 dr, respectively).

The recyclability study was done by simple filtration and washing with different solvents without any further purification. This PS-immobilized catalyst **34** was recycled and reused in 10 consecutive reactions without any loss of activity and selectivity.

A novel prolinamide organocatalyst **35** with polystyrene support was prepared by Noto et al in the same year (Figure 9).[69] Since prolinamide catalysts are highly powerful in aldol reactions,[70,71] it was also tested in the aldol reaction between acetone and *p*-nitrobenzaldehyde (Scheme 11). The optimization and the recyclability studies were done together. First trials did not work as intended. Presumably, the excess amount of acetone in the reaction medium might have caused a deactivation with imidazolidinone formation process. They found a solution to regenerate the catalyst with the treatment of formic acid, which was expected to hydrolyzed the imidazolidinone. However, some additional work needed to be done to improve low yields such as changing solvent systems.



Scheme 10. Cyclohexanone addition to nitroolefins with catalyst **34**.

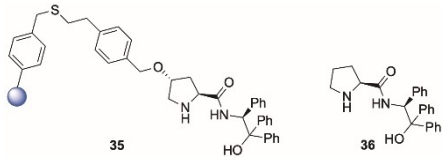
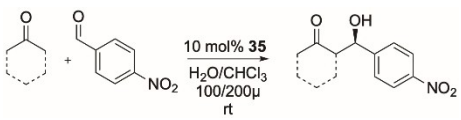


Figure 9. Polystyrene-immobilized pyrrolidine catalyst **35** and its homogeneous analogue **36**.



Scheme 11. Cyclohexanone/Acetone addition to aldehydes with catalyst **35**.

The reaction worked best in the water/$CHCl_3$ mixture (95% ee and 96% yield). Then, some additional trials were done with cyclohexanone. They figured out that the 1:2/water:solvent system was the best for this reaction in the presence of 10 mol% catalyst **35**. Thus, the scope of the reaction was extended to different aldehydes. Excellent enantioselectivities (89–97% ee) with good yields (30-98%) were achieved with many runs with recycled organocatalyst.

Cyclohexanone gave similar excellent diastereoselectivities with different aldehydes. When they tried the homogeneous catalyst **36**, they observed that the supported ones worked better than their homogeneous analog.

(*S*)-Boc-L-proline was used as the starting material of another polymer supported pyrrolidine-based recyclable ionic liquid organocatalyst. Zhang and co-workers designed a catalyst with Merrifield resin **37** (Figure 10), and examined in the Michael addition of cyclohexanone to nitroolefins (Scheme 12).[56] 10 mol% catalyst loading was used in the solvent screening at room temperature in 24 h. Most of the solvents used gave excellent stereoselectivities; however, the isolated yields were ranging between 25–95%. They decided to continue with the neat reaction condition, which resulted in 97% isolated yield with 99% ee and 99:1 diastereomeric ratio.

Under optimized condition, a large variety of nitroolefins and ketones were tested. Except acetone (98% yield, 57% ee) and cyclopentanone (84% yield, 51% ee, 81:19 dr), 20 different derivatives gave excellent results (82–98% yield, 91–99% ee, 93:7–99:1 dr, respectively).

After carrying out the reaction, the catalyst was filtered out from the reaction medium and washed with polar and nonpolar solvents without any further purification. Up to 8 more consecutive runs, the enantio- and diastereoselectivities remained same, with a slight decrease in isolated yield from 97% to 87% (Table 4).

One of the first studies of immobilized catalysts containing squaramides was reported by Pericàs and co-workers in 2012 with a polystyrene support in the Michael addition of 1,3-dicarbonyl compounds to β-nitrostyrenes (Scheme 13).[72] The target supported organocatalyst **38** was synthesized from the

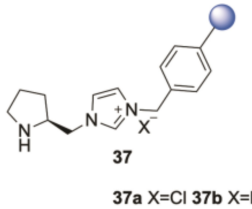
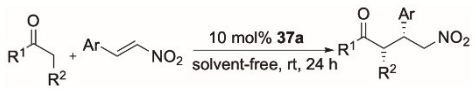


Figure 10. Polymer supported pyrrolidine-based recyclable ionic liquid organocatalyst **37**.



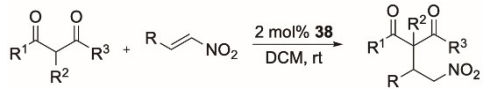
Scheme 12. Michael addition of ketones and aldehydes to β-nitrostyrenes with catalyst **37a**.

© 2021 Wiley-VCH GmbH

Table 4. Recycling studies of silica-supported catalyst **37 a**[a] in the Michael reaction of cyclohexanone to β-nitrostyrene.

Cycle	Yield[b] [%]	ee[c]	dr[d]
1	97	99	98:2
2	94	99	98:2
3	95	98	98:2
4	89	99	98:2
5	91	99	98:2
6	88	99	98:2
7	89	99	97:3
8	87	99	98:2

[a] Nitrostyrene (1.0 mmol), cyclohexanone (2.0 mmol), and reused **37 a** (contains 0.10 mmol of active loading) under solvent-free reaction conditions at room temperature (25 °C) for 24 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AD-H). [d] Diastereomeric ratio, dr (*syn*/*anti*) determined by ^{1}H NMR.



Scheme 13. Acetylacetone addition to β-nitrostyrene with catalyst **38**.

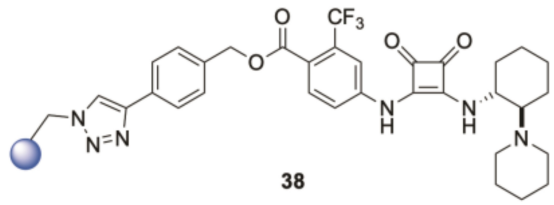


Figure 11. Polymer supported squaramide organocatalyst **38**.

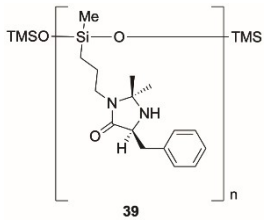


Figure 12. PMHS-supported chiral imidazole **39**.

aminoacid in four steps which involves a CuAAC reaction (Figure 11).

Screening of catalyst together with catalyst loadings were done in the reaction of acetylacetone addition to β-nitrostyrene in DCM at room temperature. Although the best enantioselectivity was obtained with 0.25 mol% catalyst as 97% ee, the reaction took 264 hours to complete with 83% isolated yield. Therefore, they decided to go further with 2 mol% catalyst **38**, which gave 95% ee in 8 h with 88% isolated yield. Then the activity of the catalyst was also investigated in the reaction of acetylacetone with different β-nitrostyrenes under optimized condition. The adducts were obtained in excellent enantioselectivities and yields (87–95% ee and 81–91% yield, respectively) in 8–24 h.

The scope of this reaction was extended to various β-dicarbonyls. The products were obtained with good to excellent yields and enantioselectivities (56–98%yield and 83–96% ee, respectively) with moderate diastereomeric ratios (1:1 to 29:1).

Recovery of this supported organocatalyst was performed by simple filtration. It was washed, dried and reused in the same model reaction. The enantioselectivities remained the same up to tenth cycle. However, isolated yields were slightly lower than the previous run for each time.

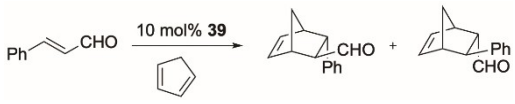
Poly(methylhydrosiloxane), PMHS-supported chiral imidazoles were designed and synthesized by Siegel and co-workers (Figure 12).[73,74] They used MacMillan's imidazolidine-4-ones and the polymer attachment was done in a few steps.

Synthesized polymer supported organocatalyst **39** was employed in the Diels-Alder reaction of cyclopentadiene with *trans*-cinnamaldehyde to evaluate the catalyst's activity and selectivity (Scheme 14). The best condition was achieved with 10 mol% catalyst as 67% yield, 52:48/exo:endo ratio and both having 91% ee in the presence of HBF_4 salt in 95:5/MeOH:H_2O at 0 °C.

Further studies to investigate the behavior of catalyst **39** was done in aqueous reaction medium. Different ratio of MeOH and water mixtures gave enantioselectivities higher than 90% in each case with the use of PMHS-supported HBF_4 salts. When the reaction was carried out in H_2O at room temperature, the isolated yield was found as 98%.

The isolation was performed by centrifugation and washing the catalyst. This method afforded excellent ee and yields up to 3rd run in water; however, after the 3rd cycle, the yield decreased drastically. The same trend was observed with 50:50/DCM:H_2O mixture. The best recycling performance was found in 95:5/CH_3CN:H_2O mixture. Up to 6th cycle the enantioselectivities were unchanged and the yields were slightly lower than the previous run.

A soluble poly(ethylene glycol) supported-9-amino-9-deoxy-epi-cinchona catalyst and an insoluble polystyrene supported catalyst were synthesized by Puglisi and co-workers in 2015 (Figure 13).[75] These supported catalysts were evaluated in the Michael addition of isobutyric aldehyde to β-nitrostyrenes (Scheme 15).



Scheme 14. Diels-Alder reaction of cyclopentadiene with *trans*-cinnamaldehyde with catalyst **39**.

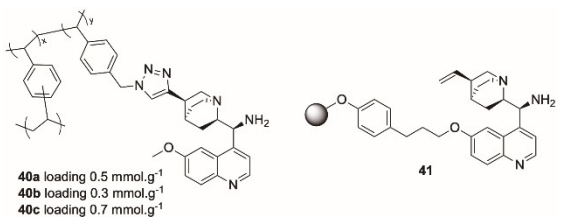
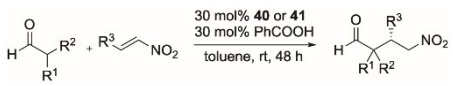


Figure 13. PS and PEG-supported 9-amino-9-deoxy-epi-cinchona **40**–**41**.

© 2021 Wiley-VCH GmbH

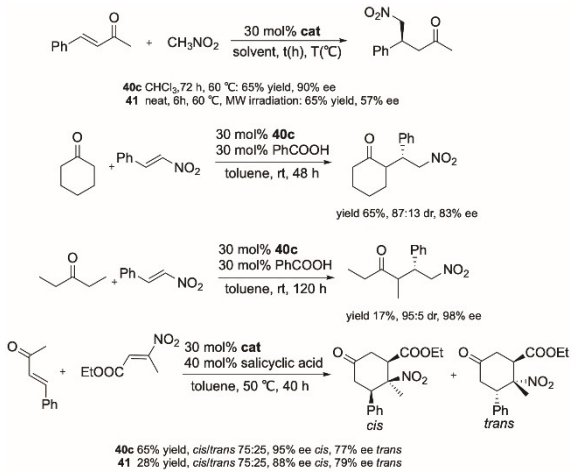


Scheme 15. Michael addition of isobutyric aldehyde to β-nitrostyrenes with catalyst **40** and **41**.

In this model reaction, 30 mol% of catalyst and 30 mol% of benzoic acid were used in toluene at room temperature for 48 h. Among them, **40c** gave the best result with 95% ee and quantitative yield. In addition, to expand the scope of the reaction with good results, nitromethane addition to benzalacetone was also tried. By using 30 mol% **40c** in $CHCl_3$ at 60 °C for 72 h, 90% ee was found with 65% isolated yield (Scheme 16).

Other reactions which were also applied and afforded good results are depicted in Scheme 16 with Puglisi's supported catalysts. Recycling of **40c** was performed with centrifugation and washing, **41** was precipitated by addition of diethyl ether to crude reaction mixture, filtered and recovered. Reusability of the catalyst were tested in consecutive reactions and up to 3rd run efficiency of the catalysts were preserved.

Homogeneous analogue of the catalyst **42** was also attempted to be recovered and reused; however, the results were not efficient. In the first run, 94% of the catalyst was recycled while it was 32% at the second run and which was impossible to recover after the third run (Figure 14).



Scheme 16. Reactions performed with catalyst **40**–**41**.

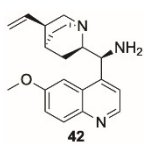


Figure 14. Homogeneous analogue, 9-amino-9-deoxy-epi-cinchona **42**.

4. Magnetic Nanoparticle Supported Organocatalysts

Attaching magnetic nanoparticles to the homogeneous catalyst allows to perform these structures under quasi-homogeneous conditions and they can be easily recovered by simple decantation or by external magnet.

A novel organocatalytic/magnetic nanoparticle catalyst system was synthesized by Liebscher and co-workers in 2012.[76] The efficiency of the catalysts was evaluated in the direct asymmetric aldol reaction between ketones and aryl aldehydes. Their nanoparticle supported catalysts consist magnetic core and polymer brush-like coating with acrylates or methacrylates and emerged 4-hydroxyproline (Figure 15).

Among the catalyst trials, they achieved good yields (73–82%) and excellent enantioselectivities (94–99% ee) in the presence of 10 mol% catalyst and benzoic acid as additive (Scheme 17).

They also employed the recyclability study to test the applicability of the catalyst in the re-runs with using an external magnet. None of the results up to 6th cycle is dropped in terms of both yield and enantioselectivity. The diastereomeric ratio is varied between 55:45 to 83:17. A few different aldehydes and ketones gave also good results with catalyst **43b** ranging from 88–99% ee with 55:45–78:22 dr.

9-Amino(9-deoxy)*epi*-quinidine was chosen once again as an organocatalyst for another recyclable catalyst system (Figure 16). Magnetic nanoparticle supported organocatalyst **45** was prepared through one-pot radical mediated thiol-ene reaction by Ma and co-workers in 2016.[77] With the core-shell morphology, they reached up to high loading capacity of the catalyst to the magnetic nanoparticle. This resultant catalyst **45** was employed in the direct α-amination of 2-methyl-3-nitro-4-

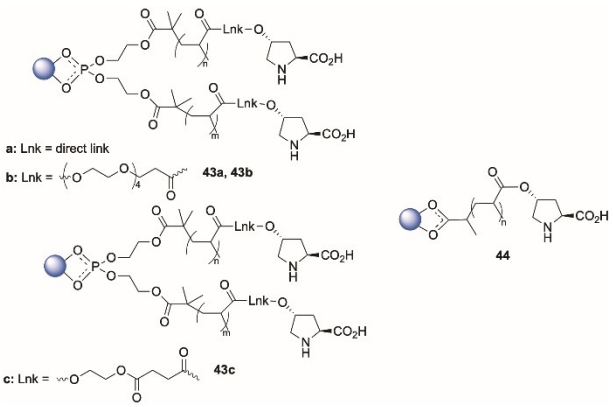
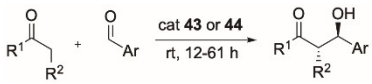


Figure 15. Magnetically tagged proline polyacrylates **43**, **44**.



Scheme 17. Direct asymmetric aldol reaction between ketones and aryl aldehydes with catalyst **43** and **44**.

© 2021 Wiley-VCH GmbH

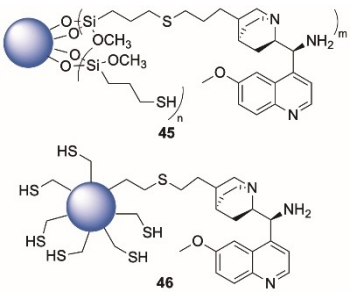


Figure 16. Magnetic nanoparticle supported organocatalyst **45** and **46**.

phenylbutyraldehyde with diisopropylazodicarboxylate (DIAD) (Scheme 18).

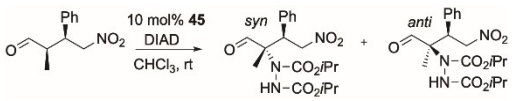
The optimization study started with the different catalysts **45** and **46**, having the different capacity of loading to the core shell. Among them, **45** (10 mol%) gave the best result as 94% ee of the *syn* product with 82:18 dr in the presence of 30 mol% TFA in chloroform. Subsequent screening of additive acid and the amount afforded the best result as 12 mol% catalyst **45** and 15 mol% of TFA in chloroform, as 89% yield, 98:2 dr with 95% ee in chloroform at room temperature in 60 h. The scope of the reaction was extended with different substituents on the phenyl ring. They all gave remarkable enantioselectivities (88–97% ee) and good isolated yields (75–89%). The catalyst was recovered from the reaction medium by using external magnet easily and washed with chloroform. Unfortunately, after 3rd run, they observed a sharp decrease in the diastereomeric ratio 95:5 to 23:77 and a slight decrease in the enantioselectivity 95% to 86% ee.

Many studies performed with the magnetic support organocatalysts were gathered in two different reviews published in 2013[78] and 2014.[79] Therefore, we did not go into further detail, want to give the audience to aspects of the subject with the aforementioned studies.

5. Gold Nanoparticle Supported Organocatalysts

Working with nanoparticles offers a better way to control the number and the accessibility of the catalyst molecules attached to the surface with the place-exchange reactions. Besides that, nanoparticles have a great advantage over the encapsulated catalysts by polymer supported ones, since the catalysts are immersed to the nanoparticle surface.

A valine derived formamide was anchored onto the surface of gold nanoparticles by Malkov et al. to be used in the



Scheme 18. Direct α-amination of 2-methyl-3-nitro-4-phenylbutyraldehyde with DIAD.

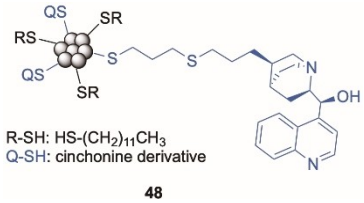
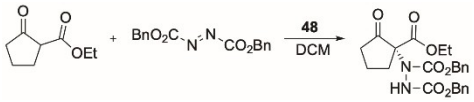


Figure 18. Gold nanoparticle supported cinchonine derived organocatalysts **48**.



Scheme 20. Asymmetric α-amination of β-ketoesters with catalyst **48**.

asymmetric reduction of ketimines with trichlorosilane (Scheme 19).[80] The gold nanoparticles were prepared from auric acid with Brust-Schiffrin synthesis and covered up with long chain thiols. The subsequent place-exchanged reaction took-place to prepare the gold nanoparticle immobilized organocatalyst with a lipoic acid linker (Figure 17).

The catalyst **47a** gave the best result as 84% ee with 90% isolated yield. The recovered catalyst was used up to 4th run, which was obtained with the same yield but with a decrease in the enantioselectivity to 68% ee.

Vallribera and co-workers described the first example of a thiol functionalized alkaloid attached onto gold nanoparticles.[81] Cinchonine was chosen to be the organocatalyst and was functionalized with a thiol linker via thiol-ene reaction. Subsequent facile ligand exchanged reaction yielded to the desired gold nanoparticle supported organocatalyst **48** (Figure 18).

Catalyst **48** was evaluated in the asymmetric α-amination of β-ketoesters (Scheme 20). The model reaction was performed between ethyl 2-oxocyclopentanecarboxylate and dibenzyl



Scheme 19. Asymmetric reduction of ketimines with trichlorosilane with catalyst **47**.

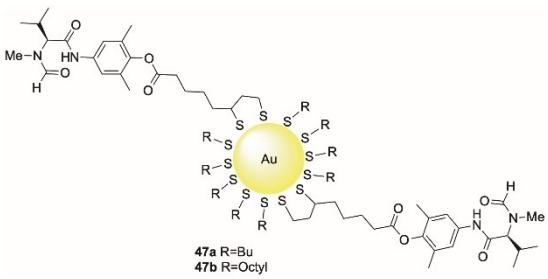


Figure 17. Gold nanoparticle supported organocatalysts **47**.

© 2021 Wiley-VCH GmbH

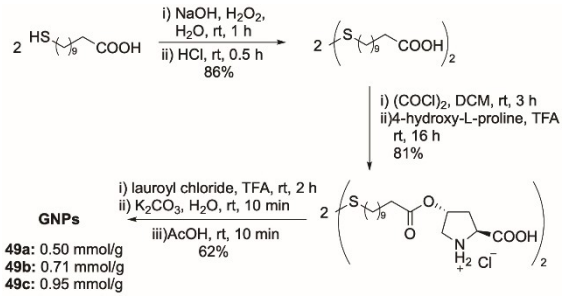
azodicarboxylate. The best result was 90% ee, in the presence of 20 mol% catalyst **48** in DCM at −78 °C in 2 h.

Another gold nanoparticle supported organocatalyst was prepared by Sóti et al. starting from 4-hydroxy-L-proline and chloroauric acid in four steps (Scheme 21).[82] The efficiency of this catalyst was tested on the direct asymmetric aldol reaction of cyclohexanone and aryl aldehydes (Scheme 22). In most cases, high enantioselectivities and chemical yields were obtained (77–89% ee, 65–99% yield, respectively).

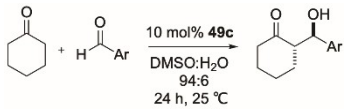
The recyclability was tested in the aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde. The supported organocatalyst was recovered by centrifugation and decantation. As shown in Table 5, the results remained unchanged in terms of enantio- and diastereoselectivity with isolated yield.

6. Ionic Liquid (IL) Organocatalysts

Headley and co-workers used (*S*)-(2-aminomethyl)-1-*N*-Boc pyrrolidine as a commercially available starting material to prepare pyrrolidine based chiral pyridinium ionic liquids in 2007.[83] The synthesized catalysts 50a-d were soluble in polar solvents such as MeOH, CH_3CN, DMF and DMSO; however, immiscible in nonpolar solvents such as hexane and Et_2O. The



Scheme 21. Synthesis of GNP-supported and *O*-lauroyl-trans-4-hydroxy-L-proline catalysts **49**.



Scheme 22. Direct asymmetric aldol reaction of cyclohexanone and aryl aldehydes with catalyst **49c**.

Table 5. Recycling studies of GNP-supported catalyst **49c** in the reaction between cyclohexanone with *p*-nitrobenzaldehyde

Cycle	Conversion[a] [%]	Yield[b] [%]	dr[c]	ee[d]	Recovery
1	98	97	90:10	88	≥99
2	99	98	91:9	88	≥99
3	99	98	91:9	88	≥99
4	99	98	92:8	88	≥99
5	99	98	92:8	88	≥99

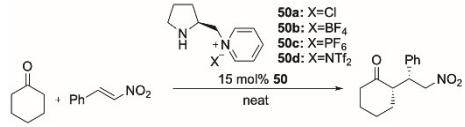
[a] Determined by ^{1}H NMR. [b] Isolated yields. [c] Determined by ^{1}H NMR (*anti*:*syn*). [d] Enantiomeric excesses of *anti*-products were determined by chiral HPLC analysis.

efficiency of these catalysts was tested in the Michael addition of cyclohexanone to β-nitrostyrenes (Scheme 23). All of them gave excellent results even in the neat case and in the TFA used as an additive as well, which increased the reaction rate without changing the enantioselectivity of the *syn* product (99% ee).

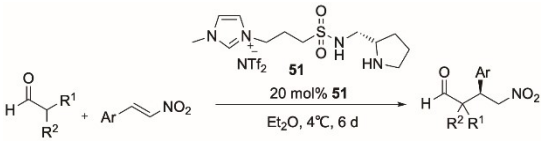
By using cat 50a/TFA and 50b/TFA a number of nitroolefins were tested and all gave great results (94–98% ee with 93:7 to 99:1 dr). Unfortunately, with the different ketones drastic decrease was observed in ee and dr (35–92% ee with 53:47 to 94:6 dr, respectively). The catalyst 50b was also recycled and reused up to third cycle with a slight decrease in the yield 90 to 82% and enantioselectivity 99 to 94%.

The same group developed another pyrrolidine sulfonamide based chiral IL catalyst 51.[84] It was evaluated in the Michael addition of isobutyraldehydes to nitrostyrenes by using 20 mol% 51 and followed by the solvent screening (Scheme 24). Among the screened solvents, Et_2O gave the best result as 82% ee with 58% isolated yield at 4 °C in 6 days. With this optimized condition in hands, a derivatization study was done. The enantioselectivities changed in the range of 64–88% ee with 38–64% yield. Also, the catalyst was recovered and reused in the same reaction for 3 more runs without any significant loss of in terms of both enantioselectivity and chemical yield.

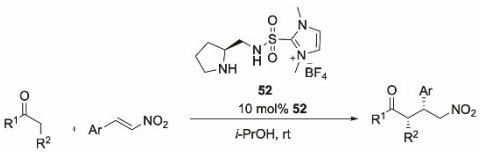
In a related work, changing the pyrrolidine sulfonamide catalyst's provided a little bit higher ee values as the reaction rate increased.[85] Headley and co-workers applied catalyst 52 to the cyclohexanone addition to the nitrostyrenes and obtained 90% ee of the major isomer with 95:5 dr and 91% isolated yield in 16 h with only using 10 mol% of catalyst in IPA at room temperature (Scheme 25).



Scheme 23. Michael addition of cyclohexanone to β-nitrostyrenes with catalyst **50**.



Scheme 24. Michael addition of isobutyraldehydes to nitrostyrenes with catalyst **51**.



Scheme 25. Cyclohexanone addition to the nitrostyrenes with catalyst **52**.

© 2021 Wiley-VCH GmbH

As shown in Table 6, recycling results yielded no significant loss in enantioselectivity and only a slight decrease in the yield up to 5th cycle.

A variety of nitrostyrenes were also tried in this reaction and afforded excellent enantioselectivities and chemical yields (80–99% ee, 83–97% yield, respectively). However, with different ketones, a drastic decrease was observed in terms of both enantioselectivity and isolated yield as 14–75% ee and 10–85% yield respectively.

A series of novel quaternary ammonium IL have been synthesized by Wang and co-workers.[86,87] Catalysts 53a and 53b with 20 mol% amount were used in the Michael addition of cyclohexanone to nitroolefins and subsequent solvent screening was performed (Scheme 26). The best result was obtained in [Bmim][BF_4] with 53a as 91% ee, 96:4 dr with full conversion. The catalyst was recycled and used up to 6th cycle with a slight decrease in the chemical yield by preserving the enantio- and diastereoselectivity.

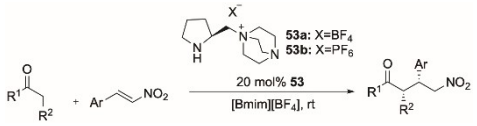
The scope of the reaction was extended with different nitrostyrenes and ketones. With different derivatives of nitrostyrenes, the stereoselectivities and yields were excellent (87–97% ee, 93:7 to 99:1 dr, 87–100% yields, respectively). In the case of different ketones, the cyclic ones gave good results (79–96% ee) whereas acyclic ones afforded moderate results (40–81% ee).

In 2017, Zlotin and co-workers synthesized tertiary amine-derived IL-supported squaramides as recyclable organocatalysts originated from cyclohexane-1,2-diamine derivatives.[88,89] Catalyst 54 was examined in the asymmetric conjugate addition of acetylacetone to β-nitrostyrenes at room temperature (Scheme 27). After the optimization study, the best condition was found as 10 mol% 54 in the presence of H_2O as 98% ee with 99% yield in 30 mins. Changing the nitroolefin derivatives gave also good results in terms of enantioselectivity and excellent yields in very short reaction time (80–99% ee, 86–99% yields, respectively). Since this IL-supported catalyst barely soluble in H_2O, recycling up to 11 times, and it gave nearly the same ee values and yields.

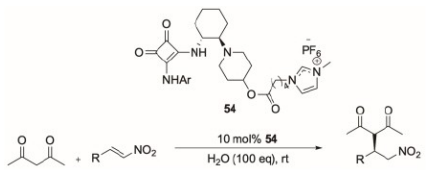
Table 6. Recycling studies of ILS **52** in the reaction between cyclohexanone with nitrostyrenes.[a]

Cycle	Time [h]	Yield[b] [%]	ee[c]	*syn*:*anti*[d]
1	12	92	90	95:5
2	16	90	90	95:5
3	18	93	90	94:6
4	24	86	89	95:5
5	40	80	88	93:7

[a] Ketone (5 eq) was used. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] Determined by ^{1}H NMR.



Scheme 26. Ketone addition to the nitrostyrenes with catalyst **53**.



Scheme 27. Acetylacetone addition to the nitrostyrenes with catalyst **54**.

7. Fluorous Supported Organocatalysts

Fluorous supported organocatalysts are recently preferred because they are soluble in common solvents and they are also easily recovered by fluorous solid-phase extraction method or fluorous-organic solvent extraction.

Curran and co-workers used chiral imidazolidinone catalyst **55** (Figure 19) in the asymmetric Diels-Alder reaction of acrolein and cyclohexadiene (Scheme 28).[90] The reaction was performed with 10 mol% **55** in CH_3CN-H_2O mixture at room temperature for 40 h. The products were obtained with 86% isolated yield, 93:7/endo:exo ratio and 93% ee (endo). The recovery of the catalyst from this reaction was 84% with 99% purity.

In the optimized condition a variety of dienes and α,β-unsaturated aldehydes were used. Good enantioselectivities (88–93% ee) and isolated yields (78–89%) were obtained with high recovery of the catalyst (80–86%).

Itoh and co-workers synthesized a catalyst derived from Takemoto's thiourea with perfluorooctyl group.[91] Conjugate addition of isobutyl aldehyde to *N*-phenyl maleimide was chosen as the model reaction in the presence of 10 mol% of **56** (Scheme 29). As a result of the solvent screening study, DCM was chosen as the best one affording 99% ee with 86% yield in 24 h at room temperature.

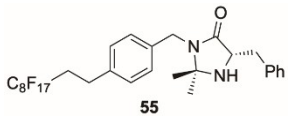
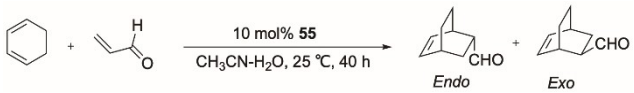
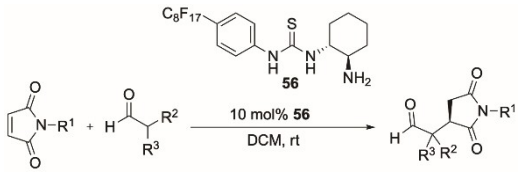


Figure 19. Fluorous supported organocatalyst **55**.



Scheme 28. Diels-Alder reaction of acrolein and cyclohexadiene with catalyst **55**.



Scheme 29. Conjugate addition of isobutyl aldehyde to *N*-phenyl maleimide with catalyst **56**.

© 2021 Wiley-VCH GmbH

Further trials were done with different maleimides and aldehydes. The enantioselectivities were excellent (91–99% ee) with good yields (43–99%). The catalyst **56** was easily recovered from the reaction medium by simple filtration. The catalytic activity and the stereoselectivity did not change for three subsequent reactions.

A fluorous sulfonamide recyclable organocatalyst **57** was prepared from phenyl alaninol through four steps.[92] It was tested in the direct asymmetric aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde in brine solution (Scheme 30). The optimized condition was determined as 10 mol% catalyst **57**, 5 mol% of TFA as additive at room temperature, which gave 87% isolated yield, 83:17 dr and 91% ee in 6.5 h.

With the optimized condition, various aldehydes and ketones were also tested with catalyst **57**, and the results were quite efficient to prove that the catalyst works well (75–96% ee).

The fluorous organocatalyst **57** was recovered via fluorous solid-phase extraction by using fluorous silica gel (89–100%) from the reaction mixture. The recovered **57** was reused without further purification and its catalytic activity and enantioselectivity was preserved up to five more cycles.

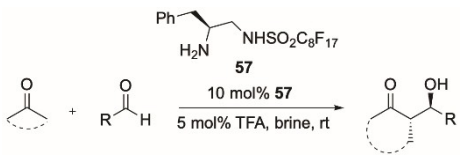
A 3,5-Bistrifluoromethylsulfonamide attached fluorous proline recyclable organocatalyst was prepared by Matsugi and co-workers and applied on the aldol reaction between cyclohexanone with *p*-nitrobenzaldehyde (Figure 20).[93] They achieved a diastereoselective result with catalyst **58a** and also reached to 99% ee with the major product in toluene with 1 mol% catalyst loading (Scheme 31). However, the reaction durations were long, so that they decided to go further with 10 mol% catalyst loading in toluene. They obtained 97:3 dr with 99% ee in 24 hours.

Additional four different aldehydes were also tried and afforded excellent dr and ee values (87:13 to 98:2 dr and 93 to +99% ee, respectively). However, the yields were low, ranged between 15–40%, except –CN derivative with quantitative yield.

The recovery of the catalyst was performed with Fluoroflash® and the resultant Fluoroflash®-supported catalyst was used in subsequent reactions. Up to 6 runs, the performance of the catalyst **58a** is preserved, and then a slight decrease was observed in terms of the yield, dr and ee values.

A fluorous anchored thiourea based bifunctional cinchona alkaloid organocatalyst **59** (Figure 21) was synthesized by Liu et al. and its efficiency was tested in a domino reaction involving Michael/aldol/cyclization for the synthesis of dihydrofuranone spirooxindoles and tetrahydropyranone spirooxindoles (Scheme 32).[94] For the dihydrofuranone derivatives, diethyl malonate, olefinic oxindole and formaldehyde were chosen as the starting materials. Toluene was found to be the proper Michael reaction solvent, whereas DCM was the best as co-solvent for aldol/cyclization process. Lowering the temperature during the course of Michael addition step causes a decrease in the isolated yields, and drastic increase in the enantioselectivity. Therefore the optimized condition was found as −25 °C for the Michael addition, 25 °C for the aldol/cyclization process with 10 mol% catalyst **59** resulted in 93% ee and 6:1 dr in 82% yields. Different olefinic oxindoles were used in the derivatization study, and the products were synthesized in 39–82% yields with >3:1 dr and up to 99% ee.

The same condition was applied for the synthesis of tetrahydropyranone spirooxindoles with ethyl acetoacetate which afforded six-membered cyclic hemiketals. The results were obtained in the range of 81–93% ee, 4:1 dr and 70–91% yields.



Scheme 30. Direct asymmetric aldol reaction of cyclohexanone and aldehydes with catalyst **57**.

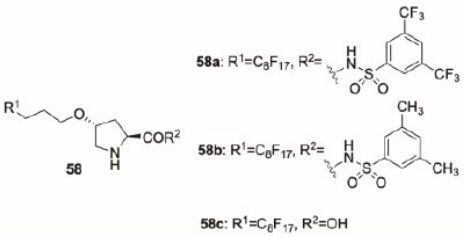
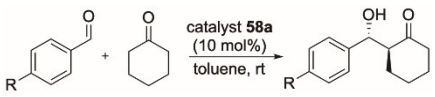


Figure 20. A 3,5-Bistrifluoromethylsulfonamide attached fluorous proline organocatalyst **58**.



Scheme 31. Asymmetric aldol reaction of cyclohexanone and aldehydes with catalyst **58a**.

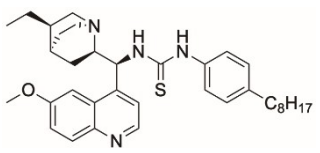
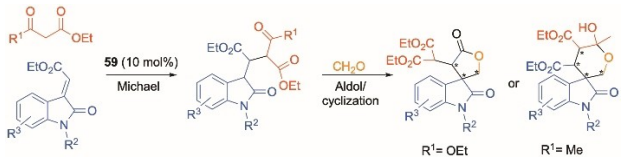


Figure 21. A fluorous anchored thiourea catalyst **59**.



Scheme 32. Synthesis of dihydrofuranone spirooxindoles and tetrahydropyranone spirooxindoles with catalyst **59**.

© 2021 Wiley-VCH GmbH

8. Miscellaneous Supported Organocatalysts

The first immobilization of an oxopyrimidinium-based phase transfer catalyst (PTC) was developed by Kobayashi and co-workers (Scheme 33).[95] Inspired by some literature examples, they aimed to immerse their catalyst into polymer backbone. After a couple of steps, they synthesized the polymer supported PTC **60** and subsequently coupled it with an insoluble polydimethylsilane (DMPSi), which prevents the polymer sticking to the flask surface.

After synthesizing the desired catalyst, its efficiency was tested in the model reaction as the addition of O'Donnell substrate to methyl vinyl ketone (Scheme 34). Among the solvent screenings, *o*-xylene gave a drastic change in 90 mins with 88% ee and 88% yield at ambient temperature. When the temperature was decreased to 0 °C, 90% yield with 95% ee was found in 300 minutes.

With this optimized condition, the recovery and the reusability of the catalyst was also studied. The ee values maintained up to 5 more consecutive runs with a very slight decrease in ee and chemical yield (91–90% ee and 87–82% yields, respectively). The recovery of the catalyst was performed via filtration, followed by washing with brine (to maintain chlorine counter ion) and acetone/water mixture.

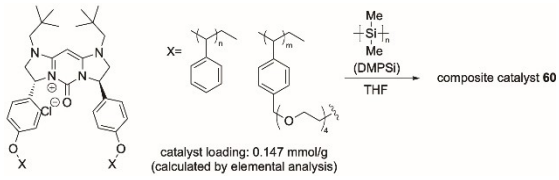
The scope of the reaction was extended with different chalcones at −20 °C with 5 mol% catalyst **60**, and very good results were obtained in terms of ee, and chemical yields in the range between 87–93% ee, 82–90% isolated yield in 3–24 h.

A recyclable hydrophobic anchor-tagged thiourea catalyst **61** was designed by Otaka and co-workers (Figure 22).[96] This catalyst was soluble in the less polar solvents such as $CHCl_3$, DCM, toluene, THF. Replacement of the solvent by polar ones, such as MeOH and CH_3CN causes a precipitation of the catalyst while dissolving the other reactants of the reaction.

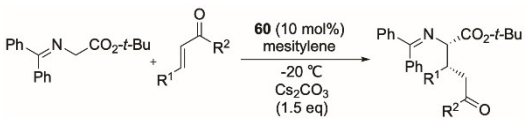
They also synthesized another supported thiourea catalyst **62** through amide linking of the known thiourea to polystyrene resin. Unsupported thiourea **63**, and the supported **61**, **62** were tested in the aza-Henry reaction of nitromethane and Boc protected imines (Figure 23). The results were depicted in Table 7. Among them, catalyst **61** gave the best result as 91% ee with 10 mol% catalyst loading in DCM at 30 °C in 24 h. The reusability of the catalyst up to four runs was also good in terms of yield, selectivity and recovery.

The catalyst **61** was also applied to the Michael addition by using various nitrostyrenes as acceptor and different donors such as malononitrile, diethylmalonate, acetyl acetone as well as the cyclic type nucleophiles (Scheme 35). They all gave good results in terms of chemical yields and selectivity ranged between 80–98% yield, 72–93% ee, respectively.

Pericàs and co-workers synthesized a polystyrene supported TRIP phosphoric acid catalyst and applied on the desymmetriza-



Scheme 33. Synthesis of catalyst **60**.



Scheme 34. Addition of O'Donnell substrate to methyl vinyl ketone with catalyst **60**.

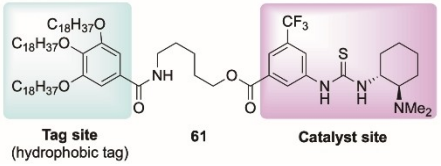


Figure 22. A recyclable hydrophobic anchor-tagged thiourea catalyst **61**.

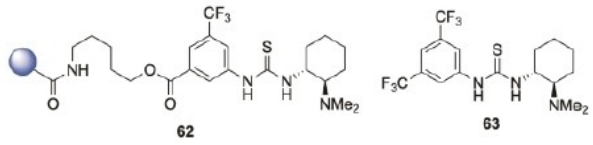
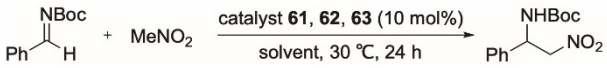


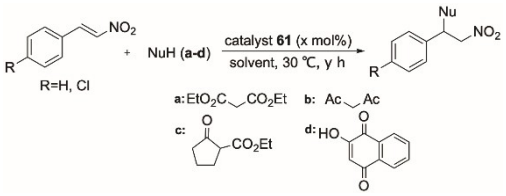
Figure 23. A recyclable hydrophobic anchor-tagged thiourea catalyst **62** and unsupported thiourea **63**.

Table 7. Asymmetric aza-Henry reaction with catalyst **61**–**63**.[a]



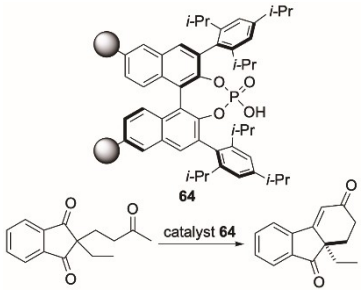
Entry	Catalyst	Solvent	Catalyst Recovery [%][b]	Yield [%][c]	ee [%][d]
1	**61**	DCM	99	77	91
2	**63**	DCM	–	76	90
3	**62**	DCM	99	N.R.	–
4[e]	**62**	DCM	99	15	89
5	**61**	$CHCl_3$	95	69	90
6	**61**	Toluene	99	30	91
7	**61**	THF	99	N.R.	–
8[f]	**61**	DCM	99	81	91

[a] Unless otherwise noted, reactions were carried out using *N*-Boc imine (0.1 mmol), nitromethane (1.0 mmol) and solvent (1.0 mL). [b] Recovered by using MeCN. [c] Isolated yields. [d] Determined by chiral HPLC analysis (chiralpak IC3, flow rate 1.0 mL/min, hexane/2-propanol = 85/15). [e] 30 mol% of **62** was used and the reaction was performed for 6 days. [f] Reaction was carried out using *N*-Boc imine (4.9 mmol), nitromethane (49 mmol) and solvent (49 mL).



Scheme 35. Michael addition of nitrostyrenes and various donors with catalyst **61**.

© 2021 Wiley-VCH GmbH



Scheme 36. Desymmetrization of meso-1,3-diones to produce chiral cyclohexanones with catalyst **64**.

tion of meso-1,3-diones to produce chiral cyclohexanones (Scheme 36).[97] They initiated their optimization study by solvent screening in the presence of 5 mol% catalyst loading at room temperature and almost had no reactivity except toluene (trace amount) and hexane (35% yield) in 32 h. However, the enantioselectivity of hexane trial was quite promising (90% ee). When they increased the temperature up to 70 °C, catalyst loading to 20 mol%, they succeeded to get 89% ee by overcoming the yield issue as 98% yield in 48 h.

With the optimized condition, various benzene fused mesodiones were tried and ended up with excellent results (84–92% ee, 60–98% yield). However, when they applied the optimized condition to the different cyclic mesodiones, the results were not quite as good as previous case, ranged between (47–73% ee with 60–79% yield). They also tested the reusability of the catalyst and found out that, up to 9 runs without loss of any effectiveness.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: chiral organocatalyst · recyclable organocatalyst · homogeneous catalyst · heterogeneous catalyst · supported organocatalyst

[1] B. List, *Chem. Rev.* **2007**, *107*, 5413–5415.
[2] P. I. Dalko, in *Enantioselective Organocatalysis*, John Wiley & Sons, Ltd, **2007**, pp. 1–17.
[3] D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308.
[4] S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621–631.
[5] H. Pellissier, *Curr. Org. Chem.* **2018**, *21*, 323–344.
[6] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
[7] M. Işık, M. Y. Unver, C. Tanyeli, *J. Org. Chem.* **2015**, *80*, 828–835.
[8] K. Świderek, A. R. Nödling, Y.-H. Tsai, L. Y. P. Luk, V. Moliner, *J. Phys. Chem. A* **2018**, *122*, 451–459.
[9] J. H. Shim, M. J. Lee, M. H. Lee, B.-S. Kim, D.-C. Ha, *RSC Adv.* **2020**, *10*, 31808–31814.
[10] D. Gryko, W. J. Saletra, *Org. Biomol. Chem.* **2007**, *5*, 2148–2153.
[11] N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas, *J. Am. Chem. Soc.* **2006**, *128*, 734–735.
[12] F. Tanaka, C. F. Barbas, in *Enantioselective Organocatalysis*, John Wiley & Sons, Ltd, **2007**, pp. 19–55.
[13] B.-L. Zhao, D.-M. Du, *Asian J. Chem.* **2015**, *4*, 778–787.
[14] M. M. Heravi, V. Zadsirjan, M. Dehghani, N. Hosseintash, *Tetrahedron: Asymmetry* **2017**, *28*, 587–707.
[15] C. G. Jacoby, P. H. V. Vontobel, M. F. Bach, P. H. Schneider, *New J. Chem.* **2018**, *42*, 7416–7421.
[16] Y.-H. Zhou, Y.-Z. Zhang, Z.-L. Wu, T. Cai, W. Wen, Q.-X. Guo, *Molecules* **2020**, *25*, 648.
[17] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
[18] P. Merino, E. Marques-Lopez, T. Tejero, R. Herrera, *Synthesis* **2010**, *1*, 1–26.
[19] I. Suzuki, M. Ando, R. Shimabara, A. Hirata, K. Takeda, *Org. Biomol. Chem.* **2011**, *9*, 3033–3040.
[20] T. Gatzenmeier, M. van Gemmeren, Y. Xie, D. Höfler, M. Leutzsch, B. List, *Science* **2016**, *351*, 949–952.
[21] L. Dell'Amico, A. Vega-Peñaloza, S. Cuadros, P. Melchiorre, *Angew. Chem. Int. Ed. Engl.* **2016**, *55*, 3313–3317.
[22] T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 929–931; *Angew. Chem.* **2006**, *118*, 943–945.
[23] B. Tan, P. J. Chua, Y. Li, G. Zhong, *Org. Lett.* **2008**, *10*, 2437–2440.
[24] H. Uehara, R. Imashiro, G. Hernández-Torres, C. F. Barbas, *PNAS* **2010**, *107*, 20672–20677.
[25] Y. Alvarez-Casao, E. Marques-Lopez, R. Herrera, *Symmetry* **2011**, *3*, 220–245.
[26] S. Mahajan, P. Chauhan, C. C. J. Loh, S. Uzungelis, G. Raabe, D. Enders, *Synthesis* **2015**, *47*, 1024–1031.
[27] A. Raja, B.-C. Hong, J.-H. Liao, G.-H. Lee, *Org. Lett.* **2016**, *18*, 1760–1763.
[28] T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625–627.
[29] A. M. Faisca Phillips, *Current Organocatalysis* **2015**, *02*, 1–1.
[30] R. Maity, S. C. Pan, *Org. Biomol. Chem.* **2015**, *13*, 6825–6831.
[31] D. Susam, C. Tanyeli, *New J. Chem.* **2017**, *41*, 3555–3561.
[32] R. R. Zalte, A. A. Festa, N. E. Golantsov, K. Subramani, V. B. Rybakov, A. V. Varlamov, R. Luque, L. G. Voskressensky, *Chem. Commun.* **2020**, *56*, 6527–6530.
[33] I. G. Sonsona, J. V. Alegre-Requena, E. Marqués-López, M. C. Gimeno, R. P. Herrera, *Chem. Eur. J.* **2020**, *26*, 5469–5478.
[34] M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 550–556; *Angew. Chem.* **2004**, *116*, 560–566.
[35] Ł. Albrecht, L. K. Ransborg, V. Lauridsen, M. Overgaard, T. Zweifel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 12496–12500; *Angew. Chem.* **2011**, *123*, 12704–12708.
[36] M. Giardinetti, J. Marrot, C. Greck, X. Moreau, V. Coeffard, *J. Org. Chem.* **2018**, *83*, 1019–1025.
[37] M. M. Heravi, V. Zadsirjan, M. Heydari, B. Masoumi, *The Chemical Record* **2019**, *19*, 2236–2340.
[38] G. G. Gerosa, M. O. Marcarino, R. A. Spanevello, A. G. Suárez, A. M. Sarotti, *J. Org. Chem.* **2020**, *85*, 9969–9978.
[39] G. Bergonzini, L. Gramigna, A. Mazzanti, M. Fochi, L. Bernardi, A. Ricci, *Chem. Commun.* **2009**, *46*, 327–329.
[40] F. Shi, G.-J. Xing, Z.-L. Tao, S.-W. Luo, S.-J. Tu, L.-Z. Gong, *J. Org. Chem.* **2012**, *77*, 6970–6979.
[41] J. B. Simões, Â. De Fátima, A. A. Sabino, F. J. T. de Aquino, D. L. da Silva, L. C. A. Barbosa, S. A. Fernandes, *Org. Biomol. Chem.* **2013**, *11*, 5069–5073.
[42] J.-X. Huang, K.-Q. Hou, Q.-L. Hu, X.-P. Chen, J. Li, A. S. C. Chan, X.-F. Xiong, *Org. Lett.* **2020**, *22*, 1858–1862.
[43] E. Bermúdez, O. N. Ventura, P. Saenz Méndez, *J. Phys. Chem. A* **2010**, *114*, 13086–13092.
[44] J. Lu, P. H. Toy, *Synlett* **2011**, *2011*, 1723–1726.
[45] P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; *Angew. Chem.* **2004**, *116*, 5248–5286.
[46] P. Wipf, M. Grenon, *Can. J. Chem.* **2006**, *84*, 1226–1241.
[47] T. P. Kumar, R. C. Shekhar, K. S. Sunder, R. Vadaparthi, *Tetrahedron: Asymmetry* **2015**, *26*, 543–547.
[48] M. Rueping, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2010**, *6*, DOI 10.3762/bjoc.6.6.
[49] F. G. Finelli, L. S. M. Miranda, R. O. M. A. de Souza, *Chem. Commun.* **2015**, *51*, 3708–3722.
[50] H. S. Kim, Y.-M. Song, J. S. Choi, J. W. Yang, H. Han, *Tetrahedron* **2004**, *7*.
[51] M. Ferré, R. Pleixats, M. Wong Chi Man, X. Cattoën, *Green Chem.* **2016**, *18*, 881–922.
[52] J. Hiratake, M. Inagaki, Y. Yamamoto, J. Oda, *J. Chem. Soc. Perkin Trans I* **1987**, *6*.

© 2021 Wiley-VCH GmbH

[53] C. Bolm, A. Gerlach, C. L. Dinter, *Synlett* **1999**, *2*, 195–196.
[54] F. Bigi, S. Carloni, R. Maggi, A. Mazzacani, G. Sartori, G. Tanzi, *J. Mol. Catal. A-Chem.* **2002**, *7*.
[55] Y.-B. Zhao, L.-W. Zhang, L.-Y. Wu, X. Zhong, R. Li, J.-T. Ma, *Tetrahedron: Asymmetry* **2008**, *4*.
[56] P. Li, L. Wang, Y. Zhang, G. Wang, *Tetrahedron* **2008**, *64*, 7633–7638.
[57] A. Monge-Marcet, X. Cattoën, D. A. Alonso, C. Nájera, M. W. C. Man, R. Pleixats *Green Chem.* **2012**, *14*, 1601–1610.
[58] S. H. Newland, D. J. Xuereb, E. Gianotti, L. Marchese, R. Rios, R. Raja, *Catal. Sci. Technol.* **2015**, *5*, 660–665.
[59] M. Ferré, X. Cattoën, M. Wong Chi Man, R. Pleixats, *ChemistrySelect* **2016**, *1*, 6741–6748.
[60] C. Bolm, T. Fey, *Chem. Commun.* **1999**, 1795–1796.
[61] R. R. Davda, J. W. Shabaker, G. W. Huber, R. D. Cortright, J. A. Dumesic, *Appl. Catal. B* **2003**, *43*, 13–26.
[62] N. A. Brunelli, C. W. Jones, *J. Catal.* **2013**, *308*, 60–72.
[63] A. Khalafi-Nezhad, E. S. Shahidzadeh, S. Sarikhani, F. Panahi, *J. Mol. Catal. A* **2013**, *379*, 1–8.
[64] S. Rostamnia, E. Doustkhah, *RSC Adv.* **2014**, *4*, 28238–28248.
[65] H. Li, M. Pérez-Trujillo, X. Cattoën, R. Pleixats, *ACS Sustainable Chem. Eng.* **2019**, *7*, 14815–14828.
[66] D. Font, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2006**, *8*, 4653–4655.
[67] Y.-X. Liu, Y.-N. Sun, H.-H. Tan, W. Liu, J.-C. Tao, *Tetrahedron: Asymmetry* **2007**, *18*, 2649–2656.
[68] T. Miao, L. Wang, *Tetrahedron Lett.* **2008**, *49*, 2173–2176.
[69] F. Giacalone, M. Gruttadauria, P. L. Meo, S. Riela, R. Noto, *Adv. Synth. Catal.* **2008**, *350*, 2747–2760.
[70] M. Gruttadauria, F. Giacalone, R. Noto, *Chem. Soc. Rev.* **2008**, *37*, 1666–1688.
[71] S. G. Zlotin, A. S. Kucherenko, I. P. Beletskaya, *Russ. Chem. Rev.* **2009**, *78*, 737–784.
[72] P. Kasaplar, P. Riente, C. Hartmann, M. A. Pericàs, *Adv. Synth. Catal.* **2012**, *354*, 2905–2910.
[73] S. Guizzetti, M. Benaglia, J. S. Siegel, *Chem. Commun.* **2012**, *48*, 3188–3190.
[74] Deepa, S. Singh, *Adv. Synth. Catal.* **2021**, *363*, 629–656.
[75] R. Porta, F. Coccia, R. Annunziata, A. Puglisi, *ChemCatChem* **2015**, *7*, 1490–1499.
[76] Z. Yacob, A. Nan, J. Liebscher, *Adv. Synth. Catal.* **2012**, *354*, 3259–3264.
[77] T. Wu, D. Feng, G. Xie, X. Ma, *RSC Adv.* **2016**, *6*, 77396–77405.
[78] M. B. Gawande, P. S. Branco, R. S. Varma, *Chem. Soc. Rev.* **2013**, *42*, 3371–3393.
[79] R. Mrówczyński, A. Nan, J. Liebscher, *RSC Adv.* **2014**, *4*, 5927–5952.
[80] A. V. Malkov, M. Figlus, G. Cooke, S. T. Caldwell, G. Rabani, M. R. Prestly, P. Kočovský, *Org. Biomol. Chem.* **2009**, *7*, 1878–1883.
[81] L. Santacruz, S. Niembro, A. Santillana, A. Shafir, A. Vallribera, *New J. Chem.* **2014**, *38*, 636–640.
[82] P. L. Sóti, H. Yamashita, K. Sato, T. Narumi, M. Toda, N. Watanabe, G. Marosi, N. Mase, *Tetrahedron* **2016**, *72*, 1984–1990.
[83] B. Ni, Q. Zhang, A. D. Headley, *Tetrahedron Lett.* **2008**, *49*, 1249–1252.
[84] B. Ni, Q. Zhang, A. D. Headley, *Green Chem.* **2007**, *9*, 737.
[85] B. Ni, Q. Zhang, K. Dhungana, A. D. Headley, *Org. Lett.* **2009**, *11*, 1037–1040.
[86] D.-Z. Xu, Y. Liu, S. Shi, Y. Wang, *Tetrahedron: Asymmetry* **2010**, *21*, 2530–2534.
[87] D. Krištofíková, V. Modrocká, M. Mečiarová, R. Šebesta, *ChemSusChem* **2020**, *13*, 2828–2858.
[88] R. S. Tukhvatshin, A. S. Kucherenko, Y. V. Nelyubina, S. G. Zlotin, *ACS Catal.* **2017**, *7*, 2981–2989.
[89] V. da G. Oliveira, M. F. do C. Cardoso, L. da S. M. Forezi, *Catalysts* **2018**, *8*, 605.
[90] Q. Chu, W. Zhang, D. P. Curran, *Tetrahedron Lett.* **2006**, *47*, 9287–9290.
[91] T. Miura, S. Nishida, A. Masuda, N. Tada, A. Itoh, *Tetrahedron Lett.* **2011**, *52*, 4158–4160.
[92] T. Miura, K. Imai, M. Ina, N. Tada, N. Imai, A. Itoh, *Org. Lett.* **2010**, *12*, 1620–1623.
[93] K. Ishihara, R. Obayashi, M. Gotoh, Y. Watanabe, Y. Kobayashi, K. Ishihara, T. Shioiri, M. Matsugi, *Tetrahedron Lett.* **2020**, *61*, 151657.
[94] M. Liu, X. Zhang, X. Huang, G. Dhawan, J. Evans, M. Kaur, J. P. Jasinski, W. Zhang, *Eur. J. Org. Chem.* **2019**, *2019*, 150–155.
[95] J. Miguélez, H. Miyamura, S. Kobayashi, *Adv. Synth. Catal.* **2017**, *359*, 2897–2900.
[96] T. Jichu, T. Inokuma, K. Aihara, T. Kohiki, K. Nishida, A. Shigenaga, K. Yamada, A. Otaka, *ChemCatChem* **2018**, *10*, 3402–3405.
[97] L. Clot-Almenara, C. Rodríguez-Escrich, M. A. Pericàs, *RSC Adv.* **2018**, *8*, 6910–6914.

Manuscript received: March 8, 2021
Revised manuscript received: April 11, 2021
Accepted manuscript online: April 15, 2021
Version of record online: May 6, 2021

© 2021 Wiley-VCH GmbH