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Solid Acids as Heterogeneous Support for Primary Amino Acid-Derived Diamines in Direct Asymmetric Aldol Reactions

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Abstract: We have achieved the non-covalent immobilization of chiral primary amino acid-derived diamines on organic and inorganic sulfonated solid acids through acid-base interaction. With the commercial sulfonated fluoropolymer nafion® NR50 as support an optimal balance was found between activity and stereoselectivity of the supported catalyst in direct asymmetric aldol reactions of linear ketones and aromatic aldehydes. Under optimized conditions aldol products were obtained in high yields and with excellent enantioselectivities for the *syn*-product (up to 98% *ee*). Furthermore, catalysis with the supported diamine was demonstrated to occur truly heterogeneously and the loaded nafion® NR50 beads could be reused several times. Ultimately, the immobilized catalyst/nafion® NR50 system was successfully implemented in a fixed-bed reactor set-up under continuous flow conditions.

Keywords: aldol reaction; chiral primary amines; continuous flow conditions; heterogeneous catalysis; nafion®; non-covalent immobilization

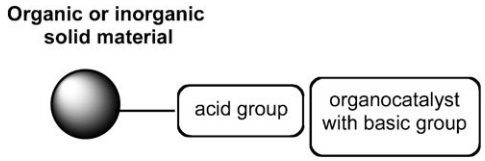
Introduction

After a decade of intensive research, organocatalysis has been established into a powerful method for enantioselective transformations, filling the gap between enzyme and metal-based catalysis.[1] The development of secondary amine catalysts for various asymmetric reactions has been breathtaking,[2] and more recently primary amines have been recognized as valuable enamine and iminium catalysts.[3] Among other driving factors, this explosive growth can be ascribed to the fundamental advantages that the application of organocatalysts offers to chemists, including their stability in water and air, their non-toxic nature and the ready accessibility of the chiral starting material, for example, from biological sources. Major drawbacks, however, are associated with high catalyst loadings and difficulties with catalyst separation and recycling, thereby limiting the efficiency of the catalytic system. Ever since the introduction of organocatalysis in asymmetric synthesis, heterogenization of successful organic catalysts has been considered to overcome these disadvantages.[4] Towards the discovery of more advanced catalysts and their implementation in larger scale asymmetric synthesis, immobilization will be justified by the requisite for high efficiency of the catalytic system.

As for other homogeneous chiral catalysts, the immobilization of aminocatalysts can be achieved by covalent linkage to a suitable support.[5] Various examples of polymer-supported enamine or iminium catalysts have been described over the past decade and this topic has been reviewed recently.[6] The attachment to a dendritic support could, aside from facilitating the recovery of the catalyst, also promote emulsion formation in aqueous conditions, thereby permitting the use of water as a solvent or co-solvent.[7] Furthermore, the use of inorganic materials as heterogeneous supports can provide some additional benefits due to their thermal and mechanical stability, lack of swelling tendency and insolubility in organic solvents. Hence, silica-based materials, among which are zeolites and other mesoporous materials, have been employed repeatedly for the covalent immobilization of

amino catalysts.[8] Another interesting application is the use of magnetic nanoparticles (MNPs) for the covalent functionalization with cyclohexanediamines.[9] These chiral MNP-supported primary amines have demonstrated high activity and stereoselectivity as enamine-based catalysts and could be easily recycled *via* magnetic forces.

A different heterogenization strategy involves the immobilization of a homogeneous catalyst by non-covalent linkage. This approach limits synthetic modifications of the parent catalyst and its modularity enables the fine-tuning of both catalyst and support. Recently, the non-covalent immobilization of enantioselective catalysts has been reviewed by Fraile et al., classifying the immobilization methods into four categories depending on the nature of catalyst-support interaction.[10] Although this review focuses on metal-based catalysts, similar principles have been applied for the immobilization of amino catalysts. For instance, Li and co-workers have immobilized proline and primary amino acids on γ-alumina by simple adsorption.[11] Interestingly, with these hybrid catalysts a remarkable inversion in enantioselectivity with respect to the free amino acids has been observed. Using a coordinative method, a homochiral metal-organic porous material (MOPM) has been synthesized very recently by post-modification of MIL-101 with a proline-derived chiral ligand and employed as catalyst in asymmetric aldol reactions.[12] Most non-covalent immobilization techniques, however, make use of electrostatic interactions through ion pairs. Examples include the intercalation of L-proline in Mg-Al layered double hydroxides[13] and the use of a L-proline-polyelectrolyte catalyst.[14] Very recently, the immobilization of a prolinamide catalyst on Montmorillonite using a cation-exchange method has been published in this journal.[15] Another interesting application of the electrostatic method was reported by Cheng et al. and Arakawa et al.[16,17] Here, chiral amines have been immobilized on polystyrene/sulfonic acid supports through acid-base interaction. In this approach, the solid acid not only acts as anchor for the amine, but also plays a crucial role in modulating the activity and stereoselectivity of the supported catalyst(Scheme 1).

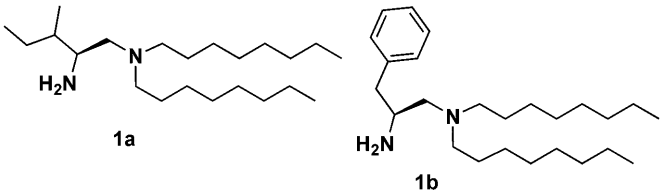


Scheme 1. Non-covalent immobilization of an organic catalyst through acid-base interactions, as introduced by Cheng et al.[16]

Results and Discussion

Clearly, the non-covalent immobilization of amino-catalysts is highly desirable and in spite of the remarkable advances mentioned above, it remains a challenging goal. Besides, except for Cheng's notable efforts,[9,16] heterogeneous systems with primary amine-based catalysts are quite rare to date. Here, we describe the successful non-covalent immobilization of primary amino acid-derived catalysts on different solid supports, following Cheng's strategy. We extended the research to both organic and inorganic solid acids. After identifying the most optimal heterogeneous catalyst/solid acid system for direct asymmetric aldol reactions of linear ketones, we developed a reactor set-up for continuous flow reactions over a fixed bed.

Very recently, we reported in this journal the use of primary amino acid-derived diamines with long alkyl tails as *syn*-selective aldol catalysts.[18] With these catalysts, in the presence of TFA as Brønsted acid and DNP as co-catalyst, *syn*-aldol products have been obtained with excellent enantioselectivities. Hence, we selected diamines **1a** and **1b** (Scheme 2) for the non-covalent immobilization on organic and inorganic solid acids.

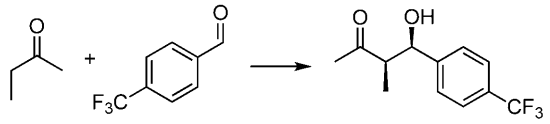


Scheme 2. Chiral primary amino acid-derived diamines used in this study.

The aldol reaction of 2-butanone and 4-(trifluoromethyl)benzaldehyde was chosen as a benchmark to evaluate the catalytic performance of the supported diamines. The heterogeneous catalysts were easily prepared *in situ* by mixing the solid acid and the diamine in a 1/1 molar ratio. The screening results are summarized in Table 1.

First, we considered the use of inorganic solids containing Brønsted acid sites as suitable supports. Among others, zeolites are crystalline inorganic solids with well-defined structures consisting of channels and cavities with molecular dimensions. Proton-exchanged zeolites have been frequently used as acid catalysts in the synthesis of fine chemicals.[19] Recent examples are, for instance, the alcoholysis of glycals,[19a] the retro-Diels–Alder reaction of masked cyclopentadienones,[19b] the dehydration and rearrangement of trioses into alkyl lactates[19c] and the hydrolysis of cellulose.[21b] Here, we selected ultrastable H-

Table 1. Screening of solid acids.[a]



Entry	Cat.	Acid additive	Yield[b][%]	rr[b] *b/l*	*dr*[b] *syn/anti*	*ee*[c] [%]
1[d]	**1a**	TFA	59	7/1	3/1	97
2[d]	**1b**	TFA	82	8/1	3/1	96
3[e]	**1a**	USY CBV 720	16	5/1	3/1	92
4	**1a**	USY CBV 760	13	4/1	3/1	88
5[e]	**1a**	H-BEA 25	17	4/1	3/1	92
6[f]	**1a**	Amberlyst® 15	<5	n.d.	n.d.	n.d.
7	**1a**	**Nafion® SAC-13**	**42**	**2/1**	**2/1**	**93**
8	**1b**	**Nafion® SAC-13**	**38**	**4/1**	**5/2**	**98**
9	**1a**	Nafion® NR50	40	4/1	2/1	70
10[g]	**1a**	**Nafion® NR50**	**77**	**4/1**	**3/1**	**90**
11	**1b**	**Nafion® NR50**	**86**	**4/1**	**2/1**	**91**
12[h]	**1a**	FA-500-75-SO_3H	12	4/1	3/1	92
13	**1b**	$Si_{33}C_{66}$-400-SO_3H	10	12/1	3/1	96
14	**1a**	$Si_{66}C_{33}$-400-SO_3H	25	4/1	3/1	90
15	**1b**	$Si_{33}C_{66}$-550-SO_3H	14	6/1	5/2	87
16	**1b**	$Si_{50}C_{50}$-550-SO_3H-HF	33	5/1	7/2	96
17[i]	**1b**	$Si_{50}C_{50}$-550-SO_3H-HF	39	6/1	3/1	97
18	**1b**	CMK-3-600-SO_3H	30	8/1	7/2	96

[a] All reactions were carried out under neat conditions in 2-butanone with aldehyde (0.125 M), 15 mol% of catalyst and 15 mol% of acid additive at room temperature, and analyzed after 20–22 h, unless indicated otherwise.
[b] Determined with chiral GC and verified with ^{1}H NMR (rr = regioisomer ratio, *b/l* = ratio of branched and linear products).
[c] The *ee* of the major *syn*-isomer, determined by chiral GC.
[d] See ref.[18]
[e] After 44–68 h of reaction.
[f] Not determined.
[g] With 15 mol% of DNP (2,4-dinitrophenol) as co-catalyst.
[h] With catalyst/solid acid ratio of 3/2.
[i] With catalyst/solid acid ratio of 2/1.

USY zeolites with varying proton density, *viz*. CBV 720 and 760, and H-beta zeolite, *viz*. H-BEA 25, for screening in the model reaction (Table 1, entries 3–5). H-USY zeolites of the CBV series are ultrastable zeolites Y containing different SiO_2/Al_2O_3 ratios as a result of the different protocols used for the hydrothermal treatment of the parent zeolites Y. In general, the higher the SiO_2/Al_2O_3 ratio, the less Brønsted acid sites are associated with the zeolite framework. Thus, USY CBV 720 contains more acidic sites (of similar acid strength) compared to CBV 760. Furthermore, both types of proton-exchanged zeolites are characterized by an excellent accessibility to their Brønsted acid sites due to the existence of mesopores (in the case of USY CBV 720 and 760) and to the large external surface area of small crystallites (in the case of H-BEA 25). Among the examined zeolites USY CBV 720 and H-BEA 25 give the best results (entries 3 and 5). Nevertheless, with these materials, the activity of **1a** is limited compared to the homogeneous reaction with TFA. Thus, it appears that the Brønsted acidity stemming from the zeolitic framework is not sufficient for good catalysis of **1a**. Next, we investigated the influence of commercial sulfonated polymers on the performance of **1a** and **1b** in the model reaction. In the presence of amberlyst® 15, a macroreticular styrene-divinylbenzene resin with sulfonic acid functionalities, almost no reaction occurs with diamine **1a** (entry 6). On the other hand, with sulfonated fluoropolymers nafion® SAC-13 and NR50, good yields and good to excellent enantioselectivities are obtained for the model reaction catalyzed by **1a** and **1b** (entries 7–11). From both materials, nafion® NR50 consisting of pure polymer beads, gives the highest activity, whereas in the presence of nafion® SAC-13, a silica-polymer nanocomposite, diamine **1b** shows better enantioselectivity but lower activity. Previously, we reported the synthesis of different types of sulfonated ordered micro- and mesoporous carbon and silica/carbon nanocomposites.[20,21] A selection of these materials

was examined as acid support for diamines **1a** and **1b** in the model reaction (entries 12–18). A detailed description of the synthesis procedure and physicochemical properties of these materials is provided in the Supporting Information. Interestingly, with these materials, a similar trend as with the commercial polymers is observed, namely that with the silica-free materials (entries 16–18) catalysts **1a** and **1b** show a better overall performance in the model reaction. As mentioned in our previous report on homogeneous catalysis with diamines **1a** and **1b**, the strength of the acid additive is crucial for efficient catalysis.[18] Hence, we presume that the acidity of the silica-containing supports is not sufficient for efficient catalysis with diamines **1a** and **1b**. Plausibly, the acidic strength of the sulfonic acid groups in these materials is leveled upon H-bond interaction with the surrounding free silanol groups in comparison to the silica-free supports. Based on the screening results, the commercial sulfonated polymers nafion® NR50 and SAC-13 emerge as most promising supports for the immobilization of diamines **1a** and **1b** and therefore were selected for further investigation.

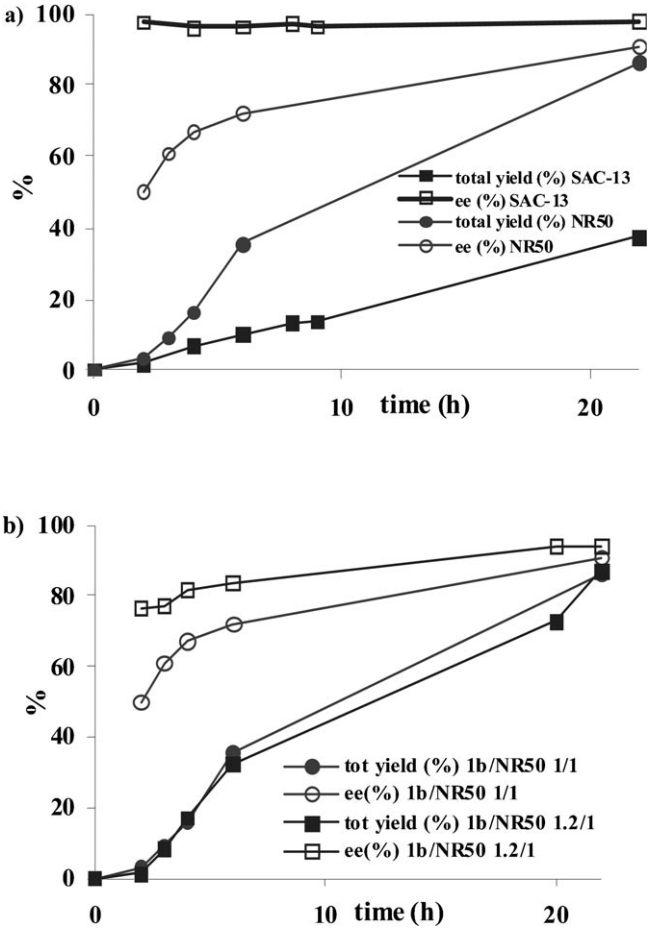


Figure 1. a) Comparison of yield (%) and *ee* (%) *versus* time in the model reaction catalyzed by **1b/**nafion® NR50 and **1b/**nafion® SAC-13. **b**) Influence of catalyst loading on initial activity and enantioselectivity of **1b/**nafion® NR50.

In order to gain more insight in the kinetics of the **1b**/nafion® catalytic system, the model reaction was monitored in time for both nafion® types. Figure 1 (panels **a** and **b**) shows that for nafion® NR50, together with the yield, the enantiomeric excess of the *syn*-aldol product is increasing as a function of time. With this nafion® type support, in the absence of **1b**, the branched aldol product is obtained in 47% yield as a racemic mixture after 20 h of reaction by general acid catalysis. Thus, the initial enantioselectivity of **1b** in the model reaction is low due to competing catalytic activity of free Brønsted acid sites.

Increasing the catalyst loading to a 1.2/1 molar ratio **1b**/nafion® NR50 instead of 1/1, has a favourable influence on the initial enantioselectivity, although as could be expected, with a small decline in initial activity (Figure 1, panel **b**). Nafion® SAC-13 acts as a weaker acid catalyst and yields only 8% of the branched aldol product after 20 h in the absence of **1b**. Consequently, the reaction with **1b**/nafion® SAC-13 proceeds with very high (initial) enantioselectivity but at the expense of its activity (Figure 1, panel **a**). With regard to the efficiency of the catalytic system, further optimization of the reaction conditions was conducted for **1b**/nafion® NR50 (Table 2). In consistency with our previous findings for the homogeneous reaction with TFA,[18] the addition of 2,4-dinitrophenol (DNP) as a co-catalyst is beneficial to both the ac-

Table 2. Optimization of catalytic system **1b**/nafion® NR50 in the model reaction.[a]

Entry	Conditions (conc. aldehyde, *T*)	Yield[b][%]	rr[b] *b/l*	*dr*[b] *syn/anti*	*ee*[c] [%]
1[d]	0.125 M, r.t.	86	4/1	2/1	91
2	**0.125 M, r.t.**	**87**	**5/1**	**5/2**	**94**
3[e]	0.125 M, r.t.	7	8/1	2/1	88
4[f]	0.125 M, r.t.	90	5/1	3/1	95
5[g]	0.25 M, r.t.	93	3/1	2/1	92
6	0.125 M, 40 °C	82	2/1	2/1	86
7	0.125 M, 45 °C	91	2/1	2/1	86
8	0.25 M, 45 °C	95	2/1	3/2	80

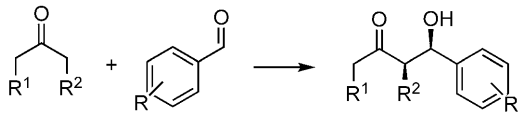
[a] All reactions were carried out under neat conditions in 2-butanone with 18 mol% of **1b** and 15 mol% of nafion® NR50 and analyzed after 20–22 h, unless indicated otherwise.
[b] Determined with chiral GC and verified with ^{1}H NMR (rr = regioisomer ratio, *b/l* = ratio of branched and linear products).
[c] The *ee* of the major *syn*-isomer, determined by chiral GC.
[d] With **1b**/nafion® NR50 ratio of 1/1.
[e] Reaction in DCM/2-butanone 3/1
[f] With 15 mol% of DNP (2,4-dinitrophenol) as co-catalyst.
[g] After 44 h of reaction.

tivity and selectivity of **1b** in the model reaction (entry 4). Further, with a more concentrated solution higher yields but lower regio- and stereoselectivities are obtained (entries 5 and 8). Elevating the temperature up to 45 °C has a similar effect on the catalytic performance of **1b**/nafion® NR50 (entries 6–8).

To further explore the scope of the optimized catalytic system, **1b/**nafion® was applied in the aldol reaction of various ketones and aromatic aldehydes under optimized conditions (Table 3). As for the model reaction, nafion®-supported **1b** shows great catalytic performance in 2-butanone (entries 3–6). With the symmetrical 3-pentanone as ketone donor (entries 7–12), high activity and enantioselectivity could be obtained by increasing both the temperature and aldehyde concentration (entry 10). Furthermore, good yields and good to excellent enantioselectivities of up to 98% *ee* are achieved with hydroxyacetone as ketone donor (entries 15–20). With acetone and 2-pentanone (entries 13 and 14), the catalytic performance of **1b/**nafion® NR50 is limited, as also was observed for the homogeneous reactions with TFA.[18]

In order to affirm the heterogeneous nature of the **1b**/nafion® NR50 catalytic system, a dual split test was accomplished (see Supporting Information for details). The model reaction was catalyzed by **1b**/nafion® NR50 under optimized conditions for 6 h, yielding 36% of aldol product. Then, after removal of the **1b**/nafion® beads, the supernatant was equally transferred into two different reaction vessels for further stirring. Since diamine **1b** requires an acidic additive to act as a catalyst,[18] in fact no further reaction could be expected in the supernatant solution, even in the presence of free diamine **1b**. Hence, in order to properly probe leaching of **1b** fresh, unloaded nafion® NR50 beads were added to one vessel. After 20 h of stirring, analysis of both solutions demonstrated that for the nafion®-free mixture the yield of aldol product was quasi unchanged whereas with freshly added nafion® NR50 the yield was only marginally increased with 4% (Figure 2). These results indicate that dissociation of diamine **1b** from the nafion® NR50 beads was negligible and catalysis with **1b**/nafion® NR50 occurs mainly heterogeneously. Furthermore, the absence of characteristic signals

Table 3. Application of the optimized system in the aldol reaction of different linear ketones and aromatic aldehydes.



Entry	nafion®	R^1, R^2, R	time [h]	Yield[b][%]	*dr*[b] *syn/anti*	*ee*[c] [%]
1	NR50	H, Me, 4-CF_3	22	87	5/2	94
2[d]	SAC-13		30	78	5/2	96
3	NR50	H, Me, 2-NO_2	44	99	1/1	93
4[e]	NR50		20	99	1/1	90
5	NR50	H, Me, 2-Cl	20	98	2/1	98
6[e]	NR50		20	96	7/2	98
7	NR50	Me, Me, 4-CF_3	48	24	2/1	69
8[e]	NR50		94	80	3/1	87
9[e,f]	NR50		20	76	3/1	91
10[e,f]	NR50		44	91	2/1	93
11[d]	SAC-13		44	8	4/1	96
12[d,e,f]	SAC-13		44	19	3/1	96
13	NR50	H, H, 4-CF_3	24	81	–	65
14	NR50	H, Et, 4-CF_3	48	37	2/1	56
15	NR50	H, OH, 2-NO_2	24	49	8/1	92
16[e]	NR50		20	79	4/1	87
17[d,e,f]	SAC-13		20	80	7/1	86
18	NR50	H, OH, 4-NO_2	24	49	4/1	94
19[e]	NR50		20	84	2/1	98
20	NR50	H, OH, 4-CF_3	24	86	7/2	89

[a] All reactions were carried out under neat conditions with aldehyde (0.125 M), 18 mol% of catalyst and 15 mol% of acid additive at room temperature, unless indicated otherwise.
[b] Determined with chiral GC or ^{1}H NMR.
[c] The *ee* of the major *syn*-isomer, determined by chiral GC or HPLC.
[d] With a **1b**/nafion® SAC-13 ratio of 1/1.
[e] Reaction at 45 °C.
[f] With 0.25 M aldehyde.

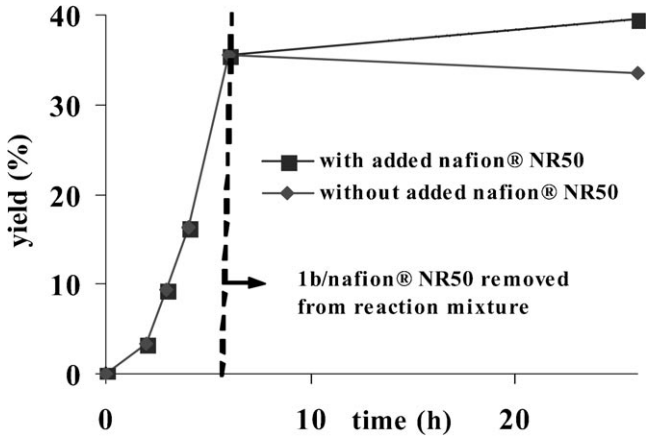


Figure 2. Dual split test.

from **1b** in the ^{1}H NMR spectrum of the nafion®-free supernatant confirms these findings (Figure S1, Supporting Information).

Next, the recycling capacity of **1b**/nafion® NR50 was investigated in the optimized model reaction at 45 °C. After each run, the reaction mixture was removed by simple decantation and fresh reagents were added to the recovered polymer beads. As shown in Table 4, the activity remains unchanged in the first two runs. In the subsequent third cycle, the activity of the recycled catalyst starts declining but the enantioselectivity is maintained. Furthermore, by prolonging the reaction time, good yields are still achieved after the fifth run.

Finally, the implementation of the immobilized chiral catalyst in a continuous system, rather than working under batch conditions, is the ultimate goal when considering large-scale synthesis. Recently, Odedra and Seeberger reported the first example of an organocatalytic asymmetric aldol reaction conducted in a microreactor under homogeneous conditions.[22] Almost simultaneously, a continuous flow system has been developed for the Mannich reaction of aldehydes and ketones with a covalently supported proline/polystyrene catalyst.[23] Hence, we integrated the loaded **1b**/nafion® NR50 beads in a fixed catalyst bed which was then continuously fed with a preheated aldehyde containing ketone solution (for details on the set-up and operating conditions, see Experimental Section and Supporting Information). The out-coming flow was monitored for 11 h and samples were taken at several time intervals. As shown in Figure 3 (panel **a**) the **1b**/nafion® NR50 fixed bed shows good cumulative activity in the model reaction under continuous conditions. To our delight, the (initial) diastereo- and enantioselectivity of the catalyst were significantly improved with respect to the batch reactions (with *syn*/*anti* = 3/1 and *ee* values of up to 97%, Figure 3, panel **b**). To the best of our knowledge, this is the first application of a chiral non-covalently immobilized amino catalyst in a continuous flow system.

Table 4. Recycling and reuse of **1b/**nafion® NR50 in the model reaction at 45 °C under optimized conditions.

Entry	Cycle	Time (h)	Yield[a] [%]	*ee*[b] [%]
1	1st	24	91	86
2	2nd	24	92	87
3	3rd	24	82	87
4	4th	24	74	87
5[c]	5th	68	82	81

[a] Determined with GC.
[b] The *ee* of the *syn*-isomer, determined by chiral GC.
[c] Yield after 44 h of reaction = 73%.

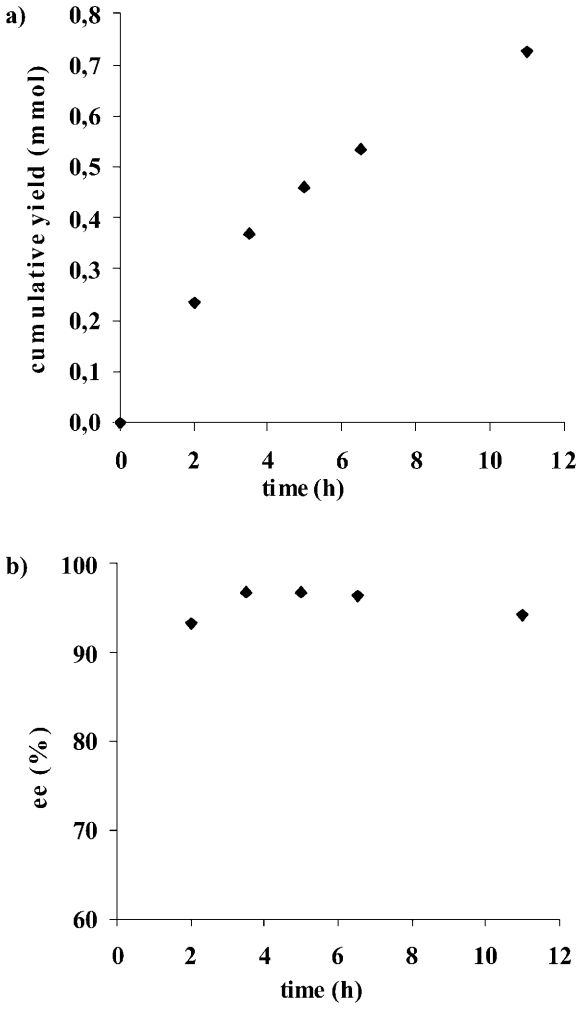


Figure 3. Continuous flow reaction.

Conclusions

We have achieved the non-covalent immobilization of chiral primary amino acid-derived diamines on both organic and inorganic sulfonated solid supports

through acid-base interactions. 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. Screening a series of home-made micro- and mesoporous carbon and silica/carbon materials and commercial polymers revealed a similar trend with regard to the catalytic performance of the immobilized diamines. With silica-containing supports lower activities are attained compared to the silica-free materials, which we presume is attributed to the reduced acidity strength of the Brønsted acid sites. With the sulfonated fluoropolymer nafion® NR50 as support an optimal balance between activity and stereoselectivity was established for diamine **1b** in the model reaction and hence, this support was chosen for further investigation. With **1b**/nafion® NR50 under optimized conditions aldol products of various challenging linear ketones and aromatic aldehydes were obtained in high yields and with excellent enantioselectivities for the *syn*-product (up to 98% *ee*). Catalysis with **1b**/nafion® NR50 was shown to occur truly heterogeneously and the robustness of the non-covalently immobilized catalyst was illustrated by the possibility of extending its use by simple recovery and recycling. Ultimately, the success of the **1b**/nafion® NR50 catalytic system was demonstrated in a reactor set-up under continuous flow conditions. We believe this work represents a valuable contribution to the current search for more efficient, heterogeneous systems in asymmetric organocatalytic transformations.

Experimental Section

Representative Procedure for Aldol Reaction

Batch reactions: Organocatalyst **1b** (18 mol%) and the acid additive (15 mol%) were mixed together with the ketone at room temperature, followed by the addition of the aldehyde (0.125 M). The reaction mixture was stirred at room temperature or 45 °C for the given time and extracted with ethyl acetate and water. The organic phase was analyzed with ^{1}H NMR and chiral GC to calculate yields and regio- and diastereomeric ratios. The enantiomeric excess (*ee*) was determined with chiral GC or chiral HPLC.

Continuous reactions: A preheated solution of 2-butanone and 4-(trifluoromethyl)benzaldehyde (0.125 M) was fed continuously with a syringe pump (flow rate 1 mL h^{-1}) over a catalyst bed consisting of 375 mg nafion® NR50 pellets (0.3 mmol) preloaded with 134 mg **1b** (0.36 mmol). The outlet of the reactor was sampled at different time intervals. The crude mixtures were directly analyzed by chiral GC. A more detailed picture of the reactor set-up is provided in the Supporting Information.

Acknowledgements

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