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Chiral Ionic Liquids Bearing *O*-Silylated α,α-Diphenyl (*S*)- or (*R*)-Prolinol Units: Recoverable Organocatalysts for Asymmetric Michael Addition of Nitroalkanes to α,β-Enals

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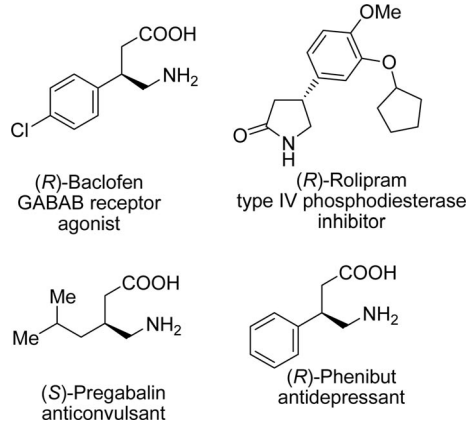
Chiral ionic liquids bearing *O*-silylated α,α-diphenyl (*S*)- or (*R*)-prolinol units tagged to the imidazolium cation were synthesized and their activity as catalysts in the Michael addition of nitroalkanes to α,β-unsaturated aldehydes was evaluated. Respective (*S*) or (*R*) adducts were obtained in the reactions in high yields (up to 95 %) and with high enantioselectivity (up to 99 % *ee*). Remarkably, the immobilized organocatalysts could be used five times without any decrease in product yields or *ee* values. (*R*)-Michael adducts could be easily transformed into the most active (*R*) enantiomers of medications Phenibut, Baclofen, and Rolipram for the treatment of CNS disorders.

Introduction

γ-Aminobutyric acid (GABA) is one of the most important inhibitory neurotransmitters of the mammalian central nervous system (CNS).[1] The derangements of GABA'ergyc system are responsible for the appearance and development of many mental disorders such as epilepsy, Huntington's and Parkinson's diseases, anxiety, and pain.[2] Unfortunately, GABA itself is inefficient for therapeutic purposes due to its hydrophilic behavior that prevents its penetration through the blood–brain barrier.[3] Thereby GABA lipophilic derivatives are commonly used for the treatment of CNS disorders.[4] Among them, Baclofen,[5] Rolipram,[6] Pregabalin,[7] and Phenibut[8] have found wide application. Enantiomers of these chiral medications exhibit quite different levels of activity;[9] therefore, efficient methods for their enantioselective preparation are needed.

Chiral GABA derivatives **1** can be synthesized by enzymatic[10] or chemical methods,[11] including those where asymmetric organometal[12] or organocatalysts[13–17] are used (Scheme 1). One of the simplest and most convenient methods is based on the asymmetric addition of nitroalkanes **2** to α,β-enals **3** (Scheme 2).[14–17] Generally, this reaction is catalyzed by α,α-diarylprolinol silyl ethers **4** that activate the aldehyde molecule through the formation of iminium cations **5** and give rise to enantiomeric enriched γ-nitroaldehydes **6**.[15–17] The regeneration of rather expensive catalysts **4** is however a challenge, and as a rule, they may be used only once. Therefore, the development of recoverable versions of α,α-diarylprolinol ethers is an important issue in terms of both atom economy and green chemistry. Moreover, the immobilization of the catalysts facilitates the isolation and purification of products **6**.



Scheme 1. Biologically active chiral GABA analogues **1**.

There are few examples of recoverable organocatalysts for Michael reactions, in particular between carbonyl compounds and nitroalkenes where an alternative enamine-type activation of a nucleophile is put into effect.[18] The chiral inductor in these catalysts is tagged to a polymer,[19] dendritic,[20] perfluoroalkyl,[21] or ionic group.[22] Yet, recoverable organocatalysts of the reactions that proceed via an iminium ion formation step had not been reported until

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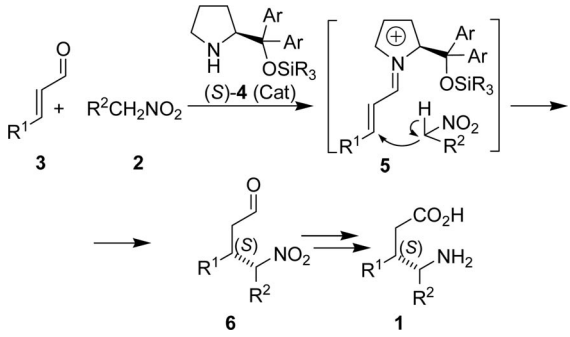


Scheme 2. Asymmetric addition of nitroalkanes **2** to α,β-enals **3** in the presence of **4**.

recently. We have found lately[23a] that α,α-diphenylprolinol **7a** with an ionic liquid moiety catalyzes the addition of dialkyl malonates to α,β-enals and can be used several times without any decrease in activity or enantioselectivity. Furthermore, the majority of or even all known pyrrolidine-based recoverable organocatalysts for asymmetric Michael reactions, including compound **7a**, have the (*S*) configuration of the C2 (C5) carbon atom and allow only one of the two enantiomers of the corresponding Michael adducts to be synthesized.[18–23] It should be noted that, with respect to curing CNS disorders, (*S*) enantiomers of γ-amino acid derivatives **1** being formed in the presence of catalysts (*S*)-**4** are usually less active than the corresponding (*R*) enantiomers (Scheme 2).[9]

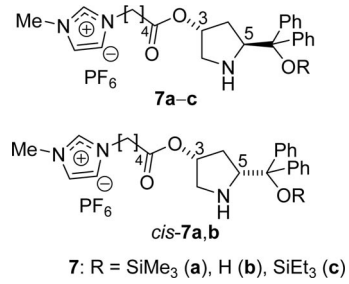
In this paper we report for the first time that (*S*)- or (*R*)-Michael adducts can be obtained from nitroalkanes **2** and α,β-unsaturated aldehydes **3** in high yields and with high enantioselectivity in the presence of recoverable chiral ionic liquids containing silylated (*S*)- or (*R*)-prolinol units that are tagged to the imidazolium cation.

Results and Discussion

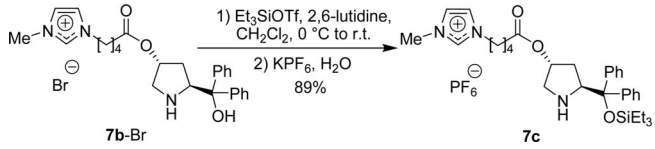
trans-(*S*)-Prolinol derivatives **7a**–**c** having the methylimidazolium cation and their analogues *cis*-**7a**,**b** with the *cis* orientation of the substituents at the 3- and 5-positions of the pyrrolidine ring were used as catalysts (Scheme 3). Compounds **7** and *cis*-**7** are not enantiomers. However, taking into account that carbon atoms C5 adjacent to the catalytic site in the catalysts have different configurations [(*S*)- in **7** and (*R*)- in *cis*-**7**], we anticipated that configurations of respective reaction products may also differ.

O-Triethylsilyl-α,α-diphenyl-(*S*)-prolinol **7c** modified with the methylimidazolium cation was prepared by silylation of known (*S*)-prolinol derivative **7b**-Br[23] with subsequent replacement of the Br^- anion for the PF_6^- anion (Scheme 4).

α,α-Diphenyl-(*R*)-prolinol derivatives *cis*-**7a**,**b** were synthesized by a sequence of reactions including the esterification of known (3*R*,5*R*)-1-benzyl-5-(hydroxydiphenylmethyl)-pyrrolidin-3-ol (**8**)[24] with 5-bromopentanoic acid in the presence of *N,N′*-dicyclohexylcarbodiimide (DCC)/4-dimethylaminopyridine (DMAP), alkylation of 1-methylimidazole with bromoester **9**, catalytic hydrogenation of imidazolium salt **10**, followed by transformation of bromide **11** into hexafluorophosphate *cis*-**7b** or its OTMS derivative *cis*-**7a** by anion metathesis and silylation reactions (Scheme 5). Total yields of compounds *cis*-**7a**,**b** were 57–58%.



Scheme 3. Studied organocatalysts.



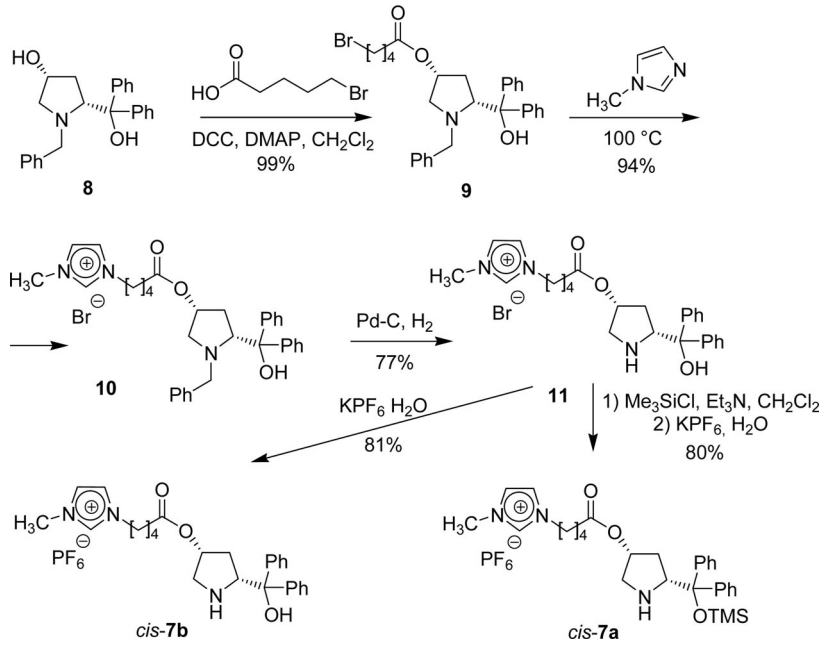
Scheme 4. Synthesis of *O*-TES-α,α-diphenyl-(*S*)-prolinol derivative **7c** modified with the ionic liquid fragment.

To the best of our knowledge, compounds *cis*-**7a** and *cis*-**7b** are the first representatives of immobilized pyrrolidine-based organocatalysts for asymmetric Michael reactions that have the (*R*) configuration of the C5 atom. They melt at 58 and 99 °C, respectively, and can be described as ionic liquids.[28]

First of all, to find suitable reaction conditions we examined the reaction of nitromethane **2a** with *trans*-cinnamaldehyde **3a** in the presence of immobilized *O*-TMS-α,α-diphenyl-(*S*)-prolinol **7a** (10 mol-%) in various solvents and under neat conditions. The reactions were performed at room temperature for 24 h with a **2a**/**3a** ratio of 3:1. High conversions of starting compounds (95–99%) were achieved in all runs. Moreover, ionic catalyst **7a**, unlike homogeneous catalysts **4**,[14–17] worked well even without an acidic or basic additive ($PhCO_2H$ or LiOAc). Evidently, these were ionic groups that played their role in the studied reactions. As a rule, compound (*S*)-**6a** was the only reaction product (90–95% *ee*), however, in water (Table 1, Entry 8) appeared lower.

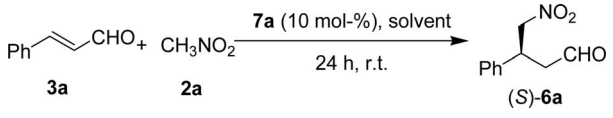
The final criteria for the solvent selection were results of reactions in the presence of recovered **7a**. After solvent removal under reduced pressure and separation of product (*S*)-**6a** by extraction, a fresh solution of **2a** and **3a** in the same solvent was added to the residue. In most cases (Table 1, Entries 1–7) the recovered catalyst was less active than the fresh one, though *ee* values of (*S*)-**6a** remained nearly the same.

However, in 96% alcohols, both the rates and selectivities were retained in the second cycle (Table 1, Entries 9–11). Among them, 96% MeOH, where the highest conversions



Scheme 5. Synthesis of α,α-diphenyl-(*R*)-prolinol derivatives *cis*-**7a**,**b** bearing the ionic liquid fragment.

Table 1. Solvent screening in the reaction of nitromethane **2a** with *trans*-cinnamaldehyde (**3a**) in the presence of compound **7a**.[a]



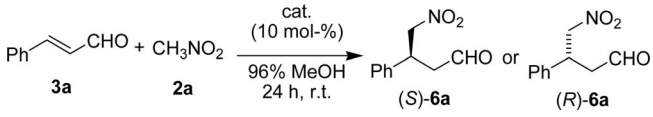
Entry	Solvent	% Conversion[b] (cycle)	% *ee*[c] (cycle)
1	C_6H_6	>99 (1), 54 (2)	91 (1), 91 (2)
2	CH_2Cl_2	>99 (1), 58 (2)	94 (1), 94 (2)
3	Et_2O	>99 (1), 60 (2)	94 (1), 94 (2)
4	neat	>99 (1), 95 (2)	90 (1), 89 (2)
5	MeOH (abs)	>99 (1), 52 (2)	95 (1), 94 (2)
6	EtOH (abs)	>99 (1), 85 (2)	94 (1), 93 (2)
7	*i*PrOH (abs)	>99 (1), 55 (2)	93 (1), 93 (2)
8	H_2O	95[d] (1)	n.d.
9	MeOH (96% aq.)	>99 (1), >99 (2), >99 (3)	94 (1), 94 (1), 94 (1)
10	EtOH (96% aq.)	>99 (1), >99 (2), >99 (3)	91 (1), 92 (1), 92 (1)
11	*i*PrOH (96% aq.)	>99 (1), >99 (2), 73 (3)	93 (1), 93 (1), 93 (1)

[a] All reactions were carried out with **3a** (26 mg, 0.2 mmol), **2a** (37 mg, 0.6 mmol), and the indicated solvent (0.4 mL) in the presence of catalyst **7a** (10 mol-%, 13 mg) at room temperature for 24 h. [b] The conversion of *trans*-cinnamaldehyde was estimated by ^{1}H NMR spectroscopy (1 H at δ = 6.73 ppm for **3a** and 2 H at δ = 4.65 ppm for **6a**). [c] Determined by chiral HPLC analysis of the isolated product. [d] The purity was below 20%.

and *ee* values were observed in the second and in the third cycles, was identified as the solvent of choice (Table 1, Entry 9).

Next, we compared catalysts **7a**–**c** and *cis*-**7a**,**b** (10 mol-% each) in the model reaction between **2a** and **3a** in 96% MeOH. Unlike catalyst **7a**, its analogue **7c** with a bulkier TES fragment as well as (*S*)-proline were nearly inactive under the studied conditions (Table 2, Entry 4). Compound **7b** with a free OH group also exhibited lower activity and selectivity than *O*-TMS-(*S*)-prolinol **7a** (Table 2, Entry 2). The difference was especially noticeable in dry MeOH (Table 2, Entry 3). Favorable impact of water on Michael and some other asymmetric reactions is known.[14,25,26] It is consistent with our finding that in 96% MeOH compounds **2a** and **3a** were completely converted in the presence of homogeneous catalyst **4a** (R = Me, Ar = Ph) into adduct (*S*)-**6a** (Table 2, Entry 5), whereas in dry MeOH having no activating additives compound (*S*)-**6a** reportedly was formed in as low as 12% yield.[17]

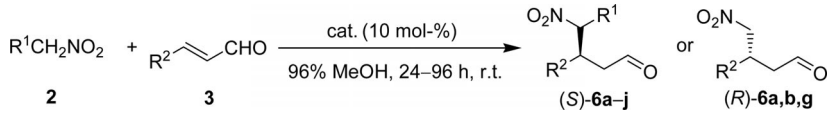
Table 2. Catalyst screening.[a]



Entry	Catalyst	Time [h]	Product	% Conversion[b]	% *ee*[c]
1	**7a**	24	(*S*)-**6a**	>99	94
2	**7b**	48	(*S*)-**6a**	>99	70
3[d]	**7b**	48	(*S*)-**6a**	66	68
4	**7c**	24	(*S*)-**6a**	5 (11[e])	n.d.
5	**4a**	24	(*S*)-**6a**	>99 (12[d,f], 90[g])	95 (95[g])
6	*cis*-**7a**	24	(*R*)-**6a**	>99	94
7	*cis*-**7b**	72	(*R*)-**6a**	>99	62

[a] Unless otherwise specified, all reactions were carried out with **3a** (26 mg, 0.2 mmol), **2a** (37 mg, 0.6 mmol), and 96% aq. MeOH (0.4 mL) in the presence of the catalyst (10 mol-%) at room temperature over the indicated time. [b] The conversion of *trans*-cinnamaldehyde was estimated by ^{1}H NMR spectroscopy (1 H at δ = 6.73 ppm for **3a** and 2 H at δ = 4.65 ppm for **6a**). [c] Determined by chiral HPLC analysis of the isolated product. [d] The reaction was carried out by using dried methanol. [e] Conversion in the presence of (*S*)-proline (10 mol-%) as a catalyst. [f] Yield according to ref.[17] in the presence of **4** (5 mol-%) without any additives. [g] Data according to ref.[15] in the presence of **4** (10 mol-%) and benzoic acid (10 mol-%).

Table 3. Scope of the Michael addition of nitroalkanes **2** to α,β-unsaturated aldehydes **3**.[a]



2 **3** (*S*)-**6a–j** (*R*)-**6a,b,g**

Entry	Catalyst	Time [h]	R^1, R^2 / Product	% Yield[b]	% *ee*[c]
1	**7a**	24	H, Ph / (*S*)-**6a**	84 (82[d], 70[e], 80[f], 90[g])	94 (96[d], 96[e], 95[f], 95[g])
2	*cis*-**7a**	24	H, Ph / (*R*)-**6a**	86 (55[e])	94 (87[e])
3	**7a**	24	H, 4-ClPh / (*S*)-**6b**	91 (75[d], 69[e], 61[f], 83[g])	90 (97[d], 95[e], 90[f], 94[g])
4	*cis*-**7a**	24	H, 4-ClPh / (*R*)-**6b**	92 (73[d])	92 (96[d])
5	**7a**	24	H, 4-BrPh / (*S*)-**6c**	95 (65[f], 87[g])	91 (92[f], 95[g])
6	**7a**	24	H, 4-NO_2Ph / (*S*)-**6d**	64 (72[d], 60[e], 76[g])	93 (99[d], 98[e], 95[g])
7	**7a**	48	H, 4-MeOPh / (*S*)-**6e**	87 (77[d], 71[e], 67[f], 88[g])	93 (99[d], 96[e], 92[f], 95[g])
8	**7a**	24	H, 4-FPh / (*S*)-**6f**	80 (66[f])	93 (96[f])
9	**7a**	24	H, 3-*c*-C_5H_9O-4-MeOPh / (*S*)-**6g**	80 (62[e])	90 (98[e])
10	*cis*-**7a**	24	H, 3-*c*-C_5H_9O-4-MeOPh / (*R*)-**6g**	83	89
11	**7a**	48	H, ferrocenyl / (*S*)-**6h**	51	99
12	**7a**	96	H, Me / (*S*)-**6i**	55 (60[e], 67[f])	85 (87[e], 81[f])
13	**7a**	48	Et, Ph / (*S*)-**6j**	94	*syn* 94/*anti* 98 (*dr* 1:1.25)

[a] Unless otherwise specified, reactions were carried out by using of α,β-unsaturated enals **3** (0.5 mmol), nitroalkane **2** (1.5 mmol), and 96 v.-% aqueous MeOH (1 mL) in the presence of **7a** or ***cis*-7a** (10 mol-%, 33 mg) at room temp. for the indicated time. [b] Isolated yield. [c] Determined by chiral HPLC analysis of the isolated product. [d] Data according to Ref.[15] [e] Data according to Ref.[14] [f] Data according to Ref.[17] [g] Data according to Ref.[16]

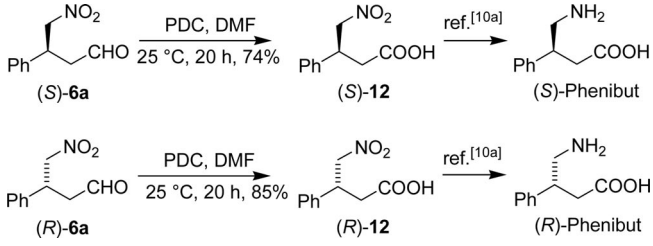
To our satisfaction, enantiomer (*R*)-**6a** was the major product of the reactions between compounds **2a** and **3a** in the presence of catalysts *cis*-**7a** and *cis*-**7b**. Moreover, conversions and enantioselectivities in these reactions were similar to those in the reactions catalyzed by *trans*-isomers **7a** and **7b**, where opposite enantiomer (*S*)-**6a** was formed.

Catalysts **7a** and *cis*-**7a** that exhibited the best performance in the model reaction were then examined in reactions between nitroalkanes **2** and various α,β-enals **3**. The reactions were carried out under the optimized conditions for 24–96 h. The molar ratio of compounds **2**/**3** was 3:1 (Table 3). High yields (up to 95%) and *ee* values (up to 93%*ee*) of adducts **6** were attained in reactions of cinnamaldehyde derivatives **3** bearing weak acceptor (4-Cl, 4-Br, 4-F) or donor substituents (4-OMe, 3-O-*c*-C_5H_9-4-OMe) in the aromatic ring, with nitromethane **2a**. 4-Nitrocinnamaldehyde (**3d**), 3-ferrocenylpropenal (**3h**), and crotonaldehyde (**3i**) were less active in the studied reactions (yields 51–64%), although *ee* values of products **6d** and **6h** remained high (93–99%*ee*). 1-Nitropropane (**2b**) and cinnamaldehyde (**3a**) afforded diastereomeric adducts **6j** with 94–98%*ee* under the studied conditions (Table 3, Entry 13).

It should be noted that yields of γ-nitroaldehydes **6** in the presence of catalysts **7a** and *cis*-**7a**, as a rule, are higher than those reported for prolinol **4** catalyzed reactions; however, the *ee* values were slightly lower.[14–17] Apparently, the spacer and/or ionic groups at the 3-position of immobilized catalyst **7** affect the reaction transient state. α,β-Unsaturated ketones [cyclohexen-3-on and (*E*)-4-(4-chlorophenyl)-but-3-en-2-one] did not react with **2a** in the presence of **7a** under the studied conditions.

Catalysts **7a** and *cis*-**7a** allowed both enantiomers of compounds **6a**, **6b**, and **6g** to be synthesized. The (*R*) enantiomers of the compounds are the key intermediates for the preparation of the most active components of Baclofen, Rolipram, and Phenibut (Table 3, Entries 1–4, 9, and 10) used in the treatment of CNS disorders. As far as we know, this is the pioneering synthesis of (*R*)-Michael adducts in the presence of recoverable chiral organocatalysts.

The absolute configurations of adducts (*S*)-**6a** and (*R*)-**6a** were established by their oxidation to known γ-nitroacids (*S*)-**12** and (*R*)-**12** with pyridinium dichromate (PDC) in DMF and comparison of the optical rotations with literature data.[10a] Compounds (*S*)-**12** and (*R*)-**12** could be easily converted into respective Phenibut enantiomers by the reported method (Scheme 6).[10a]



Scheme 6. Formal synthesis of (*S*)- and (*R*)-enantiomers of Phenibut.

An advantage of immobilized catalysts **7** against homogeneous catalysts **4** is their recoverability. They could be used five times without any decrease in enantioselectivity.

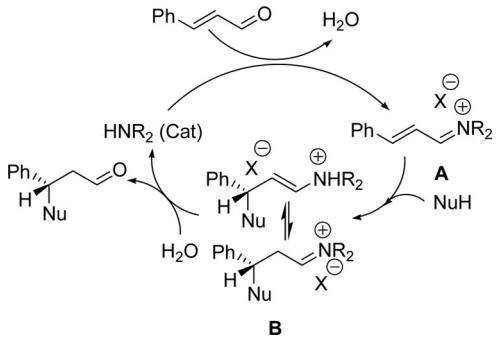
Yet, the activity of catalysts **7**, judging by the conversion of the starting compounds and the reaction time, became lower after the third regeneration (cycle 4; Table 4). The reason for that is so far not clear. Apparently, catalyst deactivation is not caused by the hydrolysis of the *O*-TMS group. According to the ^{1}H NMR spectroscopic data, catalyst **7a** remained unchanged in 96% MeOH at room tem-

Table 4. Recycling of catalysts **7a**, *cis*-**7a**, and **7b** in the reaction between compounds **2a** and **3a**.[a]

Cycle	Catalyst **7a**			Catalyst *cis*-**7a**			Catalyst **7b**		
	Time [h]	% Conversion[b]	% *ee*[c] of (*S*)-**6a**	Time [h]	% Conversion[b]	% *ee*[c] of (*R*)-**6a**	Time [h]	% Conversion[b]	% *ee*[c] of (*S*)-**6a**
1	24	>99 (>99[d], >99[e])	94 (94[d], 94[e])	24	>99	94	48	>99	70
2	24	>99	94	24	>99	93	48	>99	68
3	24	>99	94	24	>99	93	48	92	69
4	48	>99	94	48	>99	93	48	80	70
5	72	>99	94	72	>99	93	48	66	69

[a] All reactions were carried out with **2a** (37 mg, 0.6 mmol), **3a** (26 mg, 0.2 mmol), and 96% aqueous MeOH (0.4 mL) in the presence of **7** (10 mol-%) at room temperature. After the indicated time the catalyst was separated from the products by addition of ether (2 mL, 1 mL) and reused. [b] The conversion of *trans*-cinnamaldehyde (**3a**) was estimated by ^{1}H NMR spectroscopy (1 H at δ = 6.73 ppm for **3a** and 2 H at δ = 4.65 ppm for **6a**). [c] Determined by chiral HPLC analysis of the isolated product. [d] Reagents **2a** (37 mg, 0.6 mmol) and **3a** (26 mg, 0.2 mmol) were added to a mixture of **7a** (13 mg, 0.02 mmol) and 96% MeOH (0.4 mL) that had been kept for 72 h. [e] Compound **2a** (37 mg, 0.6 mmol) was added to a mixture of **3a** (26 mg, 0.2 mmol), **7a** (13 mg, 0.02 mmol), and 96% MeOH (0.4 mL) that had been kept for 2 weeks.

perature for at least 72 h and completely retained its catalytic activity (Table 4, Entry 1). It cannot be explained by catalyst leaching into the organic solvent (Et_2O) during the work-up procedure: a loss of catalyst **7a** was less than 20 wt.-% over five cycles. The catalysts deactivation may occur at the iminium ion **A** formation step (Scheme 7). A mixture of aldehyde **3a**, catalyst **7a**, and 96% MeOH, which had been kept at room temperature for 2 weeks, afforded adduct (*S*)-**6a** upon addition of **2a** with the same conversion and enantioselectivity as that in the reaction where the reagents and the catalyst were mixed simultaneously (Table 4, Entry 1). Yet, partial decomposition of catalyst **7a** took place judging by changes in its ^{1}H NMR spectra.



Scheme 7. Catalytic cycle of asymmetric Michael reactions involving the formation of iminium intermediates **A** and **B**.[27]

Gradual deactivation of catalysts **7** might also be a result of side reactions of cations **B** that led to catalytically inactive byproducts (Scheme 7). After each cycle, additional signals appeared in the ^{1}H NMR spectra of recovered catalyst **7a**. Favorable impact of water (96% solution as compared to 100% MeOH) on recoverability of **7a** is also consistent with this assumption (Table 1, Entries 5 and 9). Probably, water accelerates the hydrolysis of iminium ions **B**, facilitating the generation of the Michael adduct and catalyst recovery and suppressing side reactions. Further studies are needed to identify reaction byproducts and to propose ways for extending the operation life of organocatalysts **7**.

Conclusions

In summary, we have developed a new family of recoverable organocatalysts **7** for asymmetric Michael addition of nitroalkanes **2** to α,β-enals **3** bearing O-silylated α,α-diphenyl (*S*)- or (*R*)-prolinol units tagged to the imidazolium cation. In their presence, (*S*) and (*R*) enantiomers of γ-nitroaldehydes **6**, in particular key intermediates for preparing the most active (*R*) enantiomers of medications for curing CNS disorders such as Phenibut, Baclofen, and Rolipram, have been synthesized in high yields and with high enantioselectivity. Unlike the known prolinol-type catalysts, compounds **7** could be used five times without any decrease in product yield or *ee* values, though the catalytic activity became lower after the third regeneration.

Experimental Section

General Procedure for Michael Reaction: A mixture of catalyst **7** (33 mg, 0.05 mmol, 10 mol-%), α,β-unsaturated aldehyde **3** (0.5 mmol, 1 equiv.), nitroalkane **2** (1.5 mmol, 3 equiv.), and 96% MeOH (1 mL) was stirred at room temperature for the indicated time (Tables 1–3). The solvent was evaporated under reduced pressure, and the product was extracted with Et_2O (2 × 1 mL). The combined extracts were evaporated under reduced pressure. For analytical purposes, compounds **6** were purified by column chromatography on silica gel with EtOAc/hexane (from 1:5 to 1:2). If appropriate, the catalyst was reused.

Catalyst Recycling: A mixture of *trans*-cinnamaldehyde (**3a**; 26 mg, 0.2 mmol), nitromethane (**2a**; 37 mg, 0.6 mmol), and catalyst **7** or *cis*-**7** (10 mol-%) in the indicated solvent (0.4 mL) was stirred for the indicated time (Tables 1 and 4). The solvent was evaporated in vacuo, and product **6a** was extracted with Et_2O (2 × 1 mL). The remaining catalyst was dried under reduced pressure (2 bar) and reused in the same reaction without further purification.

General Procedure for Oxidation of Aldehydes 6a Into Carboxylic Acids 12: A mixture of aldehyde **6a** (1 mmol), pyridinium dichromate (2 mmol), and DMF (1.5 mL) was stirred at room temperature for 20 h, diluted with water (30 mL), acidified with concentrated HCl (0.3 mL), and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with water (3 × 5 mL) and

dried with $MgSO_4$. The solvent was removed under reduced pressure to afford compound (*S*)-**12** or (*R*)-**12**.

Supporting Information (see footnote on the first page of this article): Procedures for preparation of all compounds; ^1H, ^{13}C, ^{19}F, and ^{31}P NMR spectra and HPLC chromatograms.

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