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Polymer-immobilized α,α-bis[bis-3,5-(trifluoromethyl)phenyl]prolinol silyl ether: synthesis and application in the asymmetric α-amination of aldehydes

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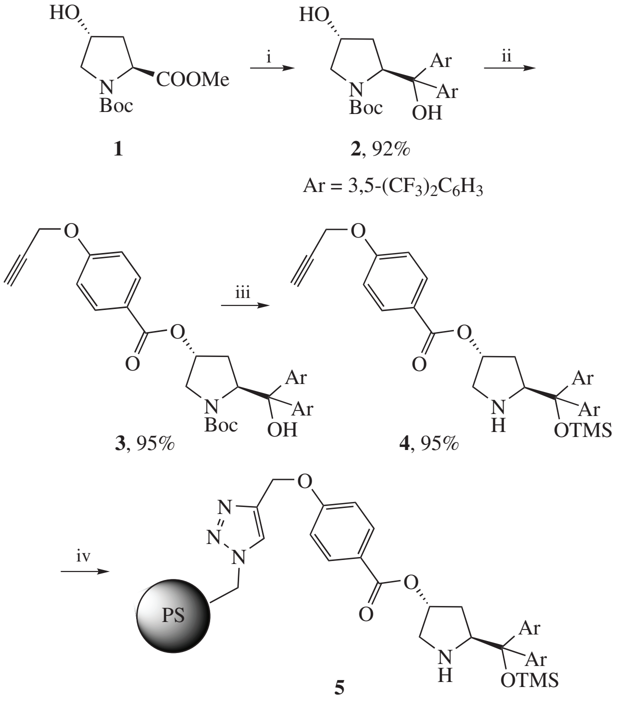
α,α-Bis[bis-3,5-(trifluoromethyl)phenyl]prolinol silyl ether anchored onto polystyrene was synthesized and tested in asymmetric α-amination of aldehydes. The catalytic activity and enantioselectivity of the immobilized catalyst persist for 3 cycles.

Chiral amino carbonyl compounds and amino alcohols are important for the synthesis of biologically active molecules and medicines.[1] Direct enantioselective α-amination of carbonyl compounds is the most efficient route to such molecules.[2] After pioneer works by List[3] and Jørgensen[4] α-amination of aldehydes and ketones with azodicarboxylates catalyzed by L-proline was used as a key step in the synthesis of valuable chiral compounds. Among them are (*S*,*S*)-ethambutol[5] and (–)-anisomycin[6] antibiotics, (*R*)-selegiline,[7] known as a remedy against Parkinson's disease, (–)-δ-coniceine alkaloid.[8] In the further works this reaction was carried out in the presence of more sophisticated organocatalysts including derivatives of *trans*-4-hydroxy-L-proline,[9–11] pyrrolidine-tetrazole,[12] quinine derivatives,[13] binaphthylphosphonium[14] and binaphthylammonium salts.[15,16] Silyl ethers of diarylprolinols are perspective catalysts of such processes,[17,18] they helped to achieve high yields and enantiomeric excess. A drawback of these catalysts is high catalyst loading (10–20 mol%). The problem can be solved by the immobilization of proline-based catalysts on the support,[19–22] that provides an easy separation after the completion of the reaction, repeated use of the catalyst and increases the efficiency of the process (TON).

We carried out the immobilization of diarylprolinol catalyst on Merrifield resin[23,24] using simple and reliable click-reaction.[25,26] A clickable derivative of prolinol **4** was synthesized *via* a 3-step procedure (Scheme 1) in an overall 83% yield. At the first step N-Boc derivative of *trans*-4-hydroxy-L-proline **1** was reacted with 3,5-bis(trifluoromethyl)phenylmagnesium bromide at –78 °C. The yield of α,α-diaryl-4-hydroxyprolinol **2** was 92% after purification by column chromatography. Acylation was employed to introduce a substituent containing triple bond into compound **2**, 4-propargyloxybenzoic acid being used as a linker for immobilization. The synthesis was carried out in the presence of DCC and catalytic amount of DMAP and compound **3** was isolated after purification by column chromatography in 95% yield. Simultaneous Boc-deprotection and silylation were achieved by the reaction with TMSOTf and preparative yield of clickable organocatalyst **4** was 95%. The click-reaction of prolinol **4** and azidopolystyrene was run in the presence of 10 mol% CuI and {tris[(1-*tert*-butyl-1*H*-1,2,3-triazol-4-yl)methyl]amine} (TTTA)[27] taken as ligand. The reaction was monitored by IR spectroscopy and the completion of the reaction was evidenced by the absence of the absorption band at 2090 cm^{-1} corresponding to azido group and by the emergence of an absorption band at 1716 cm^{-1} corresponding to the carbonyl group of the linker. Heterogeneous catalyst **5** was isolated by filtration, trace amounts of copper were removed by the treatment with 8-hydroxyquinoline in THF till solution became colorless. After prolonged drying *in vacuo* the loading of the polymer catalyst was verified by the elemental analysis.

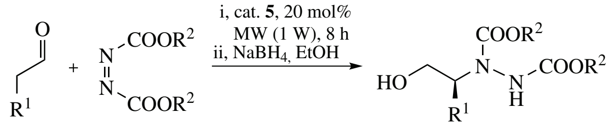


Scheme 1 *Reagents and conditions*: i, 3,5-$(\text{CF}_3)_2\text{C}_6\text{H}_3\text{MgBr}$, THF, –78 °C, 12 h; ii, 4-$\text{HC}\equiv\text{CCH}_2\text{OC}_6\text{H}_4\text{CO}_2\text{H}$, DCC, DMAP, DCM, 4 °C, 72 h; iii, TMSOTf, TEA, DCM, 4 °C, 24 h; iv, azidopolystyrene, 10 mol% CuI, 10 mol% TTTA, THF–DMF, 50 °C, 24 h (see Online Supplementary Materials).

Catalytic activity of the new immobilized organocatalyst in α-amination was investigated using convenient aliphatic aldehydes. To prevent an easy racemization, the obtained α-hydrazo aldehydes were reduced with NaBH_4 *in situ* to obtain the corresponding α-hydrazo alcohols. As the catalyst decomposes in the course of prolonged reactions, microwave irradiation of minimal power (1 W, $T < 30$ °C) and at maximal stirring (600 rpm) rate for 8 h were employed under neat conditions. The results are summarized in Table 1.

Though the chemical yields were high, enantioselectivity was poor in the reaction with diethyl azodicarboxylates (entries 1, 2). The use of a less reactive dibenzyl azodicarboxylate diminished preparative yields of α-hydrazo alcohols **6c** and **6d** (43 and 55%, respectively), while their enantiomeric purity increased significantly (over 99% *ee*, entries 3, 4).

Table 1 Enantioselective α-amination of aldehydes catalyzed by **5**.



6a–d

Entry	R^1	R^2	Product	Yield[a] (%)	*ee*[b] (%)
1	Et	Et	**6a**	66	20
2	Bn	Et	**6b**	84	2
3	Et	Bn	**6c**	43	>99
4	Pr^i	Bn	**6d**	55	>99

[a] After column chromatography. [b] By chiral HPLC.

Table 2 Recycling of catalyst **5** in asymmetric reaction between isovaleraldehyde and dibenzyl azodicarboxylate.[a]

Cycle	Yield of **6d**[b] (%)	ee[c] (%)
1	87	77
2	85	73
3	82	71
4	96[d]	25

[a] Cat. **5** (20 mol%), MW (1 W), then $NaBH_4$, EtOH. [b] After column chromatography. [c] By chiral HPLC. [d] Reaction time 48 h.

The possibility of repeated use of the polymer-supported catalyst **5** was investigated in the reaction of isovaleraldehyde with dibenzyl azodicarboxylate. At first the reaction was run for 7 h in the microwave oven (1 W, $T < 30\,°C$, 600 rpm) and then the reaction mixture was kept overnight without stirring. As one can see in Table 2 we managed to raise the yield of the product **6d** up to 87% and it retained in several catalytic cycles. Due to longer reaction time enantiomeric excess in the synthesis of **6d** was lower (77%) but it was retained in the 2nd and 3rd cycles (73 and 71% *ee*, cycles 2 and 3). In the 4th cycle the reaction mixture was kept for 2 days and the product was isolated in almost quantitative yield (96%) while its enantiomeric purity dramatically diminished (25% *ee*). We did not observe any perceptible destruction or IR-spectrum variance of the catalyst[28] (see Online Supplementary Materials) and the decrease in enantioselectivity stems from the racemization of α-hydrazo aldehyde.

In conclusion, we synthesized polymer-immobilized diarylprolinol **5** and its catalytic activity was studied in the reaction of aliphatic aldehydes addition to azodicarboxylates. Reaction products were obtained in high yields (up to 96%) and with excellent enantioselectivity (up to 99%). The catalyst can be repeatedly used at least in 3 cycles without loss of enantioselectivity.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.11.002.

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