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Mendeleev Commun., 2011, **21**, 146–148
Mendeleev Communications

Ionic polymer-supported *O*-trimethylsilyl-α,α-diphenyl-(*S*)-prolinols as recoverable organocatalysts for the asymmetric Michael reactions of carbon acids with α,β-enals

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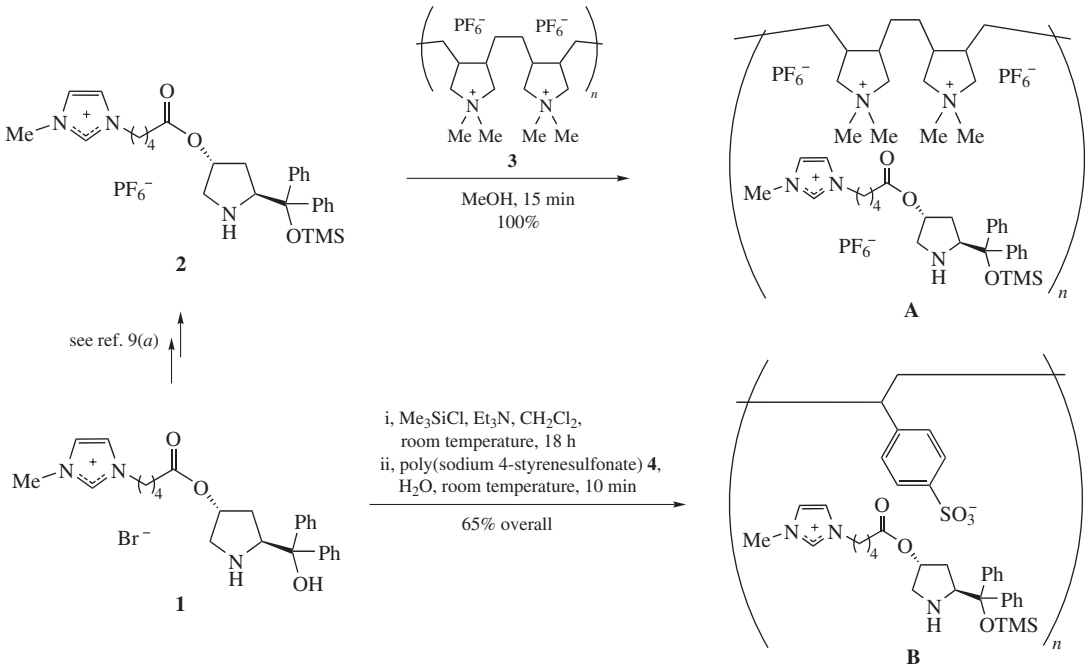
DOI: 10.1016/j.mencom.2011.04.011

A recyclable organocatalyst bearing *O*-trimethylsilyl-α,α-diphenyl-(*S*)-prolinol unit tagged to the imidazolium cation and poly(4-styrenesulfonate) anion in the reaction of CH-acids with α,β-enals provided the respective Michael adducts in high yields (up to 99%) and with high enantioselectivities (up to 98% *ee*).

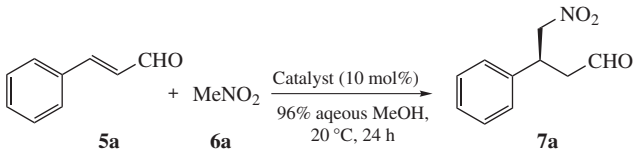
O-Trimethylsilyl-protected α,α-diarylprolinols (*O*-TMS-α,α-diarylprolinols) and their derivatives are widely applied as chiral organocatalysts in asymmetric reactions of carbonyl compounds,[1] in particular, on the key steps of the synthesis of some natural products and medicines.[2(a),(b)] However, the industrial application of these catalysts as well as of a majority of other modern organocatalysts having rather complicated structure requires developing their recyclable immobilized versions.[3,4(a)–(c)] A few immobilization strategies by tagging *O*-TMS-α,α-diarylprolinol unit to polymer,[5(a)–(e)] dendritic,[6] perfluoroalkyl,[7] paramagnetic[8] or ionic groups[9(a)–(e)] have been developed so far. The latter one is advantageous since it allows tuning catalyst properties by varying the cation and/or anion structure and monitoring the catalyst synthesis by NMR spectroscopy. Yet, some *O*-TMS-α,α-diarylprolinol derivatives bearing ionic groups[9(c)] are moderately soluble in organic solvents and partly can be washed out during work-up.[10] The catalysts containing PF_6^- anion are poorer soluble in organic phase, however, they are less resistant to moisture for their susceptibility to release the fluoride anion,[11(a),(b)] which promotes hydrolysis of the O–Si bond.

We assumed that the modification of the ionic catalyst with an ionic polymer (polyelectrolyte) as a support or a counter-ion would diminish the influence of these unfavorable factors. To verify this hypothesis, we prepared the systems **A** and **B** by the reactions of *O*-TMS-α,α-diphenyl-(*S*)-prolinols **1** or **2**[9(a)–(c)] with available poly(diallyldimethylammonium hexafluorophosphate) **3** or poly(sodium 4-styrenesulfonate) **4** (Scheme 1). We supposed that in the system **A** the catalyst **2** would be linked with the ionic polymer **3** by ion–ion interaction forces because a similar system (*S*)-proline/polyelectrolyte **3** [one molecule of (*S*)-proline per two monomer units of the polyelectrolyte **3**] can be easily recovered and retains its activity for several cycles in the asymmetric aldol reaction.[12] The catalyst **B**, in which the ions incorporated into a chiral inductor (the imidazolium cation) and into a polyelectrolyte chain (the sulfonate anion) have opposite charges, should be even more robust. The imidazolium[13] and quinuclidinium[14]



Scheme 1

Table 1 The regeneration of ionic catalysts **2**, **A** and **B** in the reaction of *trans*-cinnamaldehyde **5a** with nitromethane **6a**.[a]



5a **6a** **7a**

Entry	Catalyst	Conversion[b] (%) (cycle)	*ee*[c] (%) (cycle)
1[d]	**2**[9(a)]	100 (1); 100 (2); 100 (3); 89 (4); 70 (5)	95 (1); 94 (2); 94 (3); 94 (4); 94 (5)
2	**A**	100 (1); 100 (2); 100 (3); 95 (4); 74 (5)	92 (1); 92 (2); 92 (3); 92 (4); 92 (5)
3	**B**	100 (1); 100 (2); 100 (3); 100 (4); 80 (5)	95 (1); 96 (2); 95 (3); 95 (4); 94 (5)

[a]All reactions were carried out using *trans*-cinnamaldehyde **5a** (26 mg, 0.2 mmol) and nitromethane **6a** (37 mg, 0.6 mmol) in 96% aqueous MeOH (0.4 ml) in the presence of the indicated catalyst (10 mol% per monomer) at room temperature for 24 h. [b]Estimated by ^{1}H NMR. [c]Estimated by a chiral HPLC. [d]According to ref. 9(*b*).

salts with the poly(4-styrenesulfonate) anions have been prepared recently, however, *O*-TMS-α,α-diarylprolinol derivatives modified with polyelectrolytes have not been reported so far.

The system **A** was prepared by mixing of hexafluorophosphate **2** with polyelectrolyte **3** in MeOH followed by the solvent evaporation. The catalyst **B** was synthesized by the reaction sequence including the silylation of the hydroxy group in compound **1** and bromide-anion exchange with poly(sodium 4-styrenesulfonate) **4**.†

We examined the systems **A** and **B** in the asymmetric Michael reaction between *trans*-cinnamaldehyde **5a** and nitromethane **6a** in 96% aqueous MeOH which is known to be the most efficient solvent for this reaction.‡,9(*b*) After reaction completion (TLC-monitoring) MeOH was evaporated, the product was extracted with Et_2O, fresh portions of reactants **5a** and **6a** were added to the recovered catalyst **A** or **B**, and the reaction was re-performed. The activity and recoverability of supported catalyst **A** appeared to be similar to that of hexafluorophosphate **2**, but the enantioselectivity was somewhat lower (Table 1, entries 1 and 2). The best results were achieved in the reactions catalyzed by the polystyrene system **B** containing moisture-resistant sulfated polymeric anions, in which conversions and enantioselectivities remained extremely high at least for four reaction cycles (Table 1, entry 3). Moreover, the poorly soluble in organic phase catalyst **B** was hardly 'washed-out' during the product extraction: the loss of its mass over five cycles was less than 5% [for compound **2**, ~20%9(*b*)]. However, after the fourth regeneration a gradual deactivation of the system **B** was observed, which is characteristic of all *O*-TMS-prolinol-type organocatalysts.

Next, we examined the catalytic properties of polyelectrolyte **B** (10 mol%) in the asymmetric Michael reactions of *trans*-cinnamaldehyde derivatives **5** with various carbon acids **6** (nitromethane **6a**, dimethyl malonate **6b**, and dibenzyl malonate **6c**) in 96% aqueous MeOH. In all cases respective enantiomers of Michael adducts [(*S*)- for **7a–e** and (*R*)- for **7f–h**] were obtained, yields and *ee* values of the products were comparable with or even higher than those attained with the use of PF_6-containing catalyst **2**[9(*a*),(*b*)] (Table 2). The synthesized compounds **7a**, **7b**, **7e**, and **7f** (or **7g**) are the intermediates for the preparation of chiral medicines Phenibut,[9(*b*)] Baclofen,[15(*a*),(*b*)] Rolipram,[15(*c*)] and Paroxetin,[16(*a*),(*b*)] respectively. Unlike other organocatalysts bearing ionic groups,[9(*a*),(*b*)] the catalyst **B** remains solid (does not 'liquify') during the recovery and does not contain moisture-sensitive and corrosion-dangerous fluorinated anions, which would be undesirable in neoteric organocatalytic technologies for the preparation of chiral medications.

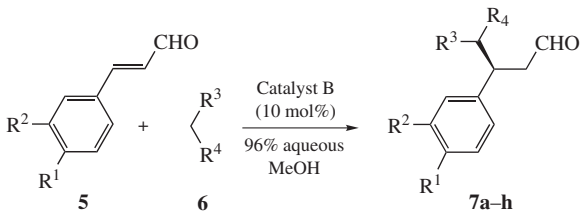
† NMR spectra were recorded in DMSO-d_6 solutions on a Bruker AM300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C, 282 MHz for ^{19}F, 121 MHz for ^{31}P). HPLC was performed on a Stayer chromatograph equipped with an UV detector using a DAICEL Chiralpak® AD–H column. Silica gel 0.035–0.070 (Acros) was used for a column chromatography. 4-Chloro- (**5b**), 4-nitro- (**5c**), 4-methoxy- (**5d**), 4-fluoro- (**5f**) (*E*)-cinnamaldehydes[17] and 3-cyclopentyloxy-4-methoxy-(*E*)-cinnamaldehyde (**5e**)[15(*c*)] were prepared according to the literature procedures. Poly(diallyldimethylammonium hexafluorophosphate) **3** was prepared from commercially available poly(diallyldimethylammonium chloride) (Aldrich, average M_W 400000–500000, CAS26062-79-3).[12] (*E*)-Cinnamaldehyde and poly(sodium 4-styrenesulfonate) **4** (Acros, average M_W 70000, CAS25704-18-1) were obtained from commercial sources and used without further purification.

Preparation of supported catalyst **A**. A mixture of poly(diallyldimethylammonium hexafluorophosphate) **3** (38 mg, 0.14 mmol per monomer), 3-(5-{(3*R*,5*S*)-5-[diphenyl(trimethylsilyloxy)methyl]pyrrolidin-3-yloxy}-5-oxopentyl)-1-methyl-1*H*-imidazol-3-ium hexafluorophosphate **2**[9(*a*)] (46 mg, 0.07 mmol), and methanol (5 ml) was stirred at room temperature for 30 min. The solvent was removed *in vacuo* (15 Torr) and the residue was dried under reduced pressure (2 Torr) at 35 °C to afford 84 mg (100%) of catalyst **A**. According to NMR data, the system **A** contained one molecule of compound **2** per two monomer units of polyelectrolyte **3**. ^{1}H NMR (28 °C) δ: –0.11 (s, 9H, $SiMe_3$), 1.26 [m, 14H, 4-H, $(CH_2)_2CH_2COO$, $MeN^+CH_2CHCH_2$], 1.77 (m, 4H, $MeN^+CH_2CHCH_2$), 2.30 (m, 2H, CH_2COO), 2.87 (m, 2H, 2-H), 3.08 (s, 12H, $MeN^+CH_2CHCH_2$), 3.72 (s, 8H, $MeN^+CH_2CHCH_2$), 3.85 (s, 3H, Me), 4.16 (m, 1H, NCH_2), 4.30 (m, 1H, 5-H), 4.80 (m, 1H, 3-H), 7.25 (m, 8H, H_{Ph}, NCHCHN), 7.44 (m, 2H, H_{Ph}), 7.69 (d, 2H, H_{Ph}, *J* 13.2 Hz), 9.06 (s, 1H, NCHN). ^{13}C NMR (28 °C) δ: 2.3, 20.8, 26.3–26.6 (polymer), 28.7, 32.7, 34.0, 35.7, 37.3–37.9 (polymer), 48.4, 51.4–54.8 (polymer), 52.7, 62.6, 69.2–69.6 (polymer), 74.6, 82.2, 122.2, 123.6, 126.5, 126.7, 127.4, 127.7, 127.8, 136.5, 145.4, 147.0, 172.3. ^{19}F NMR (28 °C) δ: –70.8 (d, *J* 710 Hz). ^{31}P NMR (28 °C) δ: –143.3 (hept., *J* 710 Hz). Found (%): C, 45.59; H, 6.00; N, 5.63. Calc. for $C_{45}H_{72}F_{18}N_5O_3P_3Si$ (1194.06) (%): C, 45.26; H, 6.08, N, 5.87.

Preparation of polyelectrolyte **B**. Chlorotrimethylsilane (326 mg, 384 μl, 3 mmol) was added dropwise to a solution of 3-{5-[(3*R*,5*S*)-5-(hydroxyphenylmethyl)pyrrolidin-3-yloxy]-5-oxopentyl}-1-methyl-1*H*-imidazol-3-ium bromide **1**[9(*a*)] (772 mg, 1.5 mmol) and Et_3N (455 mg, 606 μl, 4.5 mmol) in CH_2Cl_2 (5 ml) at 4 °C. The reaction mixture was stirred at room temperature for 15 h. The solvent was removed *in vacuo* (15 Torr) and the residue was dissolved in water (10 ml). To the obtained aqueous solution, a solution of poly(sodium 4-styrenesulfonate) **4** (619 mg, 3 mmol per monomer) in water (15 ml) was added dropwise with stirring. After 5 min, the water phase was decanted, the remaining oil was dissolved in CH_2Cl_2 (50 ml), washed with distilled water (2×10 ml) and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* (15 Torr) and the residue was dried under reduced pressure (2 Torr) at 35 °C to afford 671 mg (65%) of catalyst **B** as a reddish solid. According to NMR data, the polyelectrolyte **B** contained one imidazolium cation unit per one sulfated polystyrene anion unit. ^{1}H NMR (25 °C) δ: –0.14 (s, 9H, $SiMe_3$), 1.43 (m, 3H, 4-H, $CH_2CH_2CH_2COO$), 1.74 [m, 3H, 4-H, $CH_2(CH_2)_2COO$], 2.28 (m, 2H, CH_2COO), 2.56 (m, 2H, $ArCHCH_2$), 2.88 (m, 3H, 2-H, $ArCHCH_2$), 3.70 (s, 3H, Me), 4.11 (m, 1H, NCH_2), 4.33 (m, 1H, 5-H), 4.79 (m, 1H, 3-H), 7.13–7.38 (m, 12H, H_{Ph}, NCHCHN, H_{Ar}), 7.44 (m, 2H, H_{Ph}), 7.67 (m, 2H, H_{Ph}), 9.12 (s, 1H, NCHN). ^{13}C NMR (25 °C) δ: 2.4, 20.8, 28.7, 32.8, 33.9, 35.5, 41.2, 48.2, 52.8, 54.9, 62.5, 74.7, 82.2, 122.1, 123.5, 126.6, 127.4, 127.6, 127.8, 136.6, 145.5, 146.1, 172.3. Found (%): C, 64.51; H, 6.74, N, 6.25. Calc. for $C_{37}H_{47}N_3O_6SSi$ (689.94) (%): C, 64.41; H, 6.87, N, 6.09.

‡ *Michael reaction and recycling procedure*. A mixture of α,β-enal **5**, CH-acid **6**, catalyst **B** (10 mol% per monomer), and 96% aqueous MeOH was stirred for the indicated time at the indicated temperature (Table 2). The solvent was evaporated under reduced pressure (15 Torr) and the Michael adduct was extracted with Et_2O (2×1 ml). The combined organic extracts were concentrated *in vacuo* and purified by column chromatography using a mixture EtOAc/*n*-hexane (1:5–1:2) as an eluent. If appropriate, the catalyst that remained after the extraction of the product with Et_2O was reused by adding fresh portions of the reagents and the solvent. All analytical data of the prepared compounds **7** were identical to the reported ones.[9(*a*),(*b*)]

Table 2 The reactions of α,β-enals **5** with carbon acids **6** in the presence of polyelectrolyte **B**.[a]



5 **6** **7a–h**

a $R^1 = R^2 = R^3 = H$, $R^4 = NO_2$
b $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = NO_2$
c $R^1 = NO_2$, $R^2 = R^3 = H$, $R^4 = NO_2$
d $R^1 = MeO$, $R^2 = R^3 = H$, $R^4 = NO_2$
e $R^1 = MeO$, $R^2 = cyclo\text{-}C_5H_9O$, $R^3 = H$, $R^4 = NO_2$
f $R^1 = F$, $R^2 = H$, $R^3 = R^4 = COOBn$
g $R^1 = F$, $R^2 = H$, $R^3 = R^4 = COOMe$
h $R^1 = R^2 = H$, $R^3 = R^4 = COOMe$

Entry	Product	Time/h	Yield[b] (lit.,[9(b)]) (%)	*ee*[c] (lit.[9(b)]) (%)
1	**7a**	24	83 (84)	95 (94)
2	**7b**	24	90 (91)	91 (90)
3	**7c**	24	68 (64)	98 (93)
4	**7d**	48	72 (87)	92 (93)
5	**7e**	24	76 (80)	91 (90)
6[d]	**7f**	48	94 (93)	87 (96)
7[d]	**7g**	48	93 (95)	92 (92)
8[d]	**7h**	48	99 (93)	93 (96)

[a]Unless otherwise specified, all reactions were carried out using aldehydes **5** (0.5 mmol), nitromethane **6a** (92 mg, 1.5 mmol), and 96% aqueous MeOH (1 ml) in the presence of catalyst **B** (34 mg, 0.05 mmol per monomer) at 20 °C for the indicated time. [b]Isolated yield. [c]Estimated by a chiral HPLC. [d]Reactions were carried out using aldehydes **5** (0.6 mmol), dimethyl (**6b**) or dibenzyl (**6c**) malonates (0.3 mmol) in 96% aqueous EtOH (0.3 ml) in the presence of catalyst **B** (21 mg, 0.03 mmol per monomer) at 4 °C for 48 h.

In conclusion, we have synthesized for the first time *O*-TMS-α,α-diphenylprolinol-derived ionic systems **A** and **B** bearing polyelectrolyte units and evaluated their efficacy as recoverable organocatalysts in the asymmetric Michael reactions between α,β-enals and carbon acids. In the presence of ionic catalyst **B** bearing the sulfated polystyrene anions, the reactions afforded the corresponding Michael adducts in high yields (up to 99%) and with high enantioselectivity (up to 98% *ee*) which retained over 4 cycles. The advantages of developed catalyst **B** are its heterogeneity and the absence of fluorinated anions, which may promote practical application of similar organocatalysts.

This work was supported by the Ministry of Education and Science of the Russian Federation (contract no. 02.740.11.0630) and by the Russian Foundation of Basic Research (grant no. 09-03-00384).

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Received: 31st January 2011; Com. 11/3679