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Enantioselective Michael additions of aldehydes to nitroalkenes catalyzed with ionically tagged organocatalyst

Research Article

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Abstract: Enantioselective organocatalytic Michael additions affords useful building blocks for many biologically and medicinally relevant compounds. Ionically-tagged diphenylprolinol silyl ether efficiently catalyzes several Michael additions of aldehydes to nitroalkenes in ionic liquids. The Michael additions work well in ionic liquids; yields up to 95% and enantioselectivities up to 95% ee were achieved. Furthermore, in some cases, the catalytic system was reusable.

Keywords: *Organocatalysis • Ionic liquid • Ionic tag • Michael addition • Oseltamivir*

1. Introduction

Asymmetric organocatalysis provides access to a broad range of important chiral compounds [1-4]. One of the possible ways to increase efficiency of an organocatalytic reaction is to immobilize a catalyst. From among a large variety of immobilization strategies, an immobilization within a liquid phase offers several useful properties. Homogeneous immobilized catalysts attempt to combine positive features of both homogeneous as well as heterogeneous catalysis [5]. Thus, a catalyst having an ionic tag appended is supposed to behave similarly to analogous homogeneous catalyst. At the same time, it should be amenable to facile isolation and possible recycling. Introduction of an ionic tag into the organocatalyst structure enables use of such catalyst in ionic liquids [6-7]. There have been a number of reports of efficient organocatalytic reactions performed in ionic liquids [8-12]. Furthermore, introduction of an ionic tag into a catalyst structure can influence its catalytic properties [13].

Stereoselective organocatalytic Michael additions are important C-C [14-19] and C-heteroatom [20,21] bond forming reactions. Michael acceptors such as unsaturated carbonyl compounds, sulfones, phosphonates, and nitroalkenes react with enolizable aldehydes and ketones, nitroalkanes and other C-acids. Practicality of organocatalytic Michael addition is demonstrated also in the fact that they are part of a number of domino or one-pot reactions [22-25]. Such reactions lead to highly functionalized compounds, which often have interesting biological activities [26,27].

Diarylprolinol silyl ethers, initially developed independently by Jorgensen [28] and Hayashi [29], belong among the most effective organocatalysts [30,31]. These compounds are also highly effective catalysts for enantioselective Michael additions of aldehydes to a variety of Michael acceptors, such as nitroalkenes [29,32-37], vinyl sulfones [38,39] and unsaturated thioesters [40]. Given the high catalytic activity of diaryl silyl ether in a range of reactions, it is understandable that several immobilizations have been described with

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this organocatalyst. Zlotin and coworkers attached an imidazolium ion through an O-acyl group on position 4 in the 4-hydroxyproline [41]. The resulting organocatalyst was efficient in the Michael addition of malonates to α,β-unsaturated aldehydes. The catalyst was recycled six times in ethanol. On the other hand, Lombardo and coworkers used the silyl group of Jorgensen-Hayashi catalyst to attach the ionic moeity [42]. This catalyst was then used for catalyzing Michael addition of enolizable aldehydes to nitroalkenes. Although Lombardo also used his catalyst in an ionic liquid, recycling was not evaluated. Yet another successful way of immobilizing diarylprolinol silyl ether was developed by Headley, Ni and coworkers. They attached quaternary ammonium moieties onto the aryl groups of the catalyst [43-44]. These organocatalysts were also not used in ionic liquids, but in aqueous media.

In this context, we decided to employ 4-hydroxyproline-type catalyst for organocatalytic Michael additions in ionic liquids. The use of ionically-tagged catalyst in connection with ionic liquids constitutes a primary sense of the notion of catalyst ionic tagging. Furthermore, we have selected several useful Michael additions, which are applicable in the synthesis of biologically relevant molecules such as oseltamivir and its analogues. Attention was paid to recycling of the catalyst while retaining its high catalytic activity and practicality of the procedure.

2. Experimental procedure

All reactions were carried out in an inert atmosphere of N_2 or Ar. Solvents were dried and purified by standard methods before use. NMR spectra were recorded on Varian Mercury plus instrument (300 MHz for ^{1}H, 75 MHz for ^{13}C) and Varian NMR System 600 (600 MHz for ^{1}H, 150 MHz for ^{13}C). Chemical shifts (δ) are given in ppm relative to tetramethylsilane. Specific optical rotations were measured on Jasco instrument and are given in deg $cm^{-3}\,g^{-1}\,dm^{-1}$. Flash chromatography was performed on Merck silica gel 60. Thin-layer chromatography was performed on Merck TLC-plates silica gel 60, F-254. Diastereomeric ratios were determined by ^{1}H NMR and GC (Agilent Technologies 6850). Enantiomeric ratios were determined by HPLC on Chiralpak, OD-H and IC (Daicel Chemical Industries), column using hexane/iPrOH as a mobile phase and detection with UV-detector at 211-259 nm. Catalyst **C2** was synthesized according to literature procedure [42]. Relative and absolute configurations of products 7, 10, 12, and 14 were assigned by comparison to their retention time from enantioselective HPLC with literature values.

2.1. Synthesis of catalyst C1

(3R,5S)-1-Benzyl-5-(hydroxydiphenylmethyl)pyrrolidin-3-ol (2)

Into a solution of ester **1** (4.0 g, 17 mmol) in anhydrous THF (100 mL), PhMgBr (102 mL, 102 mmol, 18% in THF) was added over 1 h at -78°C. The reaction mixture was stirred without adding additional cooling agent for 18 h. The reaction was quenched by adding saturated NH_4Cl solution (35 mL) at 0°C. Layers were separated and aqueous layer was extracted with Et_2O (3×30 mL). The combined organic exctracts were washed with saturated NH4Cl solution (2×50 mL), dried (Na_2SO_4) and concentrated. The residue was dissolved in a mixture hexanes/EtOAc and activated charcoal was added. After filtration, the filtrate was concentrated and crystallized from hexane/EtOAc 2:3 (25 mL). The pure product 2 was obtained (2.0 g, 33%) as white crystals. The supernatant was concentrated and purified by flash chromatography (SiO_2, 250 g; hexanes/EtOAc 7:3. In this way another batch of product 2 was obtained (1.9 g, 31%). Combined yield was 64%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77 (td, *J*=1.6Hz, *J*=8.4Hz, 2H), 7.60 (td, *J*=1.7Hz, *J*=8.4Hz, 2H) 7.17 (m, 11H) 4.95 (s, 1H) 4.41 (t, *J*=7.9Hz, 1H) 4.28 (dq, *J*=8.6Hz, *J*=4.2Hz, 1H) 3.31 (d, *J*=2.6Hz, 2H) 3.09 (dd, *J*=11.2Hz, *J*=4.6Hz, 1H) 2.53 (ddd, *J*=1.1Hz, *J*=4.0Hz, *J*=11.2Hz, 1H) 1.88 (m, 2H) 1.41 (d, *J*=3.2Hz, 1H) ppm. ^{13}C NMR (75MHz, $CDCl_3$) δ: 38.7 , 61.2, 62.1, 70.4, 70.8, 76.8, 125.4, 125.6, 126.4, 126.6, 126.9, 128.1, 128.2, 128.3, 128.5, 139.5, 146.0, 147.6 ppm, $[\alpha]_D^{20}$ = +44.7 (c=1.01,$CHCl_3$), Lit.[41] $[\alpha]_D^{20}$ + 41.6 (c=1, $CHCl_3$). HRMS: m/z [M+H]+ calcd: 360.1958, found: 360.1962. Spectral data are in agreement with those in the literature [41].

(3R,5S)-1-Benzyl-5-(hydroxydiphenylmethyl)pyrrolidin-3-yl 5-bromopentanoate (3)

Into a solution of DCC (1.8 g, 4.7 mmol) and DMAP (90 mg, 0.71 mmol) in CH_2Cl_2 (50 mL) at 0°C, 5-bromopentanoic acid (1.5 g, 4.7 mmol) was added. Then, compound 2 (2.55 g, 7.1 mmol) in CH_2Cl_2 was added. The reaction mixture was stirred for 1 h at 0°C. Then another portion of DCC (0.9 g, 2.4 mmol) and 5–bromopentanoic acid (0.8 g, 2.4 mmol) was added and the reaction mixture was refluxed for 30 min. After cooling, the mixture was filtered and collected solid was washed with CH_2Cl_2 (3x15 mL). The combined organic extracts were washed with concetrated HCl (2.5 mL), saturated $NaHCO_3$ solution (25 mL) and H_2O (25 mL). Organic layer was dried (Na_2SO_4), concentrated and purified by column chromatography (SiO_2, 200 g, hexanes/EtOAc 85:15). Pure product 3 (3.23 g, 87%) was obtained as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (td, *J*=1.7Hz, *J*=8.5Hz, 2H), 7.60 (td, *J*=1.7Hz, *J*=8.4Hz, 2H), 7.18 (m, 11H), 5.06 (m, 1H), 4.84 (s, 1H), 4.35 (t, *J*=8.0Hz, 1H), 3.40 (m, 3H), 3.21 (m, 2H), 2.62 (ddd, *J*=1.0Hz, *J*=3.4Hz, *J*=12.0Hz, 1H) 2.33 (td, *J*=2.4Hz, *J*=8.2Hz, 2H), 1.86 (m, 6H) ppm. ^{13}C NMR (75MHz, $CDCl_3$) δ: 23.5, 31.8, 33.0, 33.6, 35.6, 59.4, 61.0, 70.4, 73.7, 76.7, 125.3, 125.6, 126.5, 126.7, 127.1, 128.2, 128.3, 128.5, 139.1, 145.7, 147.4, 172.5 ppm. $[\alpha]_D^{20}$ = +21.4, (c=1, MeOH); Lit.[41] $[\alpha]_D^{20}$ = +17.9 (c=1, MeOH). HRMS: m/z [M+H]+ calcd: 522.1638, found: 522.1646. Spectral data are in agreement with those in the literature [41].

3-(5-((3R,5S)-1-benzyl-5-(hydroxydiphenylmethyl) pyrrolidin-3-yloxy)-5-oxopentyl)-1-methyl -1H- imidazol-3-ium bis (trifluoromethylsulfonyl)amide (4)

The ester 3 (3.23 g, 6.18 mmol) was mixed with 1-metyl-1H-imidazol (2.54 g, 6.18 mmol) and the resulting mixture was stirred for 10 min at 100°C. After cooling, the mixture was washed with Et_2O (5×5 mL) at room temperature and with hot Et_2O (reflux, 2×5mL). The residue was dissolved in MeOH (3 mL) and into this solution again Et_2O (20 mL) was added and the mixture was stirred for 5 min. Upper layer was separated and the rest was again washed with Et_2O (3 mL). Then the residue was purified by column chromatography (SiO_2, 200 g, CH_2Cl_2/MeOH = 9:1). 3-(5-((3R,5S)-1-benzyl-5-(hydroxydiphenylmethyl)pyrrolidin-3-yloxy)-5-oxopentyl)-1-methyl-1H-imidazol-3-ium bromide (2.82 g, 76%) was obtained as white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.86 (s, 1H), 7.79 (d, *J*=7.5Hz, 2H), 7.61 (dd, *J*=2.3Hz, *J*=6.2Hz, 2H), 7.23 (m, 11H), 7.01 (d, *J*=6.2Hz, 2H), 5.03 (td, *J*=4.4Hz, *J*=9.0Hz, 1H), 4.83 (s, 1H), 4.38 (t, *J*=7.2Hz, 3H), 4.06 (s, 3H), 3.38 (m, 1H), 3.24 (m, 2H), 2.60 (m, 1H), 2.39 (ddd, *J*=6.8Hz, *J*=10.2Hz, *J*=16.7Hz, 2H), 1.99 (m, 4H), 1.64 (m, 2H) ppm. ^{13}C NMR (75MHz, $CDCl_3$) δ: 21.2, 29.4, 33.2, 35.5, 36.7, 49.7, 59.2, 60.9, 70.3, 73.6, 76.8 122.0, 123.1, 125.4, 125.6, 126.5, 126.7, 127.1, 128.2, 128.3, 128.4, 128.6, 137.8, 138.9, 145. 7, 147.2, 172.5 ppm, $[\alpha]_D^{20}$ = +5.7 (c=0.99,$CHCl_3$); Lit.[41] $[\alpha]_D^{20}$ = +1.8 (c=1, $CHCl_3$). HRMS: m/z [M+H]+ calcd: 524.2913, found: 524.2907. Spectral data are in agreement with those in the literature [41].

To a solution of 3-(5-((3R,5S)-1-benzyl-5-(hydroxydiphenylmethyl)pyrrolidin-3-yloxy)-5-oxopentyl)-1-methyl-1H-imidazol-3-ium bromide (2.82 g, 4.67 mmol) in distilled H_2O (80 mL), a solution of $LiNTf_2$ (2.68 g, 9.34 mmol) in distilled H_2O (80 mL) was added over 10 min at 20°C. Separated solid material was decanted and washed with distilled H_2O (3×300 mL). The solid material was dried under reduced pressure at 60°C. The product 4 (3.76 g, 99%) was obtained as white crystalline solid. Overal yield from 3 was 75%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.84 (s, 1H), 7.77 (dd, *J*=1.1Hz, *J*=8.4Hz, 2H), 7.59 (dd, *J*=1.1Hz, *J*=8.3Hz, 2H), 7.20 (m, 11H), 6.99 (dd, *J*=1.7Hz, *J*=7.5Hz, 2H), 5.01 (dd, *J*=4.8Hz, *J*=9.6Hz, 1H), 4.82 (s, 1H), 4.35 (t, *J*=7.9Hz, 1H), 4.18 (t, *J*=7.3Hz, 2H), 3.90 (s, 3H), 3.33 (d, *J*=12.8Hz, 1H), 3.19 (m, 2H), 2.58 (dd, *J*=3.8Hz, *J*=11.6Hz, 1H), 2.36 (dt, *J*=1.7Hz, *J*=7.1Hz, 2H), 1.92 (m, 4H), 1.60 (m, 2H) ppm. ^{13}C NMR (75MHz, $CDCl_3$) δ: 21.0, 29.1, 33.0, 35.5, 36.4, 49.8, 59.2, 60.9, 70.1, 73.6, 76.8, 119.8 (q, *J*=321Hz, 2C, CF_3), 122.1, 123.4, 125.4, 125.6, 126.5, 126.7, 127.1, 128.2, 128.3, 128.4, 128.5, 136.5, 139.0, 145.7, 147.3, 172.5 ppm, $[\alpha]_D^{20}$ = + 7.1 (c=1.0, $CHCl_3$). HRMS: m/z [M+H]+ calcd: 524.2913, found: 524.2904.

3-(5-((3R,5S)-5-(diphenyl(trimethylsilyloxy) methyl) pyrrolidin-3-yloxy)-5-oxopentyl)-1-methyl-1H-imidazol-3-ium bis(trifluoromethylsulfonyl) amide (C1)

Into a solution of alcohol 4 (3.76 g, 4.67 mmol) in CH_2Cl_2 (80 mL), Et_3N (1.04 mL, 7.47 mmol) and TMSOTf (1.66 g, 7.47 mmol) were added over 20 min at 0°C. The reaction mixture was stirred for 18 h and temperature was let to rise to r.t. Then H_2O (100 mL) was added and layers were separated. Aqueous phase was extracted with CH_2Cl_2 (3×50 mL). Combined organic extracts were vigorously stirred with $NaHCO_3$ for 15 min, then it was washed with H_2O (3x), dried (Na_2SO_4) and concentrated. Drying under reduced pressure afforded 3-(5-((3R,5S)-1-benzyl-5-(diphenyl(trimethylsilyloxy) methyl) pyrrolidin-3-yloxy)-5-oxopentyl)-1-methyl-1H-imidazol-3-ium bis (trifluoromethylsulfonyl)amide (3.97 g, 97%) as pale yellow viscous oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.08 (s, 1H) 7.57 (m, 4H), 7.21 (m, 13H) 4.46 (m, 1H), 4.20 (m, 4H), 3.94 (s, 3H), 3.59 (m, 1H), 2.61 (m, 1H), 2.31 (m, 3H), 2.10 (m, 2H), 1.90 (m, 2H), 1.57 (m, 2H), -0.18 (s, 9H) ppm. ^{13}C NMR (75MHz, $CDCl_3$) δ: 1.9, 21.0, 29.1, 33.0, 35.2, 36.4, 49.8, 58.0, 62.2, 71.5, 74.4, 84.4, 119.8 (q, *J*=321,2 Hz, 2C, CF_3), 122.2, 123.4, 127.2, 127.3, 127.4, 128.1, 128.27, 128.33, 128.6, 128.5, 129.4, 129.5, 136.4, 143.2, 143.6, 172.8 ppm. $[\alpha]_D^{20}$ = - 24.8 (c=1.01, $CHCl_3$). HRMS: m/z [M+H]+ calcd: 596.3308, found: 596.3331.

A solution 3-(5-((3R,5S)-1-benzyl-5-(diphenyl(trimethylsilyloxy)methyl)pyrrolidin-3-yloxy)-5-oxopentyl)-1-methyl-1H-imidazol-3-ium bis (trifluoromethylsulfonyl)amide (4.96 g, 4.52 mmol) in MeOH (70 mL) was stirred under H_2 atmosphere (balloon) in the presence Pd/C (5%, 770 mg, 0.36 mmol) for 20 h. Then the Pd/C was filtered off with the help of Celite. Filtrate was concentrated and dried under reduced pressure. Catalyst **C1** (3.3 g, 90%) was obtained as a yellow honey-like material.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.88 (s, 1H), 7.45 (td, *J*=2.3Hz, *J*=8.7Hz, 2H), 7.28 (m, 10H), 4.97 (td, *J*=3.5Hz, *J*=5.9Hz, 1H), 4.34 (dd, *J*=6.8Hz, *J*=9.1Hz, 1H), 4.20 (t, *J*=7.3Hz, 2H) 3.93 (s, 3H), 2.93 (m, 2H), 2.36 (dt, *J*=1.8Hz, *J*=7.0Hz, 2H), 2.15 (m, 1H), 1.90 (m, 3H), 1.63 (m, 3H), -0.10 (s, 9H) ppm. ^{13}C NMR (75MHz, $CDCl_3$) δ: 2.01, 20.98, 29.07, 33.00, 34.42, 36.45, 49.76, 52.94, 64.58, 75.05, 82.60, 119.70 (q, *J*=321,0 Hz, 2C, CF_3), 122.21, 123.44, 127.39, 127.53, 127.57, 127.93, 128.00, 128.34, 136.40, 144.22, 145.00, 172.71 ppm. $[\alpha]_D^{20}$ = -12.8 (c = 0.99, $CHCl_3$). HRMS: m/z [M+H]+ calcd: 506.2839, found: 506.2834.

2.2. Typical procedure for the Michael addition

Organocatalyst (0.025 mmol, 10 mol%) and nitroalkene (0.25 mmol) were dissolved in a solvent (0.5 mL for each 0.25 mmol of nitroalkene) and chloroacetic acid (0.05 mmol, 20 mol%). After 10 min stirring, aldehyde (0.375 mmol) was added and the resulting mixture was stirred at 20°C for 24 h. The mixture was then extracted with Et_2O (4×1.5 mL). The combined extracts were concentrated and the residue was purified by column chromatography (25 g of silica gel, hexanes/EtOAc).

2.3. Recycling

The residue after extracting the reaction mixture with Et_2O was charged with a new batch of nitroalkene and aldehyde, and the reaction was repeated.

2.4. Characterisation data

N-[(2R,3S)-1-nitro-4-oxo-3-(pentan-3-yloxy)butan-2-yl]acetamide (7)

Chromatography hexanes/EtOAc 1:1.

syn-7: Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.65 (s, 1H), 6.03 (d, *J* = 8.7 Hz, 1H), 5.12-5.02 (m, 1H), 4.58 (d, *J* = 6.6 Hz, 2H), 4.09 (d, *J* = 3.3 Hz, 1H), 3.41(q, *J* = 5.8 Hz, 1H) 1.99 (s, 3H), 1.63-1.48 (m, 4H), 0.98-0.84 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 201.01, 170.05, 83.60, 79.52, 74.05, 48.03, 25.93, 24.99, 23.07, 9.38, 9.29. MS: neg. mode (M-H) 259.

anti-7: Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.61(d, *J* = 3.1Hz, 1H), 6.10 (d, *J* = 8.5 Hz, 1H), 4.84-4.52 (m, 3H), 3.93 (dd, *J* = 8.0, 3.1Hz, 1H), 3.31-3.23 (m, 1H), 2.00 (s, 3H), 1.57-1.42 (m, 4H), 0.95-0.84 (m, 6H). ^{13}C NMR (75MHz, $CDCl_3$) δ: 201.07, 170.27, 83.19, 80.31, 74.05, 47.08, 26.05, 24.83, 23.09, 9.47, 9.13. MS: neg. mode (M-H) 259.

HPLC for triphenylphosphoranylidene derivative (Chiralcel OD-H, hexane/iPrOH=8:2, 0.75 mL min^{-1}, λ=259 nm: t_R= 7.95 (anti, minor), 9.54 (anti, major), 11.44 (syn, minor), 17.41 (syn, maJor) min. Spectroscopic data are in agreement with those in the literature [45].

(2R,3S)-2-benzyl-4-nitro-3-phenylbutanal (10)

Chromatography hexanes/EtOAc 1:1.

syn-10: Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.72 (d, *J* = 2.3Hz, 1H), 7.38-7.11 (m, 8H), 7.03 (dd, *J* = 7.9, 1.5 Hz, 2H), 4.73-4.70 (m, 2H), 3.87-3.79 (m, 1H), 3.16-2.98 (m, 1H), 2.78-2.75 (m, 2H). ^{13}C NMR (75MHz, $CDCl_3$): δ 203.02, 137.13, 136.64, 129.27, 128.81, 128.75, 128.34, 128.07, 126.95, 78.02, 55.28, 44.44, 34.24. MS: neg. mode (M-H) 282.2. HPLC: (Chiralcel OD-H, hexane/iPrOH=9:1, 1 mL min^{-1}, λ=220 nm: t_R= 50.41 (syn, minor), 55.17 syn, maJor) min. Spectroscopic data are in agreement with those in the literature [46].

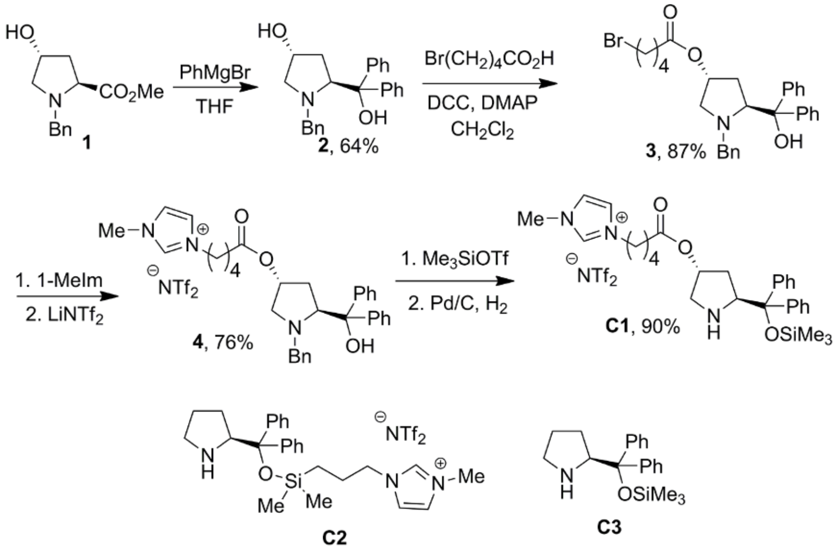
N-[(2R,3S)-1-nitro-4-oxo-3-benzyloxybutan-2-yl]acetamide (12)

Mixture of two diastereomers. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.61(s, 1H) and 9.60 (d, *J* = 2.5 Hz, 1H), 7.41-7.21(m, 5H+5H), 6.03-5.91(m, 1H + 1H), 5.21-5.13 (m, 1H), 4.87-4.69 (m, 5H), 4.58-4.49 (m, 2H+2H), 4.15 (d, *J*=2.7 Hz, 1H), 3.93 (dd, *J*=7.6, 2.5 Hz, 1H), 1.97 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ: 199.75 and 199.10, 170.32 and 170.16, 135.93 and 135.83, 129.6-127.85, 81.58 and 81.03, 74.32 and 74.08, 73.68, 46.97 and 46.85, 22.99 and 22.94. MS: (M+H) 281.1. HPLC for triphenylphosphoranylidene derivative (Chiralpak IC column, hexane/iPrOH = 82:18, 1.2 mL min^{-1}, λ=254 nm: t_R= 14.99 (anti), 19.45 (syn), 23.00 (anti), 35.52 (syn) min. Spectroscopic data are in agreement with those in the literature [45].

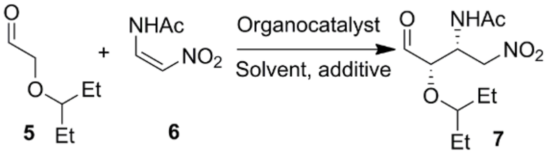
(2R,3S)-tert-butyl 2-(nitromethyl)-4-oxo-3-(pentan-3-yloxy)butanoate (14)

syn-14: Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.74 (s, 1H), 4.86 (dd, *J* = 14.3, 7.7 Hz, 1H), 4.47 (dd, *J* = 14.3, 6.2 Hz, 1H), 4.00 (d, *J* = 3.1 Hz, 1H), 3.79-3.73 (m, 1H), 3.39-3.31 (m, 1H), 1.62-1.48 (m, 4H), 1.44 (s, 9H), 0.96(t, *J* = 7.3Hz, 3H) 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ: 201.92, 167.01, 83.65, 83.39, 79.42, 72.24, 46.51, 27.82, 26.09, 25.12, 9.31.

anti-14: Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (d, *J* = 1.4Hz, 1H), 4.79 (dd, *J* = 15.0, 8.7 Hz, 2H), 4.45 (dd, *J*=15.0, 4.2 Hz, 1H), 4.24 (dd, *J* = 4.9, 1.5 Hz, 1H), 3.66-3.58 (m, 1H), 3.36-3.28 (m, 1H), 1.62-1.48 (m, 4H), 1.46 (s, 9H), 0.91(t, *J* = 7.5 Hz, 3H) 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 200.50, 168.26, 83.60, 83.15, 79.52, 71.33, 45.13, 27.82, 25.88, 25.09, 9.49. HPLC for ethyl(triphenyl-phosphoranylidene) acetate derivative (Chiralpak IC column, hexane/iPrOH = 200:1, 1mL min^{-1}, λ=211 nm: t_R= 55.97 (syn, major), 58.23 (anti, major), 105.60 (syn, minor), 146.80 (anti, minor) min. Spectroscopic data are in agreement with those in the literature [47].



Scheme 1. Synthesis of catalyst **C1**, structure of catalyst **C2** and **C3**.



Scheme 2. The reaction of aldehyde **5** with alkene **6**.

3. Results and discussion

Organocatalyst **C1** can be synthesized by known methods from simple starting materials by a sequence developed by Zlotin and coworkers [41]. When we repeated the procedure, however, this synthesis did not afford pure product. Therefore, we interchanged the order of reaction steps in the later stage of the synthesis (Scheme 1). In addition, we have prepared catalyst **C1** with bis(trifluormethylsulfonyl)imide (NTf_2) anion instead of hexafluorophosphate, because NTf_2 is considered to be more stable and does not release HF upon decomposition. We have also employed ionically tagged catalyst developed by Lombardo and coworkers (**C2**) [42] (Scheme 1). For comparison, we also used non-tagged Jorgensen-Hayashi catalyst (**C2**).

With ionically-tagged catalyst **C1** in hand, we started to assess its performance in enantioselective 1,4-additions. For the first Michael addition, we chose a reaction of aldehyde 5 with nitroalkene 6, which affords compound 7 (Scheme 2). Compound 7 is a valuable intermediate in the short organocatalytic synthesis of oseltamivir [45,48,49]. From our previous studies of this reaction with non-tagged catalyst **C3**, we knew that the best conditions comprised $CHCl_3/H_2O$ as solvent, chloroacetic acid as additive and 0°C as reaction temperature.

Ionically-tagged catalyst **C1** affords in the Michael addition of aldehyde 5 to alkene 6 mainly syn-7 isomer. The absolute configuration of product syn-7 is (S,R) that is the same as obtained with catalyst **C3**. With ionically-tagged catalyst **C1**, we again evaluated some of the reaction parameters, such as solvent, additive, temperature and reaction time. The results of condition screening in non-ionic solvents are summarized in Table 1. Several notable features can be observed. The best solvent was again chloroform/water mixture. Longer reaction times seem to be detrimental to the yield of the product as well as its stereochemical integrity (Table 1, cf. entries 3 and 4). We also attempted to use recycled catalyst **C1**, but no product 7 was isolated from this experiment (Table 1, entry 7). With catalyst **C2**, comparable results were obtained as with catalyst **C1** (Table 1, entry 12).

Although, there are examples in the literature in which ionically-tagged catalysts were used and even recycled in non-ionic media, catalyst **C1** could not be recycled in the Michael reaction of aldehyde 5 with nitroalkene 6 in $CHCl_3$/water mixture. Catalyst **C1** was designed for use in ionic liquid media. We evaluated both neat ionic liquids and their mixtures with chloroform because chloroform seems to have a beneficial effect on the reaction. The results of experiments in ionic liquids are summarized in Table 2. The Michael addition of aldehyde 5 with nitroalkene 6 was evaluated at two different temperatures, 0 and 20°C. The differences were mostly small with a predictable outcome. Lower temperature slowed down the reaction, but enantioselectivities were

Table 1. Screening for optimal reaction condition on the addition of 5 to 6.[a]

Entry	Solvent/condition	Time (h)	Yield (%)	d.r.[b]	ee (%)[c]
1	$CHCl_3$/No additive/C1	70	43	52:48[d]	66/44
2	$CHCl_3$/Cl-AcOH/C1	40	81	58:42[d]	72/54
3	$CHCl_3$/ Cl-AcOH/C1	18	72	66:34[d]	76/43
4	$CHCl_3$/ Cl-AcOH/C1[e]	70	48	50:50[d]	63/48
5	$CHCl_3$/ Cl-AcOH,0°C/C1	5	61	72:28	85/10
6	$CHCl_3$/PhCO2H, -5°C/C1	17	72	63:37	68/20
7	$CHCl_3$/recycled C1/Cl-AcOH	20	0	-	-
8	DMF/ Cl-AcOH /C1	40	49	62:38[d]	50/43
9	DMSO/ Cl-AcOH /C1	40	55	55:45[d]	21/4
10	$CHCl_3$/H_2O/No additive/C1	70	13	62:38[d]	40/30
11	$CHCl_3$/H_2O (3:2)/Cl-AcOH,0°C/C1	5	71	58:42	81/-5
12	$CDCl_3$/H_2O, Cl-AcOH/C2	18	79[e]	68:32	85/20
13	$CHCl_3$/H_2O/C3 /Cl-AcOH	18	65	57:43[d]	72/52
14	$CHCl_3$/H_2O/C3/Cl-AcOH, 0°C	5	71	80:20	93/17

[a] *Conditions: nitroalkene 6 (0.25 mmol), aldehyde 5 (0.375 mmol), C1 (0.025 mmol), $CHCl_3$ (0.5 mL), H_2O (0.5 mL), 20°C, $ClCH_2CO_2H$ (0.05 mmol);*
[b] *Ratio of syn-7/anti-7, determined by ^1H NMR of the crude reaction mixture;*
[c] *ee syn-7/anti-7, determined by enantioselective HPLC;*
[d] *d.r. of chromatographically purified product;*
[e] *0.1 mmol (40 mol%) of $ClCH_2CO_2H$ was used and conversion determined by ^1H NMR.*

slightly higher (Table 2, cf. entries 3 and 9, 6 and 7). On the other hand, structure of ionic liquid had a much larger influence on the Michael addition of 5 with 6. Three ionic liquids stand out in terms of isolated yield of product 7 and its enantiomeric purity. The best results were obtained in [bmpyr]BF_4, [bmim]NTf_2, and [bdmim] NTf_2 (Table 2, entries 7, 9-10, and 14).

Contrary to the commonly perceived notion that organic compounds are easily extracted from ionic liquids with non-polar organic solvents, we have encountered difficulties in isolating product 7 from ionic liquids by extraction with Et_2O. To test extractability of the product, we dissolved a fixed amount of compound 7 in ionic liquid ([bdmim]NTf_2) and extracted it with various solvents and procedures. Surprisingly, even when repeating extractions, we were not able to fully recover compound 7 from ionic liquids. Taking into account solubility of compound 7 and miscibility of the ionic liquid with organic solvents, only Et_2O, tBuOMe, toluene and cyclohexane were suitable. After 10 extractions, 45% of product 7 was obtained with Et_2O and 44% with toluene. However, substantial amounts of ionic liquid was also extracted. A continual extraction was more effective in obtaining product 7, where it was recovered in almost quantitative yield after 5 h with Et_2O. However, similarly to batch extraction, substantial quantities of ionic liquid was extracted and contaminated the product. The extracted ionic liquid could be separated from the product by flash chromatography. An alternative procedure for isolating product 7 was to subject the whole reaction mixture to column chromatography. However, recycling is not possible in this way.

In the Michael addition of aldehyde 5 with nitroalkene 6, we tested recyclability of the catalyst **C1**. For recycling experiments, we have selected [bdmim]NTf_2, one of the ionic liquids, in which the reaction worked best. The catalyst can be used repeatedly, but reduction of yield and enantiomeric purity of product 7 was observed. The main reason for decreased performance was probably catalyst decomposition. This was evidenced by 1H NMR analysis of the catalyst **C1** after the reaction, which showed its decomposition. The notion was also supported by the fact that yield and enantiomeric purity of product 7 increased in the fourth run, in which 10 mol% of fresh catalyst **C1** was added to the reaction mixture. The decomposition of prolinol silyl ethers in polar and acidic media was also described by Zeitler, Gschwind and co-workers [50]. Another practical issue is that quality of Et_2O, used for extracting product 7 from the ionic liquid, affecting the recyclability of catalyst **C1**. Using distilled and dried Et_2O led to considerably improved recyclability of the catalyst **C1**. Probably, removal of reactive organic peroxide from technical Et_2O was responsible for this fact. The results of the **C1** recycling are summarized in Table 3.

Table 2. Addition of aldehyde 5 to nitroalkene 6 catalyzed by **C1** in ionic liquids[a].

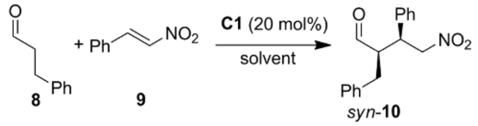
Entry	Solvent/conditions	Yield (%)	d.r. (*syn:anti*)[b]	ee (syn/anti)[c]
1	$CHCl_3$/[bmim]BF_4/A	23	2:1	84/43
2	$CHCl_3$/[bmim]PF_6/A	67	1:1.2	40/-45
3	$CHCl_3$/[bmim]NTf_2/A	61	2.3:1	85/67
4	$CHCl_3$/[bmim]$N(CN)_2$/A	11	1:1	38/37
5	$CHCl_3$/[bmim]$MeCO_3$/A	0	-	-
6	$CHCl_3$/[bmpyr]BF_4/A	32	1.9 : 1	83/25
7	$CHCl_3$/[bmpyr]BF_4/B	76[f](48)[e]	1.3 :1[d]	73/47
8	$CHCl_3$/[bmim]BF_4/B	52	1:1.3[d]	78/67
9	$CHCl_3$/[bmim]NTf_2/B	74	1.6:1[d]	75/55
10	$CHCl_3$/[bdmim]NTf_2/B	67	1.4:1[d]	86/68
11	$CHCl_3$/[bmim]OTs/B	60	1.3:1[d]	73/26
12	$CHCl_3$/[bmim]OTf/B	0	-	-
13	[bdmim]NTf_2/B	38	1.2:1[d]	78/78
14	[bdmim]NTf_2/C	95	1.3:1[d]	69/32
15	[bdmim]NTf_2/H_2O/C	65	1.3:1[d]	27/-20
16	[bdmim]NTf_2/$CHCl_3$/H_2O/B	14	1.4:1[d]	78/6
17	[bdmim]NTf_2/$CHCl_3$/H_2O/C	41	1.3:1[d]	21/25

[a] *Conditions: nitroalkene 6 (0.25 mmol), aldehyde 5 (0.375 mmol), C1 (0.025 mmol), ionic liquid (0.5 mL), 20°C, $ClCH_2CO_2H$ (0.05 mmol), time 22-24 h;*
[b] *Determined by ^1H NMR of the crude reaction mixture;*
[c] *Determined by enantioselective HPLC;*
[d] *dr of isolated product;*
[e] *product was isolated by extraction with Et_2O;*
[f] *Average of two experiments. A: $ClCH_2CO_2H$, 0°C; B: $ClCH_2CO_2H$, 20°C; C: no additive, 20°C.*

Table 3. Recycling of **C1** in the reaction of 5 with 6 in [bdmim]NTf_2[a].

Run	Yield	d.r. (*syn:anti*)[b]	ee (syn/anti)[c]
1	56	1.3 : 1	79/40
2	22	1.3 : 1	36/32
3	28	1.2 : 1	39/29
4[d]	51	1.4 : 1	60/29

[a] *Conditions: nitroalkene 6 (0.25 mmol), aldehyde 5 (0.375 mmol), C1 0.025 mmol), [bdmim]NTf_2 (1 mL), 20°C, 20 h, the product was extracted with Et_2O (7×5 mL), the residual solvent was removed under vacuum and new nitroalkene and aldehyde were added;*
[b] *Determined by ^1H NMR of the crude reaction mixture;*
[c] *Determined by enantioselective HPLC;*
[d] *0.025 mmol of new C1 was added.*



toluene: 64%, d.r. 70:30, 74% ee
[bmim]NTf_2: 84%, d.r. 76:24, 91% ee

Scheme 3. Michael addition of aldehyde 8 to nitrostyrene (9).

The catalyst **C1** was evaluated also in the reaction of 3-phenylpropanal (8) with β-nitrostyrene (9). The resulting product 10 was isolated as a mixture of two diastereomers. Usually dominant isomer syn-10 had high enantiomeric purity. Interestingly, the product 10 was isolated in higher yield and with higher enantiomer purity in ionic liquid [bmim]NTf_2 than in toluene (Scheme 3).

In the reaction of aldehyde 8 with β-nitrostyrene (9), the catalyst **C1** was recycled for seven times without loss of enantioselectivity. Its catalytic activity decreased gradually after the fifth run (Table 4). These results also suggest that stability of catalyst **C1** depends on the structure of reactants. It is therefore possible that the stability of the intermediate enamine resulting from an aldehyde and catalyst plays an important role.

Michael addition of benzyloxyacetaldehyde (11) with nitroalkene 6 affords product 12, which can lead to an oseltamivir analogue [45]. This Michael addition can also be performed with ionically-tagged catalyst **C1**, but neither diastereoselectivity or enantioselectivity was observed in ionic liquid [bdmim]NTf_2 (Scheme 4).

Table 4. **C1** recycling in the reaction of 8 with 9 in [bmim]NTf$_2$.

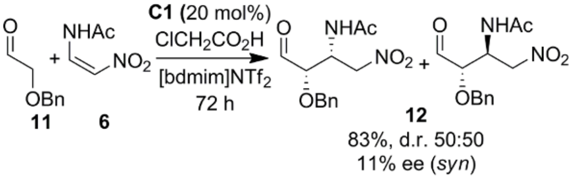
Run	Time (h)	Yield of 10 (%)	syn-10/anti-10	ee (*syn:anti*)
1	28	44	79:21	93/30
2	45	51	77:23	89/30
3	72	69	78:22	94/26
4	72	65	79:21	93/25
5	96	68	78:22	94/26
6	72	47	78:22	93/27
7	72	37	78:22	91/25
8	72	14	78:22	91/19

[a]*Conditions: nitroalkene 9 (0.5 mmol), aldehyde 8 (0.75 mmol), C1 (0.025 mmol), [bmim]NTf$_2$ (0.5 mL), 20°C;*
[b]*dr of isolated product;*
[c]*Determined by enantioselective HPLC.*

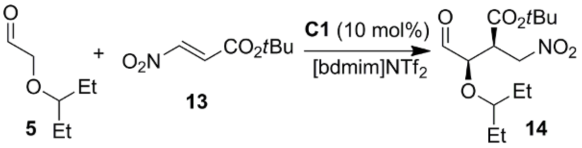
Table 5. Michael addition of 5 with 13 in [bdmim]NTf$_2$.

Entry	Conditions	Time (h)	Yield (%)	d.r.[b]	ee[c]
1	No additive	48	8 %	63:37	-
2	Cl-AcOH	24	94 %	57:43	95/94
3	Cl-AcOH, 2nd cycle	22	71%	55:45	95/91
4	Cl-AcOH, 3rd cycle	22	6%	-	-
5	Cl-AcOH, 4th cycle	22	-	-	-
6	Cl-AcOH, 5 mol% C1	24	95	62:38	93/90
7	Cl-AcOH, 2.5 mol% C1	24	37	52:48	94/94

[a]*Conditions: nitroalkene 13 (0.25 mmol), C1 (0.025 mmol), aldehyde 5 (0.375 mmol), $ClCH_2CO_2H$ (0.05 mmol), [bdmim]NTf$_2$ (0.5 mL), 20°C; the reaction mixture was extracted with Et_2O (4x);*
[b]*syn-14:anti-14 determined by ^1H NMR after chromatography;*
[c]*ee syn-14/anti-14 determined by enantioselective HPLC.*



Scheme 4. Michael addition of aldehyde **11** to alkene **6**.



Scheme 5. Michael addition of aldehyde **5** to nitroalkene **13**.

A reaction of aldehyde 5 with nitroacrylate 13 is another useful organocatalytic Michael addition (Scheme 5). The product 14 was elaborated by Hayashi into oseltamivir [47,51]. Ionically-tagged catalyst **C1** was able to efficiently catalyze this reaction as well. The product 14 was isolated in good yield and with high enantiomeric purity, although with only a modest diastereomeric ratio (Table 5, entry 2). The catalyst **C1** was recycled at least one time with good results, but, in subsequent cycles, remarkably little of the product 14 was isolated (Table 5, entries 3-5). Experiments with adding additional catalyst and only 2.5 mol% of **C1** showed that the main reason for low recyclability was again catalyst decomposition (Table 5, entries 6 and 7). The results of Michael addition of aldehyde 5 with nitroalkene 13 are summarized in Table 5.

4. Conclusions

Ionically-tagged diphenylprolinol silyl ether is a useful organocatalyst for enantioselective Michael additions of aldehydes to nitroalkenes. These reactions can be performed well in ionic liquids, and, with one exception, the results obtained in ionic liquids are comparable to classical solvents. A useful feature of the catalytic system comprising ionically tagged catalyst in an ionic liquid is its recyclability, although this depends on the structure of substrates and is, to some extent, limited by inherent instability of silyl ethers in polar media.

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