

Guanidinium-tagged Organocatalysts for Direct Aldol Reactions

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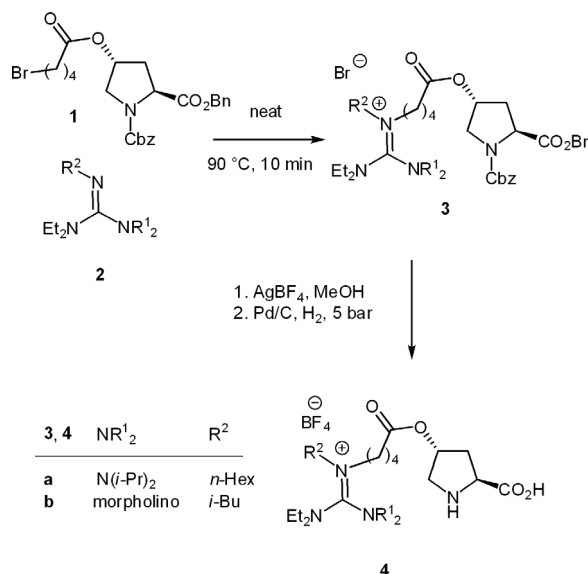
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Hexasubstituted guanidinium moieties have been used as ionic liquid tags for organocatalysts for the first time. Such conjugates were obtained in the (*S*)-proline and (*S*)-pyrrolidine-2-ylmethyl series by alkylation reactions of pentasubstituted guanidines. The resulting guanidinium-tagged organocatalysts were applied to asymmetric direct aldol reactions providing high stereoselectivities and yields and good recyclability, and thus performed better than (*S*)-proline itself.

Key words: Organocatalysis, Ionic Liquids, Guanidinium Salts, Proline, Asymmetric Synthesis, Aldol Reaction

Introduction

Organocatalysis is a rapidly developing field in asymmetric organic synthesis, and still new applications of hitherto not considered reactions are found. Thus the development of new catalysts is of high interest. From the point of view of Green Chemistry recycling of catalysts and solvents is an important issue. To meet this challenge the application of ionic liquids (IL's) was exploited [1–8]. IL's possess very high boiling points and are almost non-volatile. Thus they can be used as reaction media from which volatile products can be removed by distillation, and the remaining IL's can be reused directly. As an alternative, products formed in a polar IL as reaction medium can be separated by extraction with unpolar solvents leaving behind the IL for reuse. However, if this methodology is used for organocatalyzed reactions, unwanted leaching of the organocatalyst can occur during extraction. To overcome such problems, so called IL-tagged organocatalysts have been developed [9]. Here, the organocatalyst unit is covalently linked to an IL motif. Thus this polar conjugate is less sensitive to leaching during extraction with organic solvents. IL-tagged organocatalysts can be used in IL media as well as in common organic solvents. So far, imidazolium salts were mainly used as IL tags of organocatalysts [9, 10], while guanidinium salts as another important class of IL's [11–18] were totally neglected. Recently, we used 1,2,3-triazolium tags [19–22], and we report here first examples of organocatalysts tagged by guanidinium salts and their application in direct asymmetric aldol reactions.

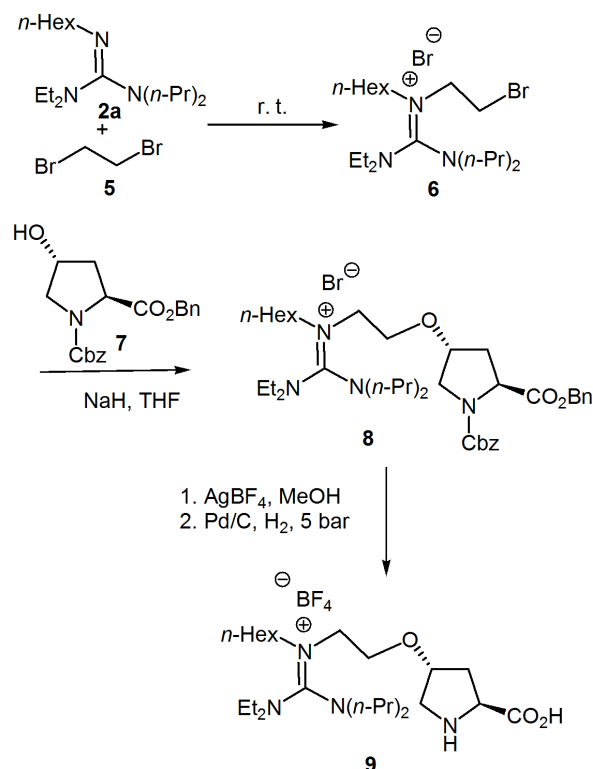


Scheme 1. Synthesis of guanidinium-tagged proline **4**.

Results and Discussion

The 4-hydroxy group of *trans*-(*S*)-4-hydroxyproline can be used as tethering site for IL tags resulting in conjugates of very good catalytic performance [21, 23–26]. Accordingly, we used the 5-bromopentanoylated *N*-Cbz-(*S*)-proline benzyl ester **1** and pentaalkyl-guanidines **2** to obtain the corresponding hexasubstituted guanidinium bromides **3** (Scheme 1).

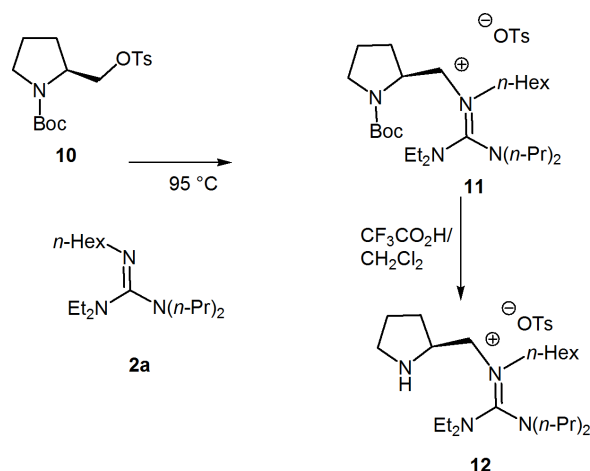
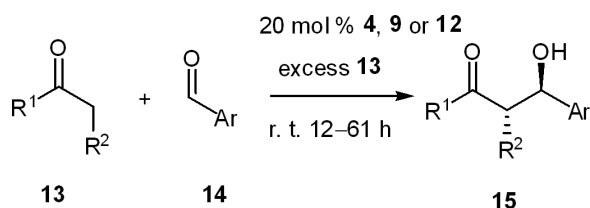
After salt metathesis with Ag-tetrafluoroborate the proline moiety was deprotected by Pd-catalyzed hy-

Scheme 2. Synthesis of the guanidinium-tagged proline **9**.

drogenation providing the guanidinium-tagged prolines **4** in good yields. In another approach, the pentasubstituted guanidine **2a** was alkylated with 1,2-dibromoethane, and the resulting guanidinium salt **6** served as alkylating reagent for the diprotected *trans*-(*S*)-4-hydroxyproline **7** giving the ether **8**. Salt metathesis and hydrogenative deprotection provided the guanidinium-tagged proline **9** (Scheme 2).

In a different strategy, a chiral pyrrolidine **12** was targeted wherein the IL tag is connected to the methyl group in position 2 (Scheme 3). Thus *N*-Boc-protected prolinol tosylate **10** [27] was applied as alkylating reagent for the pentasubstituted guanidine **2a**. Acidic deprotection of the resulting guanidinium salt **11** led to the free secondary amino group (formation of **12**) necessary for enamine or iminium salt formation in organocatalysis.

With these IL-tagged organocatalysts **4**, **9** and **12** in hand, we applied them in direct aldol reactions of aromatic aldehydes **14** with cycloaliphatic and aliphatic ketones **13**. The reactions were performed in an excess of ketone **13** as solvent with 20 mol-% of the organocatalyst (Scheme 4).

Scheme 3. Synthesis of the guanidinium-tagged methylpyrrolidine **12**.Scheme 4. Aldol reaction catalyzed by guanidinium-tagged organocatalysts **4**, **9** or **12**.

High yields (often above 90%), diastereoselectivities (usually 95:5) and enantioselectivities (up to 98 %) were obtained in most cases (Table 1). While not much difference was found in the performance of the IL-tagged organocatalysts **4a** and **4b**, catalyst **9** showed less satisfactory results in the majority of cases. This fact demonstrates that the linker between the organocatalytic proline unit and the guanidinium tag has some effect on the catalytic properties. As far as the scope of reactants is concerned, better results were achieved with cyclohexanone than with cyclopentanone (compare Table 1, products **15a** and **15f**). Remarkably, also acetone could be transformed into the corresponding aldol **15g** in high yields and *ee* up to 88 % (Table 1). On the carbonyl side **14**, aromatic aldehydes with electron withdrawing substituents perform better than those with electron donating groups (compare Table 1, products **15a** and **15e**). The guanidinium-tagged pyrrolidinemethyl-substituted guanidinium salt **12** was also applied to aldol reactions, but **15** was formed with no enantioselectivity. This phenomenon is probably caused by interaction of the secondary amino group with the guani-

Table 1. Aldols **15** obtained with guanidinium-tagged organocatalysts **4** or **9**.

15	R ¹ R ²	Ar	Catalyst 4a				Catalyst 4b				Catalyst 9			
			t (h)	Yield (%)	<i>anti</i> / <i>syn</i> ^a	<i>ee</i> (%) ^a	t (h)	Yield (%)	<i>anti</i> / <i>syn</i> ^a	<i>ee</i> (%) ^a	t (h)	Yield (%)	<i>anti</i> / <i>syn</i> ^a	<i>ee</i> (%) ^a
a	(CH ₂) ₄	4-NO ₂ -Ph	28	94	97:3	98	31	99	97:3	92	25	92	97:3	94
b	(CH ₂) ₄	4-Br-Ph	29	89	95:5	72	24	90	95:5	64	36	87	95:5	76
c	(CH ₂) ₄	4-Cl-Ph	18	70	95:5	92	25	79	95:5	92	22	76	95:5	64
d	(CH ₂) ₄	4-F-Ph	12	90	90:10	94	17	95	90:10	88	27	86	90:10	70
e	(CH ₂) ₄	4-MeOPh	36	81	97:3	46	42	84	97:3	52	61	79	97:3	39
f	(CH ₂) ₃	4-NO ₂ -Ph	44	87	67:33	86	41	91	67:33	81	50	81	67:33	74
g	CH ₃ H	4-NO ₂ -Ph	39	91	–	80	32	88	–	77	37	80	–	67

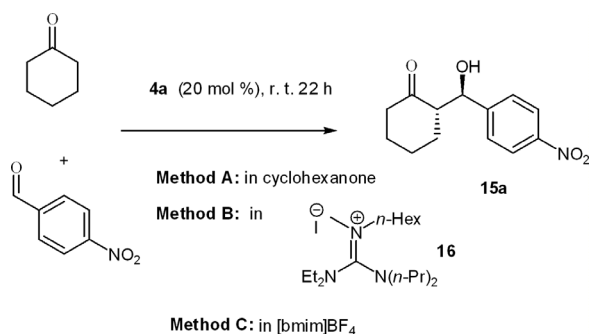
^a *ee* of the major diastereomer, determined by HPLC on a chiral column (Chiralcel AD column (*n*-hexane/*i*-PrOH 90:10), assignment of configuration by comparison with literature data: ref. [28]).

Table 2. Recycling experiments with IL-tagged catalyst **4a** using Methods A, B, C.

Cycle ^a	Yield (%) / time (h) ^a			<i>anti</i> / <i>syn</i> ^b			<i>ee</i> (%) ^b		
	Method			Method			Method		
	A	B	C	A	B	C	A	B	C
1	96/26	97/21	97/29	99:1	97:3	98:2	98	98	99
2	95/33	96/28	95/37	98:2	97:3	98:2	98	95	98
3	90/39	93/35	90/42	95:5	96:4	95:5	94	85	77
4	88/48	92/45	85/51	95:5	96:4	94:6	79	72	62

^a Extraction of product with diethyl ether;

^b *ee* of major diastereomer, determined by HPLC on a chiral column (Chiralcel AD column (*n*-hexane/*i*-PrOH 90:10); assignment of configuration by comparison with literature data: ref. [28]).



dinium C atom which reduces the nucleophilicity of the former and thus the enamine formation necessary for the aldol reaction is hampered.

At this point it can be resumed that guanidine tagging of proline results in effective catalysts for directed aldol reactions. In all cases results are much better than in analogous aldol reactions catalyzed just by proline [29].

As another issue, recycling of IL-tagged organocatalysts was investigated. The experiments were exerted with cyclohexanone and 4-nitrobenzaldehyde using three different methods A, B, C (Table 2). Method A was the same (excess cyclohexanone as solvent) as used above in Table 1. As an alternative, the reaction was performed with equimolar quantities of reactants in the guanidinium salt **16** as IL (Method B) or in the commercial IL 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄) (Method C). In each method, the product **15a** was extracted with diethyl ether leav-

ing behind **4a** (Method A) or so-called working solutions of the IL with **4a** (Methods B, C). New reactants were added to the remainder in order to perform the next run.

Table 2 reveals that *ee*'s higher than 90 % can be obtained up to the third run by method A. Methods B and C working in ionic liquids gave the same high *ee* in the first run but showed a significant decrease after the second run. Diastereoselectivities were high throughout all experiments. The reduction of *ee*'s after the third run observed in all cases was likely caused by gradual leaching of the IL-tagged organocatalyst during the extraction with diethyl ether.

Conclusion

In summary, ionic liquid tagging of organocatalysts by guanidinium salts was implemented for the first time. Such conjugates were obtained by alkylation of pentaalkyl-substituted guanidines with (*S*)-4-hydroxyproline or an (*S*)-pyrrolidin-2-methyl derivative. Application in aldol reactions of ketones with aromatic aldehydes gave excellent yields and stereoselectivities which are significantly better than results obtained by (*S*)-proline, proving the usefulness of guanidinium salts as advantageous IL tags. As compared with IL-tagging of 4-hydroxyproline by 1,2,3-triazolium salts [19, 21], the guanidinium-tagged organocatalysts reported here performed equally well but allowed improved recycling.

Experimental Section

^1H NMR and ^{13}C NMR spectra in CDCl_3 were recorded at 300 and 75 MHz, respectively, with a Bruker AC 300 instrument. Chemical shifts δ are given in ppm with TMS as internal standard. Silica gel (0.04–0.063 mm, Merck) was used for preparative column chromatography. Starting materials were purchased from commercial suppliers. Configurations of major products were elucidated by comparing their optical rotation with literature data [28]. Compounds **1**, **7** and **10** [27] were synthesized according to literature procedures. Pentasubstituted guanidines **2** and the guanidinium iodide **16** were provided by Prof. W. Kantlehner, University of Stuttgart. All other materials were purchased from commercial suppliers.

N-((5-((3*R*,5*S*)-5-Carboxypyrrolidin-3-yloxy)-5-oxopentyl)-*N*-((diethylamino)(dipropylamino)methylene)hexan-1-aminium tetrafluoroborate (**4a**)

A mixture of the proline derivative **1** (1.10 g, 2.12 mmol) and 1,1-diethyl-2-hexyl-3,3-dipropylguanidine (**2a**) (0.72 g, 2.54 mmol) was heated to 90 °C for 10 min, cooled to 20 °C and washed with Et_2O (6×15 mL). The residue was dissolved in MeOH (3 mL), and Et_2O (15 mL) was gradually added to the stirred solution. The separated oil was put under vacuum (0.5 Torr) for 2 h to afford the bromide intermediate **3a**. Yield: 1.29 g (76 %); yellow, viscous oil. – $R_f = 0.21$. – ^1H NMR (300 MHz, CDCl_3): $\delta = 7.31$ – 7.26 (m, 10H, Ph), 5.14–5.13 (m, 2H, $\text{CH}_2\text{-CO}_2\text{-N}$), 5.12 (m, 2H, $\text{CH}_2\text{-CO}_2\text{-CH}$), 5.03 (m, 1H, $\text{CO}_2\text{-CH-C}$), 4.42–4.38 (m, 1H, N-CH-CO₂), 4.22–4.19 (m, 2H, $\text{N}^+\text{-CH}_2\text{-(CH}_2)_3\text{-CO}$), 4.11–4.07 (m, 2H, $\text{N}^+\text{-CH}_2\text{-(CH}_2)_4\text{-CH}_3$), 3.88–3.76 (m, 2H, N-CH₂-CO), 2.67–2.61 (dd, 4H, N-CH₂-CH₃), 2.56–2.52 (t, 4H, N-CH₂-CH₂-CH₃), 2.40–2.32 (m, 1H, $\text{CO}_2\text{-CH-CH}_2\text{-CH}$), 2.04–1.97 (m, 1H, $\text{CO}_2\text{-CH-CH}_2\text{-CH}$), 2.37–2.25 (m, 2H, $\text{CO}_2\text{-CH}_2$), 1.74–1.67 (m, 2H, $\text{CO}_2\text{-CH}_2\text{-CH}_2$), 1.85–1.78 (m, 2H, $\text{CO}_2\text{-(CH}_2)_2\text{-CH}_2$), 1.85–1.78 (m, 2H, $\text{N}^+\text{-CH}_2\text{-CH}_2\text{-(CH}_2)_2\text{-CO}$), 1.74–1.67 (m, 2H, $\text{N}^+\text{-(CH}_2)_2\text{-CH}_2\text{-CH}_2\text{-CO}$), 1.77–1.69 (m, 2H, $\text{N}^+\text{-CH}_2\text{-CH}_2\text{-(CH}_2)_3\text{-}$), 1.60–1.52 (m, 2H, $\text{N}^+\text{-(CH}_2)_2\text{-CH}_2\text{-CH}_2\text{-}$), 1.29–1.20 (m, 2H, $\text{N}^+\text{-(CH}_2)_3\text{-CH}_2\text{-}$), 1.39–1.32 (m, 2H, $\text{N}^+\text{-(CH}_2)_4\text{-CH}_2\text{-}$), 1.44–1.35 (m, 4H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-N}$), 0.96–0.94 (m, 6H, $\text{CH}_3\text{-CH}_2\text{-N}$), 0.81–0.78 (m, 6H, $\text{CH}_3\text{-(CH}_2)_2\text{-N}$), 0.71 (m, 3H, $\text{CH}_3\text{-(CH}_2)_5\text{-N}$). – ^{13}C NMR (75 MHz, CDCl_3): $\delta = 171.1$, 168.6, 154.6, 136.3, 135.7, 127.0–128.4, 73.2, 67.4, 67.1, 62.8, 53.2, 53.1, 51.4, 47.9, 43.3, 36.1, 33.4, 31.2, 28.6, 28.1, 26.9, 22.2, 21.6, 19.3, 13.7, 13.4, 8.1. – HRMS ((+)-ESI: $m/z = 722.4969$ (calcd. 722.4971 for $\text{C}_{42}\text{H}_{66}\text{N}_4\text{O}_6^+$, $[\text{M}+\text{H}]^+$).

For transformation into the corresponding tetrafluoroborate, the bromide **3a** (0.5 g, 0.62 mmol) was dissolved in dry methanol (15 mL). In a second flask AgBF_4 (0.12 g, 0.62 mmol) was dissolved in dry methanol (15 mL) (to ex-

clude light, the flask was wrapped in aluminum foil, or a brown flask was used). This AgBF_4 solution was added dropwise to the solution of **3a** until no more precipitate (AgBr) was formed. After the precipitate had settled the supernatant clear solution was separated, dried and evaporated giving a quantitative yield of the tetrafluoroborate as a yellow oil. The NMR spectra are identical to those of **3a**. For deprotection, to a solution of the tetrafluoroborate (1 g, 1.23 mmol) in dry methanol (15 mL) Pd/C (80 mg) was added, and the mixture was pressurized under H_2 at 5 bar. After stirring over night the Pd/C was filtered off, and the filtrate was concentrated under vacuum giving the final product **4a**. Yield: 611 mg (85 %); yellow oil. – ^1H NMR (300 MHz, CDCl_3): $\delta = 5.22$ (m, 1H, $\text{CH}_2\text{-CO}_2\text{-CH}$), 4.97 (m, 2H, $\text{N}^+\text{-CH}_2\text{-(CH}_2)_4\text{-CH}_3$), 4.22 (m, 1H, N-CH-CO₂), 3.24 (m, 2H, $\text{N}^+\text{-CH}_2\text{-(CH}_2)_3\text{-CO}$), 3.00 (m, 2H, N-CH₂-CH-O), 2.88 (m, 1H, $\text{CO}_2\text{-CH-CH}_2\text{-CH}$), 2.52 (m, 4H, N-CH₂-CH₃), 2.45 (m, 1H, $\text{CO}_2\text{-CH-CH}_2\text{-CH}$), 2.29 (t, 4H, N-CH₂-CH₂-CH₃), 1.61 (m, 2H, $\text{CO}_2\text{-CH}_2$), 1.42 (m, 2H, $\text{N}^+\text{-CH}_2\text{-CH}_2\text{-(CH}_2)_2\text{-CO}$), 1.25 (m, 2H, $\text{N}^+\text{-CH}_2\text{-CH}_2\text{-(CH}_2)_3\text{-}$), 1.17 (m, 2H, $\text{N}^+\text{-(CH}_2)_2\text{-CH}_2\text{-CH}_2\text{-CO}$), 1.11 (m, 2H, $\text{N}^+\text{-(CH}_2)_2\text{-CH}_2\text{-CH}_2\text{-}$), 1.06 (m, 4H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-N}$), 1.01 (m, 2H, $\text{N}^+\text{-(CH}_2)_4\text{-CH}_2\text{-}$), 0.98 (m, 2H, $\text{N}^+\text{-(CH}_2)_3\text{-CH}_2\text{-}$), 0.98–0.94 (m, 6H, $\text{CH}_3\text{-CH}_2\text{-N}$), 0.81 (m, 6H, $\text{CH}_3\text{-(CH}_2)_2\text{-N}$), 0.76 (m, 3H, $\text{CH}_3\text{-(CH}_2)_5\text{-N}$). – ^{13}C NMR (75 MHz, CDCl_3): $\delta = 172.9$, 163.8, 135.7, 73.0, 60.9, 51.1, 50.9, 49.2, 43.8, 34.8, 33.5, 32.8, 29.0, 28.7, 26.9, 22.0, 21.4, 20.5, 13.7, 10.5. – HRMS ((+)-ESI: $m/z = 498.4133$ (calcd. 498.4134 for $\text{C}_{27}\text{H}_{54}\text{N}_4\text{O}_4^+$, $[\text{M}+\text{H}]^+$).

*5-((3R,5S)-5-Carboxypyrrolidin-3-yloxy)-N-((diethylamino)(morpholino)methylene)-N-isobutyl-5-oxopentan-1-aminium tetrafluoroborate (**4b**)*

A mixture of the 4-(ω -bromovaleroyloxy)-proline **1** (1.10 g, 2.12 mmol) and the guanidine **2b** (0.61 g, 2.54 mmol) was heated at 90 °C for 10 min, cooled to 20 °C and washed with Et_2O (6×15 mL). The residue was dissolved in MeOH (3 mL), and Et_2O (15 mL) was gradually added to the stirred solution. The separated oil was put under vacuum (0.5 Torr) for 2 h to afford the guanidinium bromide **3b**. Yield: 1.41 g (88 %); yellow viscous oil. – ^1H NMR (300 MHz, CDCl_3): $\delta = 7.34$ – 7.15 (m, 10H, Ar), 5.21–5.06 (m, 4H, $\text{CH}_2\text{-CO}_2\text{-CH}$), 4.98–4.92 (m, 1H, $\text{CO}_2\text{-CH-C}$), 4.51–4.31 (m, 1H, N-CH-CO₂), 3.91–3.81 (m, 2H, $\text{N}^+\text{-CH}_2\text{-(CH}_2)_3\text{-CO}$), 3.78–3.64 (m, 2H, $\text{N}^+\text{-CH}_2\text{-CH-(CH}_3)_2$), 3.60–3.54 (m, 2H, N-CH₂-CH-O), 3.49–3.44 (m, 4H, N-CH₂-CH₂-O), 3.42–3.36 (dd, 4H, N-CH₂-CH₃), 3.23–3.19 (m, 4H, N-CH₂-CH₂-O), 2.96–2.57 (m, 1H, $\text{CO}_2\text{-CH-CH}_2\text{-CH}$), 2.43 (m, 2H, $\text{CO}_2\text{-CH}_2\text{-CH}_2$), 2.04–1.97 (m, 1H, $\text{CO}_2\text{-CH-CH}_2\text{-CH}$), 2.18–1.88 (m, 2H, $\text{N}^+\text{-CH}_2\text{-CH}_2\text{-(CH}_2)_2\text{-CO}$), 1.65 (m, 2H, $\text{N}^+\text{-(CH}_2)_2\text{-CH}_2\text{-CH}_2\text{-CO}$), 1.60 (m, 1H, $\text{N}^+\text{-CH}_2\text{-CH-(CH}_3)_2$),

1.27–1.16 (m, 6H, $N^+-CH_2-CH-(CH_3)_2$), 0.92–0.79 (m, 6H, CH_3-CH_2-N). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 172.01, 163.2, 154.6, 154.1, 136.1, 135.3, 128.5–127.1, 71.8, 67.2, 66.7, 59.8, 57.6, 52.6, 50.9, 49.9, 44.8, 43.6, 36.4, 35.4, 26.8, 26.4, 20.5, 20.3, 20.2, 13.2, 13.0. – HRMS ((+)-ESI: m/z = 680.4136 (calcd. 680.4138 for $C_{38}H_{56}N_4O_7$, $[M+H]^+$).

The guanidinium bromide **3b** was transformed into the corresponding tetrafluoroborate and finally deprotected in the same way as described for **4a** giving the final product **4b**. Yield: 585 mg (83 %); yellow oil. – 1H NMR (300 MHz, $CDCl_3$): δ = 5.28 (m, 1H, CH_2-CO_2-CH-C), 4.01 (m, 1H, $N-CH-CO_2$), 3.98 (m, 2H, $N^+-CH_2-(CH_2)_3-CO$), 3.74 (m, 2H, $N^+-CH_2-CH-(CH_3)_2$), 3.38 (m, 2H, $N-CH_2-CH-O$), 3.20 (m, 4H, $N-CH_2-CH_2-O$), 2.72–2.30 (dd, 4H, $N-CH_2-CH_3$), 2.40–2.31 (m, 4H, $N-CH_2-CH_2-O$), 1.76–1.43 (m, 1H, $CO_2-CH-CH_2-CH$), 1.74–1.67 (m, 2H, $N^+-(CH_2)_2-CH_2-CH_2-CO$), 1.62 (m, 2H, CO_2-CH_2), 1.56 (m, 2H, $N^+-CH_2-CH_2-(CH_2)_2-CO$), 1.22 (m, 1H, $N^+-CH_2-CH-(CH_3)_2$), 0.87 (m, 6H, $N^+-CH_2-CH-(CH_3)_2$), 0.76 (m, 6H, CH_3-CH_2-N). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 171.6, 163.1, 133.5, 73.2, 65.8, 65.5, 65.4, 64.5, 57.5, 56.4, 49.8, 48.9, 43.8, 36.1, 33.5, 26.3, 25.9, 21.4, 20.2, 12.7. – HRMS: ((+)-ESI: m/z = 456.3300 (calcd. 456.3301 for $C_{23}H_{44}N_4O_5$, $[M+H]^+$).

N-(2-Bromoethyl)-*N*-((diethylamino)(dipropylamino)methylene)hexane-1-aminium bromide (**6**)

1,1-Diethyl-2-hexyl-3,3-dipropylguanidine (**2a**) (1.00 g, 3.7 mmol) was mixed with 1,2-dibromoethane (1.09 g, 5.5 mmol). The reaction mixture was stirred at r. t. over night. The resulting sticky material was washed with diethyl ether (3×25 mL). After keeping under vacuum for 1 h product **6** was obtained as a colorless oil; yield 1.3 g (64 %). – 1H NMR (300 MHz $CDCl_3$): δ = 4.09–3.91 (m, 2H, $N^+-CH_2-CH_2-O$), 3.79–3.58 (m, 2H, $N^+-CH_2-CH_2-O$), 3.41–2.91 (m, 10H, $N(CH_2-CH_2-CH_3)_2$, $N(CH_2-(CH_2)_4-CH_3)$, $N(CH_2-CH_3)_2$), 1.79–1.43 (m, 6H, $N(CH_2-CH_3)_2$), 1.22–1.27 (m, 12H, $N-(CH_2)-(CH_2)_4-CH_3$), $N-((CH_2)-(CH_2)-CH_3)_2$), 0.86–0.96 (m, 9H, $N(CH_2-CH_2-CH_3)_2$, $N-(CH_2)_5-CH_3$). – ^{13}C NMR (75 MHz $CDCl_3$): δ = 163.78, 53.24, 53.15, 51.69, 51.56, 51.07, 31.26, 27.40, 27.22, 26.46, 22.48, 20.97, 13.93, 13.55, 13.26, 12.97, 11.37.

N-(2-((3*R*,5*S*)-5-Carboxypyrrolidin-3-yloxy)ethyl)-*N*-((diethylamino)(dipropylamino)methylene)hexan-1-aminium tetrafluoroborate (**9**)

A solution of the diprotected 4-hydroxyproline **7** (3.2 g, 9 mmol) in dry DMF (25 mL) was added to a suspension of sodium hydride (0.3 g, 13 mmol) in dry DMF (25 mL) at $-20^\circ C$ under argon. The reaction mixture was stirred for 20 min. *N*-(2-Bromoethyl)-*N*-((diethylamino)(dipropylamino)methylene)hexan-1-aminium bromide (**6**) (6.12 g,

13 mmol) was added, and the reaction mixture was stirred at r. t. over night. The reaction mixture was extracted with diethyl ether (3×50 mL), giving a quantitative yield of **8**. – 1H NMR (300 MHz, $CDCl_3$): δ = 7.11–6.87 (m, 10H, Ar), 5.10–5.02 (m, 4H, $Ph-CH_2-CO_2$), 4.95–4.77 (m, 1H, CO_2-CH-C), 4.16–4.02 (m, 1H, $N-CH-CO_2$), 3.83–3.76 (m, 2H, $N^+-CH_2-CH_2-O$), 3.61–3.47 (m, 1H, $O-CH-CH_2$), 4.11–4.07 (m, 2H, $N^+-CH_2-(CH_2)_4-CH_3$), 3.92–3.80 (m, 2H, $N^+-CH_2-CH_2-O$), 3.71–3.52 (m, 2H, $N-CH_2-CO$), 2.94–2.80 (dd, 4H, $N-CH_2-CH_3$), 2.56–2.52 (t, 4H, $N-CH_2-CH_2-CH_3$), 2.40–2.32 (m, 1H, $CO_2-CH-CH_2-CH$), 1.82–1.64 (m, 1H, $CO_2-CH-CH_2-CH$), 1.77–1.69 (m, 2H, $N^+-CH_2-CH_2-(CH_2)_3-$), 1.60–1.52 (m, 2H, $N^+-(CH_2)_2-CH_2-CH_2-$), 1.29–1.20 (m, 2H, $N^+-(CH_2)_3-CH_2-$), 1.18–1.14 (m, 2H, $N^+-(CH_2)_4-CH_2-$), 1.01–0.91 (m, 4H, $CH_3-CH_2-CH_2-N$), 0.78–0.72 (m, 6H, CH_3-CH_2-N), 0.61–0.56 (m, 6H, $CH_3-(CH_2)_2-N$), 0.55–0.52 (m, 3H, $CH_3-(CH_2)_5-N$). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 159.7, 159.1, 154.1, 142.6, 127.6–126.1, 77.1, 63.3, 59.8, 57.6, 50.6, 49.4, 42.3, 41.9, 31.1, 29.4, 22.2, 21.2, 21.1, 20.5, 13.8, 13.0, 12.6, 11.1. – HRMS: ((+)-ESI: m/z = 666.4708 (calcd. 666.4709 for $C_{39}H_{62}N_4O_5^+$, $[M+H]^+$).

In a 50 mL dry round bottom flask the bromide **8** (0.5 g, 0.67 mmol) was dissolved in 15 mL of dry methanol (15 mL). $AgBF_4$ (0.13 g, 0.67 mmol) was dissolved in dry methanol (15 mL) under the exclusion of light. This $AgBF_4$ solution was added dropwise to the solution of **8** until no more precipitate ($AgBr$) was formed. After the precipitate had settled down the supernatant clear solution was separated, dried and evaporated to give a quantitative yield of the corresponding guanidinium tetrafluoroborate as a yellow oil. It was dissolved in dry methanol (1.00 g, 1.3 mmol in 15 mL), and Pd/C (80 mg) was added. The mixture was pressurized under H_2 at 5 bar. After stirring over night the Pd/C was filtered off, and the filtrate was concentrated under vacuum giving the unprotected tetrafluoroborate **9** (0.62 g, 91 %) as a yellow oil. – 1H NMR (300 MHz, $CDCl_3$): δ = 4.25 (m, 2H, $N^+-CH_2-CH_2-O$), 4.08 (m, 1H, $N-CH-CO_2$), 3.95–3.88 (m, 1H, $O-CH-CH_2$), 4.11–4.07 (m, 2H, $N^+-CH_2-(CH_2)_4-CH_3$), 3.92–3.78 (m, 2H, $N^+-CH_2-CH_2-O$), 3.91–3.76 (m, 2H, $N-CH_2-CO$), 2.67–2.61 (dd, 4H, $N-CH_2-CH_3$), 2.56–2.52 (t, 4H, $N-CH_2-CH_2-CH_3$), 2.40–2.32 (m, 1H, $CO_2-CH-CH_2-CH$), 2.04–1.97 (m, 1H, $CO_2-CH-CH_2-CH$), 1.87–1.69 (m, 2H, $N^+-CH_2-CH_2-(CH_2)_3-$), 1.60–1.52 (m, 2H, $N^+-(CH_2)_2-CH_2-CH_2-$), 1.25–1.19 (m, 2H, $N^+-(CH_2)_3-CH_2-$), 1.39–1.29 (m, 2H, $N^+-(CH_2)_4-CH_2-$), 1.39–1.35 (m, 4H, $CH_3-CH_2-CH_2-N$), 0.96–0.94 (m, 6H, CH_3-CH_2-N), 0.81–0.78 (m, 6H, $CH_3-(CH_2)_2-N$), 0.66–.59 (m, 3H, $CH_3-(CH_2)_5-N$). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 148.6, 77.2, 61.4, 60.7, 56.5, 52.9, 51.4, 45.5, 43.3, 32.5, 31.2, 28.6, 26.9, 22.2, 19.3, 13.7, 8.1. – HRMS: ((+)-ESI: m/z = 442.3870 (calcd. 442.3872 for $C_{24}H_{50}N_4O_3^+$, $[M+H]^+$).

(*S*)-*N*-((Diethylamino)(hexyl(pyrrolidin-2-ylmethyl)-amino)methylene)-*N*-propylpropan-1-aminium 4-methylbenzenesulfonate (**12**)

A mixture of (*S*) – *N*-Boc-*O*-tosylprolinol **10** (1.00 g, 2.81 mmol) and the pentasubstituted guanidine **2a** (1.2 eq., 955 mg, 3.37 mmol) was heated to 90 °C for 1 h, then cooled to 20 °C and washed with Et₂O (6 × 15 mL). The remainder was put under vacuum (0.5 Torr) for 2 h to afford the Boc-protected guanidinium salt **11**. The Boc group was removed by adding 6 N aq. HCl (15 mL) and refluxing for 4 h giving the tosylate **12** as a pale-yellow oil in 73 % yield. – ¹H NMR (300 MHz, CDCl₃): δ = 7.01 (d, 2H, Ar), 6.39 (d, 2H, Ar), 4.69 (1H, NH), 3.25 (m, 2H, N⁺-CH₂-CH-NH), 3.11 (m, 2H, N⁺-CH₂-CH₂), 3.06 (m, 1H, N⁺-CH₂-CH-NH), 2.94 (m, 2H, CH₂-CH₂-NH), 2.55 (m, 4H, N-CH₂-CH₃), 2.33 (m, 4H, N-CH₂-CH₂-CH₃), 2.52–2.47 (m, 1H, CH₂-CH-NH), 2.27–2.19 (m, 1H, CH₂-CH-NH), 2.08–1.89 (m, 2H, CH₂-CH₂-NH), 1.59 (s, 3H, CH₃-Ph), 1.77–1.69 (m, 2H, N⁺-CH₂-CH₂), 1.52 (m, 2H, N⁺-(CH₂)₂-CH₂), 1.44–1.39 (m, 4H, N-CH₂-CH₂-CH₃), 1.13 (m, 2H, N⁺-(CH₂)₃-CH₂), 1.10 (m, 2H, N⁺-(CH₂)₄-CH₂-CH₃), 1.01 (t, 6H, N-CH₂-CH₃), 0.76 (m, 3H, N⁺-(CH₂)₅-CH₃), 0.69 (m, 6H, N-(CH₂)₂-CH₃). – ¹³C NMR (75 MHz, CDCl₃): δ = 143.5, 138.1, 127.6, 125.2, 114.3, 53.6, 50.1, 45.2, 45.0, 30.5, 28.8, 25.9, 21.8, 20.5, 20.1, 20.0, 13.3, 12.3, 12.2, 10.5. – HRMS: ((+)-ESI: *m/z* = 368.3866 (calcd. 368.3868 for C₂₂H₄₈N₄⁺, [M+H]⁺).

Typical experimental procedure for asymmetric direct aldol reaction (in excess of ketone as solvent) catalyzed by 4a

A catalytic amount of catalyst **4a** (58 mg, 20 mol-%) was added to a flask containing 4-nitrobenzaldehyde (76 mg, 0.5 mmol) and cyclohexanone (0.26 mL, 2.5 mmol) in a closed system under argon. The reaction mixture was stirred at r. t. for 24 h and subsequently extracted with diethyl ether (5 × 10 mL). The combined organic extracts were dried with anhydrous MgSO₄ and the solvent was removed under re-

duced pressure. The crude aldol product **15** was purified by silica-gel column chromatography (*n*-hexane/AcOEt = 4 : 1) to afford the aldol product as a colorless solid (118 mg, 94 % yield).

(*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclohexanone (**15a**)

The diastereomeric *anti*:*syn* ratio was determined by ¹H NMR analysis of the crude product: δ = 5.48 (d, *J* = 1.8 Hz, 1H, *syn*, minor), 4.89 (d, *J* = 8.8 Hz, 1H, *anti*, major). Enantiomeric excess was determined by HPLC with a Chiralcel AD column (*n*-hexane/*i*-PrOH 90 : 10, 1.0 mL/min, λ = 254 nm, 25 °C): *t_R* = 26.3 min (minor) and 34.9 min (major). – ¹H NMR (300 MHz, CDCl₃): δ = 8.20 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 4.89 (d, *J* = 8.4 Hz, 1H), 4.07 (s, 1H), 2.63–2.57 (m, 1H), 2.49–2.32 (m, 2H), 2.12–1.31 (m, 6H). – ¹³C NMR (75 MHz, CDCl₃): δ = 214.8, 148.4, 147.6, 127.9, 123.5, 74.0, 57.2, 42.7, 30.8, 27.7, 24.7.

Typical experimental procedure for recycling catalyst 4a for asymmetric aldol reactions

The reaction mixture of the aldol reaction (*vide supra*) was extracted with diethyl ether (3 × 15 mL). The combined organic layers were concentrated under vacuum, and after column chromatography the pure aldol product was obtained. The residual catalyst was concentrated under vacuum to remove residual ether and was reused for the next run.

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