1,2,3-Triazolium-Tagged Prolines and Their Application in Asymmetric Aldol and Michael Reactions

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Received 3 April 2009; revised 20 July 2009

Abstract: Novel 1,2,3-triazolium-tagged proline derivatives were synthesized by copper-catalyzed click-reaction of alkynes with azides and N-alkylation of the resulting 1,2,3-triazoles. They were applied as recyclable organocatalysts in direct asymmetric aldol and Michael reactions with high enantioselectivity and diastereoselectivity. These catalysts performed better than (*S*)-proline itself; that is to say, a synergistic effect of the triazolium and the proline moiety exists. The reactions could be carried out either in conventional solvents or in ionic liquids. The catalysts were easily recycled and reused several times.

Key words: aldol reaction, Michael reaction, asymmetric synthesis, organocatalysis, ionic liquids, click reaction

The rapidly developing field of organocatalysis is in the focus of contemporary research, in particular, in asymmetric organic synthesis.[1,2] It finds wide application in academia and also in industries. Various classes of organocatalysts, such as amino acids, thioureas, chiral diols (BINOL, TADDOL, etc.) are useful in this field. Amongst them, (*S*)-proline has found manifold applications, e. g. in aldol, Mannich and Michael reactions, and its use has resulted in high yields and often good stereoselectivities.[3] From the point of view of green chemistry, recycling of catalysts and solvents is an important issue. In this field, the application of ionic liquids (ILs) became a novel method with which to meet this challenge.[4–6] ILs possess very high boiling points and are essentially non-volatile. Thus, they can be applied as reaction medium, wherein volatile products can be removed by distillation and the remaining IL can be directly reused. As an alternative, products formed in polar IL as reaction medium can be separated by solvent extraction, whilst retaining the IL for reuse. Recently, a number of organocatalyzed reactions were implemented in ILs.[7–10] In general, it is convenient to retain the catalyst in the IL as a so-called working solution in such procedures. This goal can be achieved by equipping the organocatalyst with an IL-tag. Such IL-tagged organocatalysts can either be used in the IL as reaction medium as outlined above or can be used in traditional organic solvents where recycling is possible by extracting the products from the reaction mixture and reusing the remaining IL-tagged organocatalyst. Several examples have been developed in this field over the last few years.[11,12] In such cases, imidazolium and pyridinium salts were used as IL-tags, which were covalently linked to amines, proline, sulfonic acids or alcohols as organocatalytic units.[13,14] In addition to an easier recycling of these conjugates, better catalytic performance was observed in a few cases as compared with non-tagged organocatalysts; that is to say that synergistic effects can occur by combining IL-tags with organocatalysts.[15,16]

1,2,3-Triazolium salts were recently developed by us as a new class of ILs.[17] They can be synthesized in a straightforward and versatile way by a copper-catalyzed cycloaddition of azides with alkynes (Huisgen–Meldal–Sharpless click reaction), followed by N-alkylation of the resulting 1,2,3-triazoles. This methodology has already been used to attach triazolium tags to a chiral amines derived from (*S*)-prolinol.[18] These IL-tagged amines catalyzed Michael additions to β-nitrostyrenes in excellent yields and enantioselectivities and could be easily recycled and reused.

We herein report attempts to apply the triazolium-based IL-tagging to (*S*)-prolines in order to obtain novel IL-tagged organocatalysts. Furthermore, their catalytic performance in aldol reactions and Michael additions is disclosed.

The syntheses of all new triazolium-tagged prolines started with *trans*-4-hydroxy-(*S*)-proline. Position 4 was chosen as the tethering point for the triazolium unit while the amino and carboxyl functions were protected by Cbz and benzyl, respectively (formation of **1**)[19] by known procedures. Three different synthetic strategies were used. In a first strategy (Scheme 1) the 4-hydroxy group of **1** was transformed into the azido group to give the functionalized proline **2** via the tosylate by inversion of configuration according to a known procedure.[20] Click reaction of **2** with 1-hexyne was catalyzed by copper sulfate, in the presence of sodium ascorbate, affording high yields of the 1,2,3-triazole **3**. Methylation with methyl iodide to the 1,2,3-triazolium iodide **4** and salt metathesis with silver tetrafluoroborate ($AgBF_4$) gave **5** in excellent yields. Deprotection by Pd/C-catalyzed hydrogenation resulted in the triazolium-tagged proline **6**.

In a second approach, the proline part was used as the alkyne reactant in the click reaction. We maintained the 4-hydroxy function of the diprotected proline **1** and introduced a propargyl unit by adopting a reported Williamson ether synthesis for *N*-boc-protected *t*-butyl 4-hydroxyprolinate.[21] Click reaction of the resulting propargyl ether **7** with dodecyl azide gave 71% of the triazole **8** after chro-

SYNTHESIS 2009, No. 23, pp 3975–3982
Advanced online publication: 12.10.2009
DOI: 10.1055/s-0029-1217039; Art ID: T07009SS

matographic separation (Scheme 2). Its transformation into the triazolium salt tagged proline **11** was implemented again by methylation to **9**, salt metathesis to **10** and final hydrogenative deprotection. All steps proceeded in excellent yields.

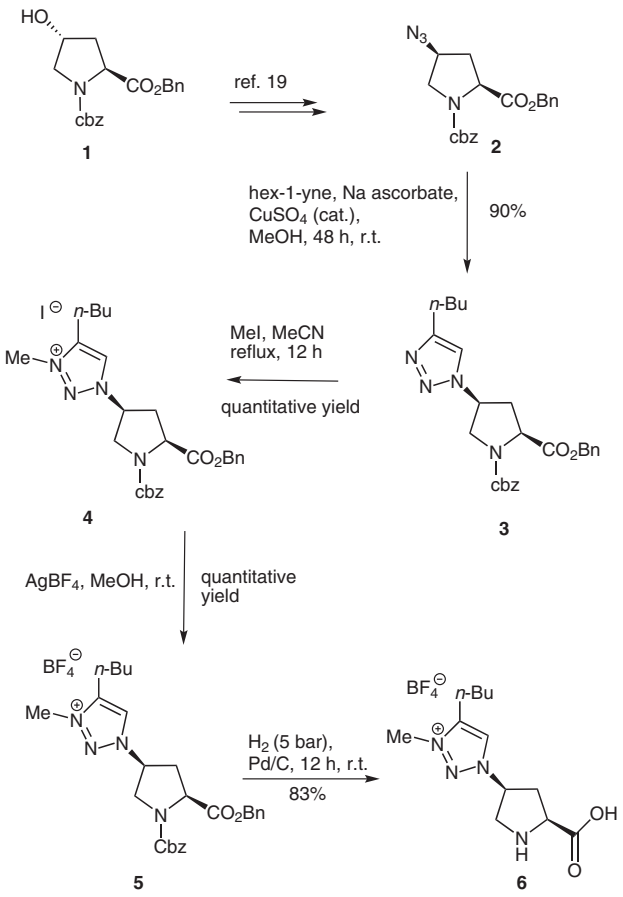
As a third target, we chose proline **16**, wherein the triazolium unit is connected to the 4-hydroxy function by a longer tether (Scheme 3) and applied the proline moiety as alkylating reagent for the 1,2,3-triazole unit. Thus, the diprotected proline **1** was esterified with 5-bromovaleric acid giving the known ester **12**,[22] which was further used as alkylating reagent for 1,4-di(*n*-butyl)-1,2,3-triazole (**13**). Salt metathesis of the resulting triazolium bromide **14** (76% yield) with $AgBF_4$ and hydrogenative deprotection led to the triazolium-tagged proline **16**.

With the three new triazolium-tagged prolines **6**, **11** and **16** in hand we approached their application in organocatalyzed reactions. The asymmetric aldol reaction was one of the first examples wherein (*S*)-proline and its derivatives were used as organocatalysts, giving high yields and good enantioselectivities. Since the pioneering work of List and Barbas in 2000/2001,[23–25] numerous applications have been published, amongst them, aldol reactions in ionic liquids[26,27] as well as the use of imidazolium- or ammonium-tagged prolines in organic solvents or ionic liquids.[15,16]

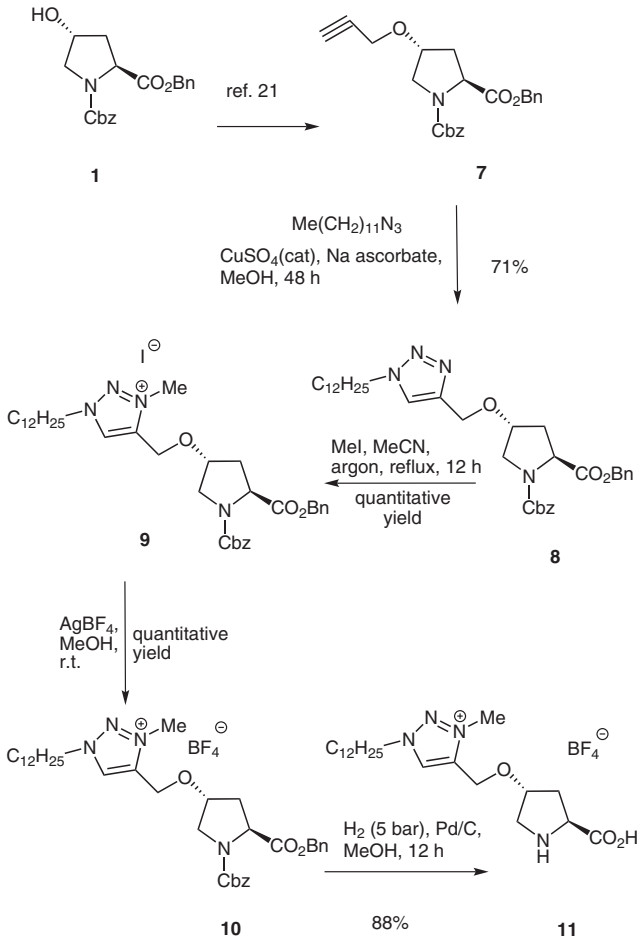
We applied 20 mol% of the corresponding triazolium-tagged (*S*)-proline **6**, **11** or **16** in the direct aldol reactions of aromatic aldehydes **18** with acetone, cyclohexanone, or cyclopentanone as CH-acidic components, using an excess of the ketone **17** as solvent (Scheme 4). All three catalysts performed similarly well, although catalyst **11** was slightly inferior (Table 1).

Excellent diastereoselectivities and ee values above 90% were obtained with cyclohexanone in most cases. Cyclopentanone gave lower diastereoselectivities and enantioselectivities as compared with cyclohexanone (see **19a** and **19g** in Table 1). 81% ee could be achieved in the aldol reaction of acetone with 4-nitrobenzaldehyde, in the presence of catalyst **16**, giving **19h**. At this point it can be concluded that triazolium-tagged prolines **6**, **11**, and **16** are useful organocatalysts for aldol reactions. Obviously the type of tethering of the triazolium unit to the 4-position of the proline does not affect the catalytic performance significantly.

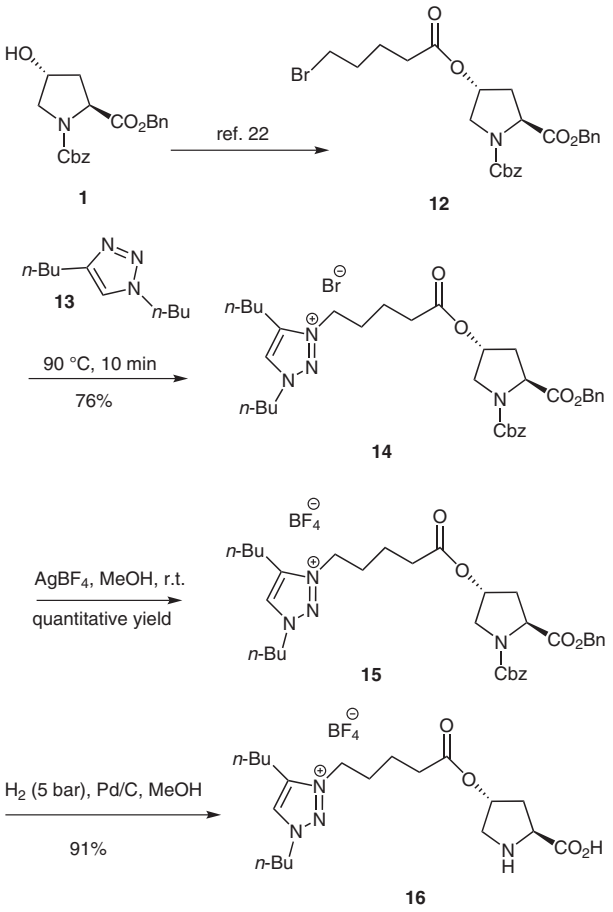
We further investigated the behavior of the triazolium-tagged proline **6** in recycling experiments for the aldol reaction of cyclohexanone with 4-bromobenzaldehyde (Scheme 5, Table 2). At first, we chose the same reaction conditions as before, i. e. an excess of cyclohexanone as solvent and 20 mol% of the catalyst (Method A). The re-



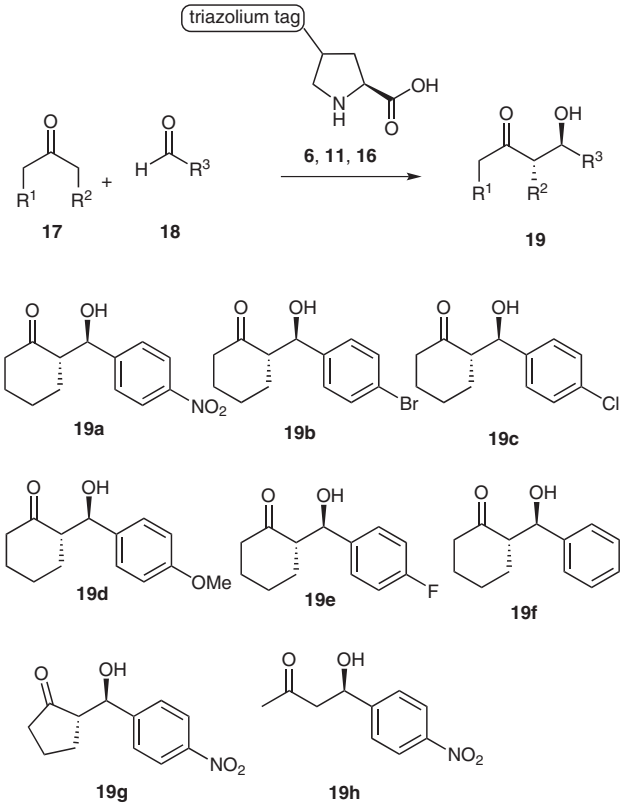
Scheme 1



Scheme 2



Scheme 3



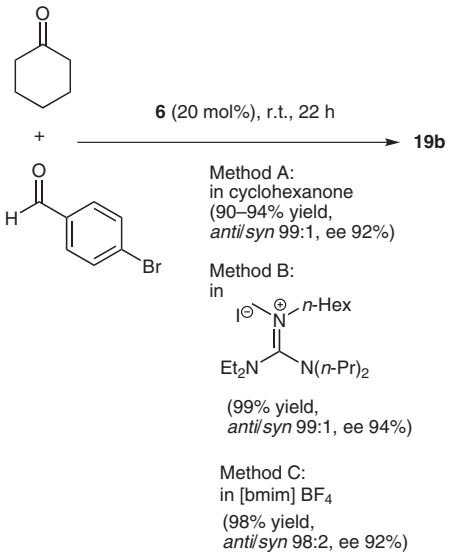
Scheme 4

action mixture was worked up by extraction with diethyl ether or cyclohexane. The triazolium-tagged organocatalyst **6** remained as an oil, which was concentrated under vacuum and combined with fresh reactants to run the next cycle. High yields above 80% were achieved until the 5th cycle and the diastereoselectivity remained excellent. However, the enantioselectivity diminished after each recycling, finally reaching 44% ee. We supposed that leaching of the organocatalyst during the extraction with diethyl ether occurred (Table 2, footnote a). Indeed, extraction with less polar cyclohexane gave better results in recycling experiments (Table 2, footnote b). Under these conditions, 88% yield with 68% ee and a diastereomeric ratio of 97:3 could be achieved in the 5th cycle. However, as reported in other recycling efforts in organocatalysis, there was still a drop in yields and enantioselectivities. Leaching of the organocatalyst can lower the reaction rates thus leading to lower yields in the same reaction time. However, enantioselectivities should not be affected by this loss unless a relative increase of a non-enantioselective background reaction occurs. On the other hand, a

Table 1 Aldol Reactions Catalyzed by Ionic Liquid Tagged Prolines **6**, **11** and **16**

	Catalyst **6**				Catalyst **11**				Catalyst **16**			
Product	Time (h)	Yield (%)	*anti*/ *syn*	ee[a] (%)	Time (h)	Yield (%)	*anti*/ *syn*	ee[a] (%)	Time (h)	Yield (%)	*anti*/ *syn*	ee[a] (%)
19a	24	98	99:1	98	27	94	99:1	96	26	99	99:1	94
19b	22	99	98:2	92	22	96	98:2	74	21	97	98:2	84
19c	31	96	99:1	90	34	99	99:1	82	34	95	99:1	94
19d	40	91	97:3	99	41	92	97:3	91	48	92	97:3	95
19e	18	95	96:4	90	13	90	96:4	62	20	90	96:4	72
19f	27	92	88:12	81	25	87	88:12	77	29	79	88:12	83
19g	48	89	67:33	89	42	91	67:33	86	51	83	67:33	90
19h	37	84	–	76	39	79	–	69	39	79	–	81

[a] Of major diastereomer.



Scheme 5

partial epimerization at the 2-position of the proline moiety could occur, as observed in the application of (*S*)-proline and 4-hydroxy-(*S*)-proline in coupling reactions, due to intermediate enolization.[28] We are presently developing an IL-tagged hydroxyproline derivative with a quaternary C-atom at the 2-position which cannot epimerize and will investigate its performance in recycling experiments.

The next recycling experiments were performed in ionic liquids, namely *N*,*N*-diethyl-*N*′-hexyl-*N*′-methyl-*N*′′,*N*′′-dipropylguanidinium iodide (Method B) and 1-butyl-3-methylimidazolium tetrafluoroborate (bmim BF_4^-, Method C) as solvents (Table 2). Equimolar ratios of cyclohexanone and 4-bromobenzaldehyde were used and the reaction mixture was extracted with diethyl ether. Working in the guanidinium salt (Method B) gave somewhat better results than the neat reaction (Method A[a]). The commercially available bmim BF_4^-, however, led to a more rapid decrease in enantioselectivity after recycling (Table 2, Method C, cycles 4 and 5).

We further envisaged applying triazolium-tagged prolines to Michael reactions with β-nitrostyrene. Proline itself was applied in the addition of propionaldehyde to β-nitrostyrene affording unsatisfactory yield (44%) and enantioselectivity (28%).[29] However, an improvement in the ee was achieved by introducing a TBDMSO group in the 4-position of proline.[29] High yields (94–95%) and low ee values (23%) were obtained in the (*S*)-proline catalyzed Michael addition of cylohexanone to β-nitrostyrene.[30,31] Chiral pyrrolidines derived from (*S*)-proline via reduction or Grignard reaction allowed such Michael additions to be run in a satisfactory manner.[32] Amongst them, triazolium salt and imidazolium salt tagged chiral pyrrolidines were also successfully employed.[18,33]

We applied the triazolium-tagged proline **6** in the Michael addition of cyclohexanone, cyclopentanone and acetone to β-nitrostyrene (Scheme 6, Table 3). High yields were obtained and the ee values were higher (48–54% for cyclohexanone adducts) than in known cases, in which (*S*)-proline was used.[33,34] Thus, a synergistic effect apparently occurs, caused by the combination of (*S*)-proline with the triazolium tag within the catalyst **6**. The reason for this is not clear but it is possible that the IL-tag could act as a Lewis acid to activate the nitrostyrene in the cyclic transition-state proposed in such reactions.[35] Cyclopentanone reacted with lower diastereoselectivity and enantioselectivity (entry 5). The outcome of the Michael addition of acetone to β-nitrostyrene was totally unsatisfactory from the point of view of stereoselectivity (6% ee, entry 6).

Table 3 Products **21** of the Michael Addition to Nitrostyrenes Catalyzed by **6**

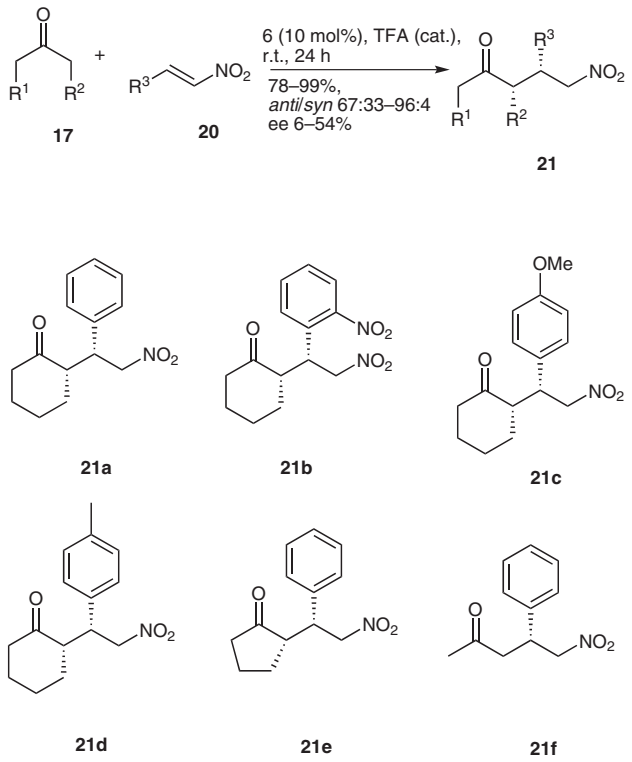
Entry	Product	Yield (%)	*anti*/*syn*	ee (%)[a]
1	**21a**	98	95:5	50
2	**21b**	94	90:10	54
3	**21c**	99	88:12	48
4	**21d**	93	96:14	52
5	**21e**	82	67:33	27
6	**21f**	79	–	6

[a] Of major diastereomer.

Table 2 Recycling Experiments in Aldol Reaction to Aldol **19b** Catalyzed by **6**

Cycle	Yield (%)/Time (h)				*anti*/*syn*				ee (%)[c]			
	Method				Method				Method			
	A[a]	A[b]	B	C	A[a]	A[b]	B	C	A[a]	A[b]	B	C
1	90/22	94/22	99/22	99/22	99:1	99:1	99:1	98:2	92	92	94	92
2	90/25	92/23	96/25	97/25	98:2	98:2	98:2	98:2	86	84	78	75
3	88/29	91/32	90/29	95/29	98:2	98:2	98:2	97:3	74	74	76	64
4	85/38	91/38	89/38	90/38	99:1	97:3	96:4	97:3	64	72	74	49
5	84/41	88/43	88/41	89/41	97:3	97:3	96:4	95:5	44	68	66	36

[a] Extraction with Et_2O.
[b] Extraction with cyclohexane.
[c] Of major diastereomer.



Scheme 6

Since the performance of the triazolium-tagged proline **6** as organocatalyst in Michael additions could not compete with known chiral pyrrolidine derivatives, we refrained from investigating the recyclability of **6** as well as from testing the other triazolium-tagged prolines **11** and **16** in these Michael reactions.

In summary, we have developed three triazolium-tagged (*S*)-prolines **6**, **11** and **16** as organocatalysts, and thus demonstrated their ability to establish ionic liquid tags by the combination of copper-catalyzed Huisgen–Meldal–Sharpless cycloaddition reaction of alkynes with azides and alkylation of the resulting 1,2,3-triazoles. The tagged prolines were applied in direct aldol reactions of ketones either without an additional solvent or in ionic liquids, affording high yields and stereoselectivities. The triazolium-tagged proline **6** could be recycled and reused several times, maintaining good performance until the fourth cycle. After this, the enantioselectivity decreased below 70% ee. Improved catalytic performance of **6**, as compared with proline, was also observed in Michael addition to β-nitrostyrene. However, the outcome of this reaction was not good enough to compete with other known organocatalysts. At present we are investigating ways to improve the recyclablity of our IL-tagged organocatalysts by variation of the anions, by special filtration techniques and by using proline derivatives which are devoid of possible racemization through epimerization.

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with a Bruker AC 300, in $CDCl_3$ with TMS as internal standard. MS analyses were carried out on Varian MAT 711 and Thermo Finnigan LTQ-FT-ICR-MS spectrometers. Silica gel (0.04–0.063 mm, Merck) was used for preparative column chromatography. Compounds **1**,[19] **2**,[20] **7**,[21] and **12**[22] were synthesized according to literature procedures. All the other materials were purchased from commercial suppliers. Configurations of major products were elucidated by comparing optical rotation with literature data.[30,36]

(2*S*,4*S*)-Dibenzyl-4-(4-butyl-1*H*-1,2,3-triazol-1-yl)pyrrolidine-1,2-dicarboxylate (3)

To a solution of **2** (0.3 g, 0.79 mmol) in MeOH (10 mL), 1-hexyne (0.1 ml, 0.79 mmol), sodium ascorbate (0.313 g, 1.58 mmol, 20 mol%) and $CuSO_4$ (0.188 g, 1.8 mmol, 15 mol%) were added. The reaction mixture was stirred for 48 h (reaction monitored by TLC) then quenched by adding H_2O (30 mL). The mixture was extracted with EtOAc (3 × 30 mL) and the organic layer was washed with brine (3 × 30 mL) and then dried and evaporated. The product **3** was purified by column chromatography (R_f = 0.37; $CHCl_3$–acetone, 2:1).

Yield: 328 mg (90%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.33 (m, 10 H, Ar), 7.22 (br s, 1 H, N-CH=C), 5.24–5.06 (m, 4 H, 2 × CH_2-Ar), 5.02 (m, 1 H, N-C*H*-CH_2-N), 4.57 (m, 1 H, N-C*H*-CO_2), 4.22 (m, 1 H, N-C*H*$_2$-CH-N), 3.92 (m, 1 H, N-C*H*$_2$-CH-N), 2.94 (m, 1 H, N-CH-C*H*$_2$-CH), 2.68 (t, *J* = 7.2 Hz, 2 H, C-C*H*$_2$-CH_2), 2.58 (m, 1 H, N-CH-C*H*$_2$-CH), 1.62 (m, 2 H, CH_3-CH_2-C*H*$_2$), 1.37 (m, 2 H, CH_3-C*H*$_2$), 0.94 (t, *J* = 7.3 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1 (O=CO), 154.0 (O=C-N), 148.9 (C-triazole), 135.9 (C-Ar), 135.2 (C-Ar), 128.6–127.9 (Ar-CH), 119.3 (N-C*H*=C), 67.6 (C*H*$_2$-Ar), 67.3 (C*H*$_2$-Ar), 57.9 (N-C*H*-CO_2), 57.0 (N-C*H*-CH_2-N), 51.8 (N-C*H*$_2$-CH-N), 35.2 (N-CH-C*H*$_2$-CH), 31.5 (CH_3-CH_2-C*H*$_2$), 25.3 (C-C*H*$_2$-CH_2), 22.3 (CH_3-C*H*$_2$), 13.8 (C*H*$_3$-CH_2).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{31}N_4O_4$: 463.234; found: 463.234.

3-[(3*S*,5*S*)-1,5-Bis(benzyloxycarbonyl)pyrrolidin-3-yl]-5-butyl-1-methyl-3*H*-1,2,3-triazol-1-ium Iodide (4)

To a solution of the triazole **3** (0.6 g, 1.5 mmol) in MeCN (50 mL), MeI (0.48 mL, 1.1 g, 8 mmol) was added. The reaction mixture was refluxed under an argon atmosphere overnight. After completion of the reaction, the solvent was removed to obtain **4**.

Yield: 1.2 g (100%); brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.0 (s, 1 H, N-C*H*=C), 7.30–7.20 (m, 10 H, Ar), 5.89 (m, 1 H, N-C*H*-CH_2-N), 5.14–4.98 (m, 4 H, 2 × CH_2-Ar), 4.57 (m, 1 H, N-C*H*-CO_2), 4.21 (m, 2 H, N-C*H*$_2$-CH-N), 4.07, 4.02 (s, 3 H, CH_3-N)*, 3.15 (m, 1 H, N-CH-C*H*$_2$-CH), 2.78 (t, *J* = 7.2 Hz, 2 H, C-C*H*$_2$-CH_2), 2.68 (m, 1 H, N-CH-C*H*$_2$-CH), 1.69 (m, 2 H, CH_3-CH_2-C*H*$_2$), 1.44 (m, 2 H, CH_3-C*H*$_2$), 0.94 (t, *J* = 7.2 Hz, 3 H, CH_3). * Partially doubled sets of peaks due to rotamers.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9 (O=C-O), 153.6 (O=C-N), 144.7 (C-triazole), 135.6 (C-Ar), 134.9 (C-Ar), 128.5–127.6 (Ar-CH), 127.6 (N-C*H*=C), 67.4 (C*H*$_2$-Ar), 67.0 (C*H*$_2$-Ar), 61.8 (N-C*H*-CO_2), 57.1 (N-C*H*-CH_2-N), 51.0 (N-C*H*$_2$-CH-N), 38.3 (CH_3-N), 35.6 (N-CH-C*H*$_2$-CH), 28.6 (CH_3-CH_2-C*H*$_2$), 23.4 (C-C*H*$_2$-CH_2), 21.9 (CH_3-C*H*$_2$), 13.4 (C*H*$_3$-CH_2).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{34}N_4O_4^+$: 478.257; found: 478.255.

3-[(3*S*,5*S*)-1,5-Bis(benzyloxycarbonyl)pyrrolidin-3-yl]-5-butyl-1-methyl-3*H*-1,2,3-triazol-1-ium Tetrafluoroborate (5)

In a 50 mL dry, round-bottom flask, **4** (0.5 g, 0.82 mmol) was dissolved in anhydrous MeOH (15 mL). In a second flask (which was either brown colored or wrapped in aluminum foil to exclude light),

$AgBF_4$ (0.159 g, 0.82 mmol) was dissolved in anhydrous MOH (15 mL). The $AgBF_4$ solution was added dropwise to the solution of **4** until no more precipitate (AgI) was formed. After the precipitate had settled down, the clear supernatant solution was separated, dried and evaporated giving a quantitative yield of **5** as yellow oil. NMR spectra were identical to **4**.

5-Butyl-3-[(3*S*,5*S*)-5-carboxypyrrolidin-3-yl]-1-methyl-3*H*-1,2,3-triazol-1-ium Tetrafluoroborate (6)

To a solution of **5** (1 g, 1.77 mmol) in anhydrous MeOH (15 mL), Pd/C (80 mg) was added and the mixture was pressurized under H_2 at 5 bar. After stirring overnight, the Pd/C was filtered off and the filtrate was concentrated under vacuum to give **6**.

Yield: 0.5 g (83%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (s, 1 H, N-C*H*=C), 5.66 (m, 1 H, N-C*H*-CH_2-N), 4.37 (m, 1 H, N-C*H*-CO_2), 4.24 (s, 3 H, CH_3-N), 4.07 (m, 2 H, N-CH_2-CH-N), 3.12 (m, 2 H, N-CH-CH_2-CH), 2.88 (t, *J* = 7.2 Hz, 2 H, C-CH_2-CH_2), 2.7 (m, 2 H, N-CH-CH_2-CH), 1.77 (m, 2 H, CH_3-CH_2-CH_2), 1.52 (m, 2 H, CH_3-CH_2), 1.02 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.4 (C-triazole), 127.6 (N-*C*H=C), 62.4 (N-*C*H-CO_2), 60.1 (N-*C*H-CH_2-N), 49.4 (N-*C*H_2-CH-N), 36.7 (CH_3-N), 34.3 (N-CH-*C*H_2-CH), 28.3 (CH_3-CH_2-*C*H_2), 22.4 (C-*C*H_2-CH_2), 21.7 (CH_3-*C*H_2), 12.5 (*C*H_3-CH_2).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{22}N_4O_2^+$: 254.173; found: 254.171.

Dibenzyl (2*S*,4*R*)-4-[(1-Dodecyl-1*H*-1,2,3-triazol-4-yl)methoxy]pyrrolidine-1,2-dicarboxylate (8)

To a solution of **7** (0.9 g, 2 mmol) and 1-azidododecane (0.5g, 2 mmol) in MeOH (50 mL), sodium ascorbate (0.1 g, 0.5 mmol, 20 mol%) and $CuSO_4$ (0.1 g, 0.4 mmol, 15 mol%) were added. The reaction mixture was stirred for 48 h (monitored by TLC) and quenched by adding H_2O (30 mL). After extraction with EtOAc (3 × 30 mL), the combined organic layer was washed with brine (3 × 30 mL), dried and concentrated under vacuum. The remainder was purified by column chromatography (R_f = 0.32; $CHCl_3$–acetone, 6:1) to give product **8**.

Yield: 1.0 g (71%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49, 7.51, (2 × s, 1 H, N-CH=C)*, 7.36–7.23 (m, 10 H, Ar), 5.23–5.01 (m, 4 H, 2 × CH_2-Ar), 4.63 (m, 2 H, C-CH_2-O), 4.50 (m, 1 H, C*H*-O-CH_2), 4.34 (m, 2 H, N-CH_2-CH_2), 4.31 (m, 1 H, CH-COOBn), 3.69 (m, 2 H, CH_2-N), 2.42 (m, 1 H, *C*H_2-CH-O), 2.11 (m, 1 H, *C*H_2-CH-O), 1.73 (m, 2 H, N-CH_2-*C*H_2), 1.33–1.27 (m, 18 H, 9 × CH_2), 0.90 (t, *J* = 6.0 Hz, 3 H, CH_3). * Doubled sets of peaks due to rotamers.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4 (CH-*C*OOBn), 154.9 (N-*C*OO-CH_2), 136.3 (N-*C*-CH_2), 128.5 (10 × CH, Ar), 122.3 (N-*C*H=C), 67.1 (O-*C*H_2-Ar), 62.7 (*C*H_2-O-CH), 57.8 (*C*H-COOBn), 52.1 (CH_2-N), 50.4 (CH_2-*C*H_2-N), 35.4 (*C*H_2-CH-O), 31.9 (CH_3-CH_2-*C*H_2), 29.6 (7 × CH_2), 26.5 (*C*H_2-CH_2-N), 22.6 (CH_3-*C*H_2), 14.1 (CH_3 and *C*H_2-CH-O).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{49}N_4O_5$: 605.370; found: 605.369.

5-{[(3*R*,5*S*)-1,5-Bis(benzyloxycarbonyl)pyrrolidine-3-yloxy]methyl}-3-dodecyl-1-methyl 3*H*-1,2,3-Triazol-1-ium Iodide (9)

The triazole **8** (0.6 g, 1.5 mmol) was dissolved in MeCN (50 mL), MeI (0.48 mL, 1.1 g, 8 mmol) was added and the reaction mixture was refluxed under an argon atmosphere overnight. After completion of the reaction, the solvent was removed to obtain **9**.

Yield: 1.2 g (100%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.26, 9.30 (2 × s, 1 H, N-CH=C)*, 7.40–7.21 (m, 10 H, Ar), 5.20–5.02 (m, 4 H, 2 × CH_2-Ar), 5.04 (m, 2 H, C-CH_2-O), 4.62 (m, 2 H, N-CH_2-CH_2), 4.50 (m, 1 H, C*H*-O-CH_2), 4.47 (m, 1 H, CH-COOBn), 4.25 (s, 3 H, CH_3), 3.65 (m, 2 H, CH_2-N), 2.53 (m, 1 H, C*H*$_2$-CH-O), 2.19 (m, 1 H, C*H*$_2$-CH-O), 1.82 (m, 2 H, N-CH_2-C*H*$_2$), 1.33–1.25 (m, 18 H, 9 × CH_2), 0.90 (t, *J* = 6.0 Hz, 3 H, CH_3). * Doubled sets of peaks due to rotamers.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8 (CH-*C*OOBn), 154.4 (N-*C*OO-CH_2), 140.2 (N-*C*-CH_2), 128.5 (10 CH, Ar), 67.2 (O-*C*H_2-Ar), 59.3 (*C*H_2-O-CH), 57.7 (*C*H-COOBn), 54.4 (CH_2-N), 50.3 (CH_2-*C*H_2-N), 39.5 (N-*C*H_3), 36.5 (*C*H_2-CH-O), 31.8 (CH_3-CH_2-*C*H_2), 29.6 (7 × CH_2), 26.1 (*C*H_2-CH_2-N), 22.6 (CH_3-*C*H_2), 14.1 (CH_3, *C*H_2-CH-O).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{52}N_4O_5^+$: 620.393; found: 620.390.

5-{[(3*R*,5*S*)-1,5-Bis(benzyloxycarbonyl)pyrrolidin-3-yloxy]methyl}-3-dodecyl-1-methyl-3*H*-1,2,3-triazol-1-ium Tetrafluoroborate (10)

In a 50 mL dry, round-bottom flask, the iodide salt **9** (0.5 g, 0.66 mmol) was dissolved in anhydrous MeOH (15 mL). In a second flask (which was either brown-colored or wrapped in aluminum foil to exclude light), $AgBF_4$ (0.128 g, 0.66 mmol) was dissolved in anhydrous MeOH (15 mL) and the $AgBF_4$ solution was added dropwise to the solution of **9** until no more precipitate (AgI) was formed. After the precipitate had settled down, the clear supernatant solution was separated, dried and evaporated giving a quantitative yield of **10** as a yellow oil. NMR spectra were identical to **9**.

5-{[(3*R*,5*S*)-5-Carboxypyrrolidin-3-yloxy]methyl}-3-dodecyl-1-methyl-3*H*-1,2,3-triazol-1-ium Tetrafluoroborate (11)

To a solution of **10** (0.6 g, 1.41 mmol) in anhydrous MeOH (15 mL), Pd/C (80 mg) was added and the mixture was pressurized under H_2 at 5 bar. After stirring overnight, the Pd/C was filtered off and the filtrate was concentrated under vacuum to give **11**.

Yield: 0.825 g (88%); yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.89 (s, 1 H, N-CH=C), 4.82 (m, 2 H, C-CH_2-O), 4.58 (m, 2 H, N-CH_2-CH_2), 4.36 (m, 1 H, C*H*-O-CH_2), 4.02 (m, 1 H, CH-CO_2H), 4.23 (s, 3 H, CH_3-N), 3.34 (m, 2 H, CH_2-N), 2.50 (m, 2 H, C*H*$_2$-CH-O), 2.08 (m, 2 H, C*H*$_2$-CH-O), 1.89 (m, 2 H, N-CH_2-C*H*$_2$), 1.37–1.27 (m, 18 H, 9 × CH_2), 0.84 (t, *J* = 6.4 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.4 (COOH), 140.5 (N-*C*-CH_2), 129.9 (N-*C*H=C), 78.7 (*C*H_2-O-CH), 59.5 (*C*H-COOH), 53.5 (CH_2- N), 50.3 (CH_2-*C*H_2-N), 38.5 (N-*C*H_3), 35.0 (*C*H_2-CH-O), 31.7 (CH_3-CH_2-*C*H_2), 29.6 (7 × CH_2), 25.8 (*C*H_2-CH_2-N), 22.5 (CH_3-*C*H_2), 14.3 (CH_3, *C*H_2-CH-O).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{40}N_4O_3^+$: 396.309; found: 396.307.

1,4-Dibutyl-1*H*-1,2,3-triazole (13)

To a solution of butyl azide (2.5 g, 25.2 mmol, 1 equiv) in MeOH (75 mL), sodium ascorbate (1 g, 5 mmol, 20 mol%), $CuSO_4$ (0.61g, 3.8 mmol, 15 mol%) and 1-hexyne (25.2 mmol, 2.9 mL) were added. The mixture was stirred until the reaction went to completion (reaction monitored by TLC; typically 2–3 d), then H_2O (250 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL) and dried over $NaSO_4$. Evaporation of the solvent under vacuum gave a yellow oily residue which was purified by column chromatography (R_f = 0.65; $CHCl_3$–acetone, 9:1).

Yield: 82%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23 (s, 1 H, C*H*), 4.22 (t, *J* = 7.2 Hz, 2 H, $CH_3CH_2CH_2CH_2N$), 2.62 (t, *J* = 7.7 Hz, 2 H,

$CH_3CH_2CH_2CH_2C$), 1.77 (m, 2 H, $CH_3CH_2CH_2CH_2N$), 1.56 (m, 2 H, $CH_3CH_2CH_2CH_2C$), 1.27 (m, 4 H, CH_2CH_3), 0.83 (m, 6 H, CH_3CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.2 (*C*-triazole), 120.4 (*C*H-triazole), 49.7 ($CH_3CH_2CH_2CH_2N$), 32.2 ($CH_3CH_2CH_2CH_2C$), 31.5 ($CH_3CH_2CH_2CH_2C$), 25.2 ($CH_3CH_2CH_2CH_2N$), 22.2 ($CH_3CH_2CH_2CH_2C$), 19.6 ($CH_3CH_2CH_2CH_2N$), 13.7 ($CH_3CH_2CH_2CH_2N$), 13.3 ($CH_3CH_2CH_2CH_2C$).

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{19}N_3$: 182.1657; found: 182.1673.

1-{5-[(3*R*,5*S*)-1,5-Bis(benzyloxycarbonyl)pyrrolidin-3-yloxy]-5-oxopentyl}-3,5-dibutyl-3*H*-1,2,3-triazol-1-ium Bromide (14)

A mixture of compound **12** (1.10 g, 2.12 mmol) and 1,4-dibutyl-1*H*-1,2,3-triazole (**13**; 0.46 g, 2.54 mmol) was heated at 90 °C for 10 min, then 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 placed under vacuum (0.5 Torr) for 2 h to afford compound **14**.

Yield: 1.12 g (76%); yellow, viscous oil; R_f = 0.36 ($CHCl_3$–acetone, 4:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 9.52 (s, 1 H, N-C*H*=C), 7.32–7.20 (m, 10 H, Ar), 5.26 (m, 1 H, C*H*-CO_2-CH_2), 5.25–4.98 (m, 4 H, CH_2-Ar), 4.77 (m, 1 H, N-CH-CO_2), 4.53 (m, 2 H, N^+-CH_2), 4.29 [t, *J* = 7.2 Hz, 2 H, CH_3-$(CH_2)_2$-C*H*$_2$-N], 3.74 (m, 2 H, N-C*H*$_2$-CH-O), 2.89 [t, *J* = 7.2 Hz, 2 H, CH_3-$(CH_2)_2$-C*H*$_2$-C], 2.37 (m, 1 H, CO_2-CH-C*H*$_2$), 2.21 (m, 2 H, CH_2-C*H*$_2$-CO_2), 2.01 (m, 2 H, N^+-CH_2-C*H*$_2$), 1.99 (m, 1 H, C*H*$_2$-CH-CO_2), 1.76 (m, 2 H, CO_2-CH_2-C*H*$_2$-CH_2), 1.64 (m, 2 H, N-CH_2-C*H*$_2$), 1.37 (m, 6 H, CH_3-CH_2-CH_2), 0.95 (m, 6 H, C*H*$_3$-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 171.6 (CO-O-C), 154.6 (CO-O-CH_2), 144.1 (CO-O-CH_2), 136.0 (N-*C*-CH_2), 135.3, 135.0 (C-Ph), 129.8–127.8 (CH-Ar), 120.4 (C-*C*H-N), 72.7 (O-*C*H-CH_2), 67.3 (CH_2-Ph), 57.9 (N^+-CH_2), 53.9 (N-*C*H-CH_2), 52.6 (N-*C*H$_2$-CH), 50.9 (N-CH_2), 36.4 (CH-*C*H$_2$-CH), 32.9 (*C*H$_2$-CO2), 31.4 (N-N-CH_2-*C*H$_2$), 29.4 (C-CH_2-*C*H$_2$), 28.0 (C-*C*H$_2$), 23.3 (N^+-CH_2-*C*H$_2$), 22.2, 21.2 (*C*H$_2$-CH_2-COO), 19.4 (CH_3-*C*H$_2$), 13.4, 13.4 (CH_3).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{35}H_{47}N_4O_6^+$: 619.349; found: 619.348.

1-{5-[(3*R*,5*S*)-1,5-Bis(benzyloxycarbonyl)pyrrolidin-3-yloxy]-5-oxopentyl}-3,5-dibutyl-3*H*-1,2,3-triazol-1-ium Tetrafluoroborate (15)

In 50 mL dry, round-bottom flask, the iodide salt **14** (0.5 g, 0.71 mmol) was dissolved in anhydrous MeOH (15 mL). In a second flask (which was either brown-colored or wrapped in aluminum foil to exclude light), $AgBF_4$ (0.14 g, 0.71 mmol) was dissolved in anhydrous MeOH (15 mL) and the solution was added dropwise to the solution of **14** until no more precipitate (AgI) was formed. After the precipitate had settled down, the clear supernatant solution was separated, dried and evaporated giving a quantitative yield of **15** as a yellow oil. NMR spectra were identical to **14**.

3,5-Dibutyl-1-{5-[(3*R*,5*S*)-5-carboxypyrrolidin-3-yloxy]-5-oxopentyl}-3*H*-1,2,3-triazol-1-ium Tetrafluoroborate (16)

To the solution of **15** (1 g, 1.42 mmol) in anhydrous MeOH (15 mL), Pd/C (80 mg) was added and the mixture was pressurized under H_2 at 5 bar. After stirring overnight, the Pd/C was filtered off and the filtrate was concentrated under vacuum to give **16**.

Yield: 0.62 g (91%); yellow oil.

^1H NMR (300 MHz, CD_3OD): δ = 8.55 (s, 1 H, N-C*H*=C), 5.45 (m, 1 H, CO_2-C*H*), 4.92 (m, 1 H, N-CH-CO_2H), 4.60 (m, 2 H, N^+-CH_2), 4.37 [t, *J* = 7.0 Hz, 2 H, CH_3-$(CH_2)_2$-C*H*$_2$-N], 3.66 (m, 2 H, N-C*H*$_2$-CH-O), 2.90 [t, *J* = 7.0 Hz, 2 H, CH_3-$(CH_2)_2$-C*H*$_2$-C], 2.50 (m, 2 H, C*H*$_2$-CH-CO_2), 2.17 (m, 2 H, CH_2-C*H*$_2$-CO_2), 2.0 (m, 2 H, N^+-CH_2-C*H*$_2$), 1.88 (m, 2 H, C*H*$_2$-CH_2-CO_2), 1.76 (m, 2 H, CH_2-C*H*$_2$-CH_2-CO_2), 1.65 (m, 2 H, N-CH_2-C*H*$_2$), 1.37 (m, 6 H, CH_3-CH_2-CH_2), 0.98 (m, 6 H, C*H*$_3$-CH_2).

^{13}C NMR (75 MHz, CD_3OD): δ = 172.3 (CO-O-C), 144.6 (N-*C*-CH_2), 121.8 (C-*C*H-N), 72.7 (O-CH-CH_2), 53.2 (N^+-CH_2), 50.9 (N-*C*H-CH_2), 50.2 (N-*C*H$_2$-CH), 49.6 (N-CH_2), 31.9 (CH-*C*H$_2$-CH), 31.3 (*C*H$_2$-CO_2), 30.7 (N-N-CH_2-*C*H$_2$), 28.7 (C-CH_2-*C*H$_2$), 27.4 (C-*C*H$_2$), 24.5 (N^+-CH_2-*C*H$_2$), 21.8, 21.7 (*C*H$_2$-CH_2-COO), 19.2, 19.0 (CH_3-*C*H$_2$), 12.7, 12.4 (*C*H$_3$).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{36}N_4O_4^+$: 396.273; found: 396.273.

Asymmetric Direct Aldol Reaction to 19; Typical Procedure

A catalytic amount of catalyst **6** (34 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. The reaction mixture was stirred at r.t. for 28 h and subsequently extracted with Et_2O (5 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude aldol product **19a** was purified by silica gel column chromatography (*n*-hexane–EtOAc, 4:1) to afford the aldol product as a white solid[36] (107 mg, 86% yield).

The diastereomeric *anti*/*syn* ratio was determined by ^1H NMR analysis of the reaction mixture [δ = 5.48 (d, *J* = 1.8 Hz, 1 H, *syn*, minor), 4.89 (d, *J* = 8.8 Hz, 1 H, *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, $CDCl_3$): δ = 8.20 (d, *J* = 8.6 Hz, 2 H), 7.50 (d, *J* = 8.7 Hz, 2 H), 4.89 (d, *J* = 8.4 Hz, 1 H), 4.07 (s, 1 H), 2.57–2.63 (m, 1 H), 2.32–2.49 (m, 2 H), 1.31–2.12 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.8, 148.4, 147.6, 127.9, 123.5, 74.0, 57.2, 42.7, 30.8, 27.7, 24.7.

Recycling the Catalyst; Typical Experimental

The reaction mixture was extracted with either Et_2O or cyclohexane (3 × 15 mL). The combined organic layers were concentrated under vacuum and, after column chromatography, the pure aldol product was obtained. The residual catalyst (Method A) or catalyst with ionic liquid (Method B, C) was concentrated under vacuum to remove residual solvent and then reused for the next run.

Aldol Reaction in Ionic Liquid and Recycling; Typical Procedure

A catalytic amount of catalyst **6** (34 mg, 20 mol%) was added to 4-nitrobenzaldehyde (76 mg, 0.5 mmol), cyclohexanone (0.26 mL, 2.5 mmol) and ionic liquid (0.5 mL). The flask was closed and the reaction mixture was stirred at r.t. for 28 h and subsequently extracted with Et_2O (5 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude aldol product was purified by silica gel column chromatography (*n*-hexane–EtOAc, 4:1) to afford aldol product. The residual ionic liquid containing catalyst was concentrated under vacuum to remove solvent and then reused in the next run.

Michael Addition of Cyclohexanone to Nitrostyrene; Typical Procedure

Nitrostyrene (37 mg, 0.25 mmol) and catalyst **6** (17 mg, 10 mol%) were mixed with cyclohexanone (0.5 mL, 5 mmol) in the presence of TFA (0.00625 mmol, 0.2 μL) at r.t. [the bulk solution of TFA in cyclohexanone was freshly prepared from TFA (5 μL) and cyclohexanone (12.5 mL)]. After stirring for 24 h, the homogeneous re-

action mixture was diluted with Et_2O (15 mL) to precipitate the catalyst. The organic layer was separated, concentrated and loaded onto a silica gel column to afford the Michael product **21a**.[30,37]

Yield: 60 mg (98%); white solid; *syn*/*anti* 99:1, 99% ee [HPLC on a Chiralpak AD column, λ = 215 nm; *i*-PrOH–*n*-hexane, 10:90; flow rate = 0.8 mL/min; t_R = 10.90 (minor), 15.53 min (major)].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 3 H), 7.20–7.14 (m, 2 H), 4.94 (dd, *J* = 12.4, 4.4 Hz, 1 H), 4.43 (dd, *J* = 12.4, 10.0 Hz, 1 H), 3.76 (m, 1 H), 2.74–2.64 (m, 1 H), 2.52–2.34 (m, 2 H), 2.13–2.03 (m, 1 H), 1.83–1.50 (m, 4 H), 1.30–1.18 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.0, 137.7, 128.9, 127.7, 78.9, 52.5, 43.9, 42.7, 33.2, 28.5, 25.0.

Acknowledgment

We thank Claudia Köthe for experimental assistance and Prof. Dr. Willi Kantlehner, Fachhochschule Aalen for providing substituted guanidines as precursors for ionic liquids. We acknowledge donation of chemicals from Saltigo GmbH, Bayer Services GmbH & Co. OHG, BASF AG and Sasol GmbH.

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