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Synthesis of new ionic-liquid-tagged organocatalysts and their application in stereoselective direct aldol reactions

Sadaf S. Khan, Jabbar Shah, Jürgen Liebscher *

Institute of Chemistry, Humboldt-University Berlin, Brook-Taylor-Str. 2, 12489 Berlin, Germany

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ABSTRACT

New amino acid—1,2,3-triazolium conjugates were synthesized by establishing a 1,2,3-triazolium unit to the amino acid through Cu-catalyzed alkyne-azide cycloaddition and subsequent N-methylation. These products were applied as ionic-liquid-tagged organocatalysts in asymmetric direct aldol reactions. Remarkably, a lysine-derived conjugate performed better than proline derivatives. Evidence was found that IL-tagging improved the catalytic performance. Recycling of the organocatalyst was easily possible by extraction of products.

1. Introduction

Since the first disclosure of the ability of amino acids to catalyse direct aldol reactions with high stereoselectivities by List and Barbas[1] many activities were reported to find out scope and limitations of this methodology and to develop related catalytic systems providing higher efficiency.[2–6] At beginning, it was believed that the field of enantioselective aldol reaction is reserved for proline while other natural amino acids are not suitable. However, Cordova et al., Amedjkouh and Teo et al. achieved excellent stereoselectivities with other amino acids too when the reactions were performed in ionic liquids or DMSO in the presence of small amounts of water or in water, respectively.[7–11] In intramolecular aldol reaction phenylalanine was even more efficient than proline.[12,13] Protonated arginine and lysine also performed well in aldol reactions in IL.[14] On the other hand, many derivatives of proline were developed and successfully applied in aldol reactions.[4–6,15] Although the natural amino acids are cheap, recycling of organocatalysts can be an issue if one thinks in terms of large scale production or of green chemistry. One strategy to enable effective recycling of catalysts also applied to (*S*)-proline catalyzed aldol reactions is based on the idea to work in polar ionic liquids as solvents. The products can be removed from the reaction mixture either by extraction or by distillation.[16–18] The catalyst remains in the ionic liquid and this so-called working solution can be re-used in the next run. However, leaching can occur in the extractive working up leading to a loss of the catalyst in the working solution on the one hand and requests additional efforts to purify the extracted product. To overcome such problems, IL-tagged organocatalysts were developed.[19] In these catalysts, an ionic liquid moiety (often proline) is covalently fixed to the organocatalytic unit providing a low solubility in the solvents used for extraction of the products on the one hand and a high solubility in the reaction medium on the other hand.[19–28] This strategy was also applied to aldol reactions providing high yields and stereoselectivities and good recyclablity of the organocatalyst (e.g., **3**). Recently, we reported on IL-tagging of (*S*)-proline by 1,2,3-triazolium salts and the successful application of these IL-tagged organocatalysts in direct aldol reactions.[29] The 1,2,3-triazolium tag substituents were limited to unbranched alkyl groups (see Scheme 1, **1** (R=alkyl)).

We became interested in how far the performance of such catalysts will be affected by the introduction of functionalities in the triazolium tag, which can somehow interfere with the catalytic process by hydrogen bonding or even by enamine formation. Furthermore, we wanted to find out, if proline can be replaced by a non-cyclic amino acid.

2. Results and discussion

Following up these ideas we synthesized the new 1,2,3-triazolium salts **1a**, **1b**, **1c** and **2**. In compound **1a** an additional carboxyl group is present. In order to get information about the effect of

* Corresponding author. Fax: +49 30 20937552; e-mail address: liebscher@chemie.hu-berlin.de (J. Liebscher).

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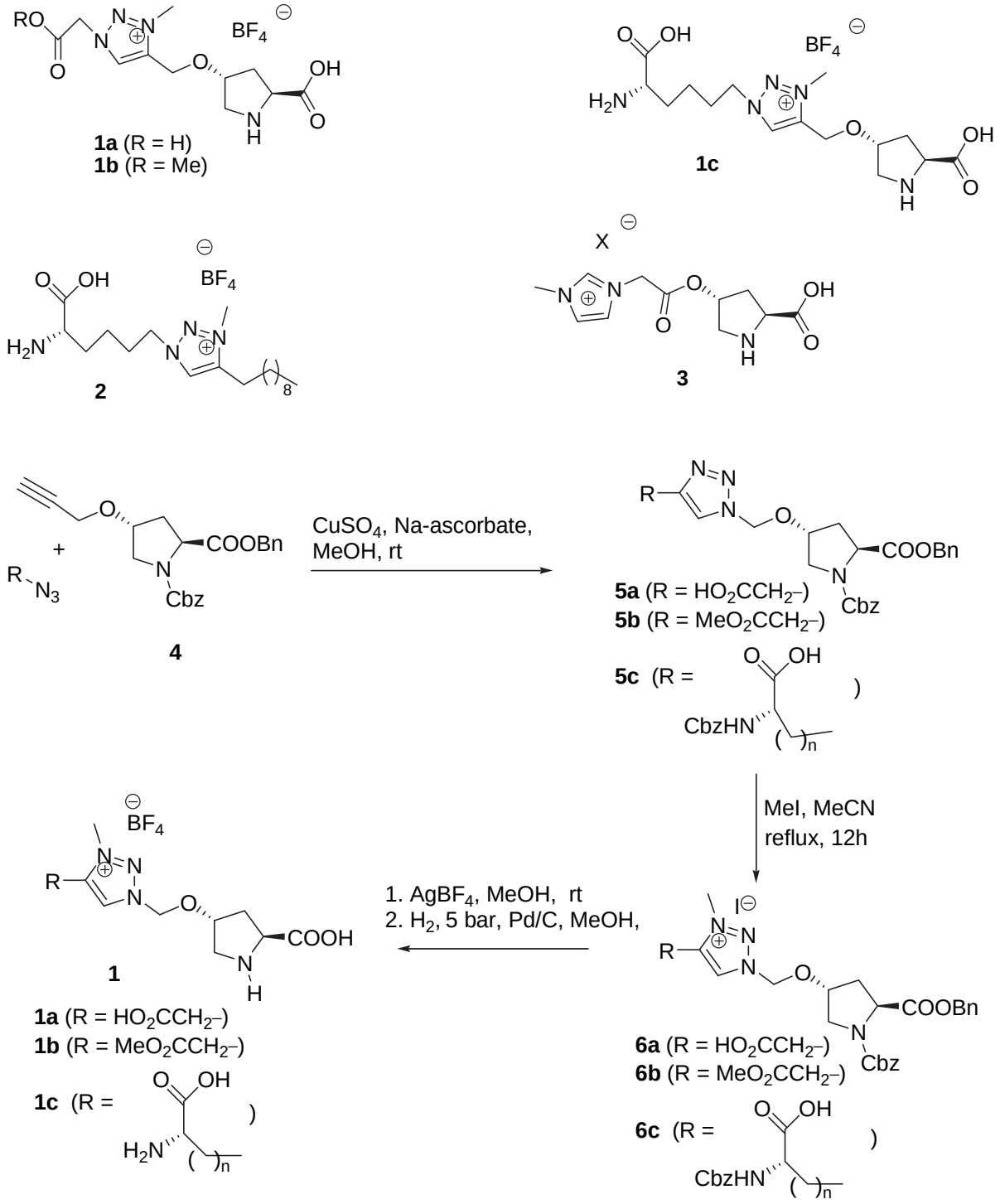
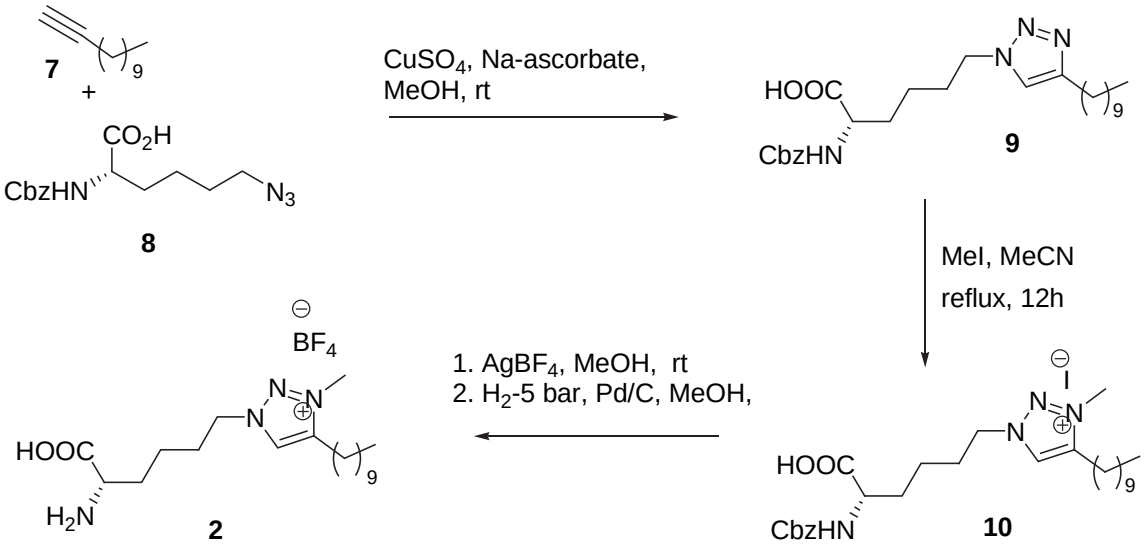


Scheme 1. Synthesis of triazolium salts **1a**–**c**.

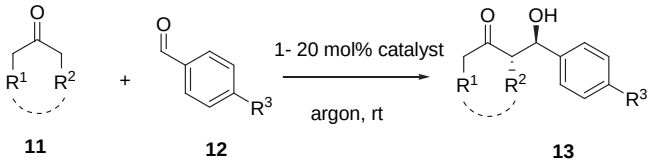
the acidity of this function we also prepared the corresponding methyl ester **1b** lacking an acidic centre. In product **1c** both proline and an acyclic α-amino acid were tethered to a triazolium unit while in **2** an acyclic (*S*)-amino acid was found instead of a proline moiety. The syntheses of these products **1** and **2** were implemented in a similar way as we used before namely via Cu-catalyzed alkyne-azide cycloaddition and N-methylation.[30,31] Thus the protected *trans*-4-hydroxyproline **4** gave the 1,2,3-triazoles **5** in Cu-catalyzed reaction with azido acetic acid, its methyl ester or a lysine-derived azide (Scheme 1), which later on were *N*-methylated by heating in methyl iodide to give the triazolium salts **6** in high yields. Salt metathesis with silver tetrafluoroborate and deprotection by Pd-catalyzed hydrogenation provided the desired triazolium tetrafluoroborates **1** as oils. In case of the triazolium iodide **6c** also the Cbz-protective group of the side chain was split off in the final step thus giving the product **1c** with two unprotected α-amino acid units.

Similarly, the non-cyclic 1,2,3-triazolium tetrafluoroborate **2** was obtained starting from the lysine derivative **8** and 1-dodecyne **7** (Scheme 2) appearing as a colourless solid (mp 91 °C). In this context it has to be mentioned that a similar Cu-catalyzed alkyne-azide cycloaddition was performed to obtain a lower homologue of **9** for a biochemical application.[32]



Scheme 2. Synthesis of triazolium salt **2**.

These four IL-tagged organocatalysts **1a**, **1b**, **1c** and **2** were tested in aldol reactions of aromatic aldehydes (Scheme 3, Table 1). As nucleophiles cyclic as well as open chain ketones **11** were used. While cyclic ketones have performed well in reported aldol reactions giving high diastereo- and enantioselectivities, acetone and other open chain ketones often caused problems.[6,7,11,14]



Scheme 3. Aldol reactions catalyzed by IL-tagged organocatalysts **1** and **2**.

The configuration of the products **13** was determined by comparison of the HPLC-retention times with literature data.[33]

Despite of all the successful applications of (*S*)-proline and its derivatives as organocatalysts it was surprising to realize that the acetic acid- and acetate-derived 1,2,3-triazolium salts **1a** and **1b** performed unsatisfactory in aldol reaction according Scheme 3. E.g. ee's of 12 or 54% in the reaction of 4-nitro-benzaldehyde and cyclohexanone (see entry 1, Table 1) are significantly lower than those obtained before with analogous (*S*)-proline-conjugates bearing a simple alkyl chain rather than the carboxylic or ester functionality in the side chain of the 1,2,3-triazolium moiety.[29,34] One could argue that the worse performance of **1a** (12% ee) as compared with the corresponding ester **1b** (54% ee) is caused by the additional carboxylic group exerting a non-stereoselective competing catalysis. However, this assumption is not in agreement with some examples where the sequence of ee's is reversed (Table 1, entries 3 and 5). The application of the IL-tagged organocatalyst **1c** gave better results in all cases wherein cyclic ketones **11** were used (Table 1, entries 1–5). Yet, the enantioselectivities were lower as compared with 1,2,3-triazolium tagged 4-hydroxyprolines with simple alkyl chains attached to the triazolium ring.[29] To our surprise, the triazolium salt **2** lacking a (*S*)-proline moiety behaved much well in all examples. In most cases, enantioselectivities higher than 90% were achieved even with cyclopentanone. Again, the previous paradigm is refuted that (*S*)-proline works better than non-cyclic amino acids. The reason for this phenomenon could eventually be found in a type of supramolecular assembly of **2** exposing the α-amino acid moiety in a favourable way to the reactants. Considering the better performance of catalyst **2** over catalyst **1c** (Table 1) as well as over 3-hydroxyproline ethers **1** (R=alkyl)[29] where two simple alkyl chains are found in the triazolium tag leads to the conclusion that the two amino acid units namely proline and lysine found in **1c** somehow counteract.

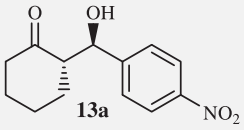
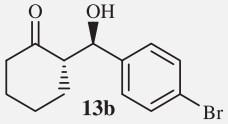
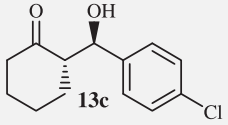
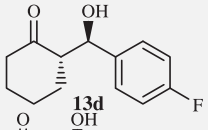
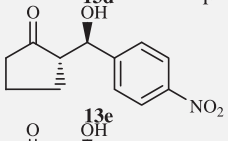
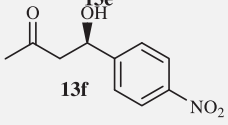
In view of the weak performance of acetone in many known organocatalyzed aldol reaction the ee of 82% ee achieved with the IL-tagged organocatalyst **2** is worth mentioning. Because of the good performance of the lysine-derived 1,2,3-triazolium salt **2** we investigated its catalytic performance in more detail (Table 2).

Extension of the reaction time from 24 h to 48 and 96 h resulted in lower diastereoselectivities and chemical yields (Table 2, entries 5 and 6). This phenomenon is likely to be caused by the reversibility of aldol reaction as also found by other authors.[7] Reducing the amount of organocatalyst **2** from 20 mol % to 10 and 5 mol % gave a slight reduction in the enantioselectivity and the chemical yield while the diastereoselectivity was not affected (Table 2, entries 1–3). However, further reduction of the quantity of **2** to 1 mol % led to a collapse in enantioselectivity (Table 2, entry 4). The addition of water did not affect the stereoselectivity but led to lower yields (Table 2, entries 7 and 8). The organocatalyst **2** was also tested in aldol reactions of cyclohexanone with aromatic aldehydes lacking electron-withdrawing substituents. While benzaldehyde performed well (97% ee, *anti*/*syn*=98/2, Table 2, entry 11) 4-methoxybenzaldehyde gave an unsatisfactory enantioselectivity 34% ee (Table 2, entry 12). This trend was also observed before with other organocatalysts. 3-Pentanon ketone often appears to be a problem in asymmetric direct aldol reactions. In our methodology 46% ee was achieved in this case (Table 2, entry 10).

In order to find out in how far the 1,2,3-triazolium moiety of **2** is responsible for the good catalytic performance, the deprotected analog of **9** was applied in the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone (Table 2, entry 9). The aldol product was formed with considerably lower stereoselectivity 52% ee versus 98% in case of **2** thus demonstrating that the triazolium tag contributes to the good catalytic performance of **2**.

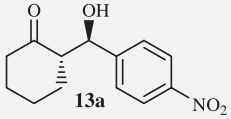
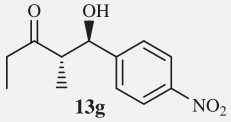
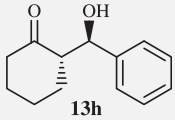
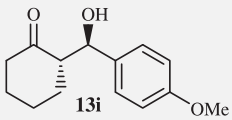
Finally recycling of the 1,2,3-triazolium tagged organocatalyst **2** was investigated (Table 3). Recycling was performed by extracting the reaction mixture with diethyl ether and reusing the remainder. It turned out that the reaction became slower after each recycling, i. e. the reaction time had to be extended for complete conversion. Enantioselectivity dropped a bit after each recycling but exceeded 90% till the fifth run. There was also a drop in diastereoselectivities (Table 3, entries 2–5), which might be caused by the necessary

Table 1
Results of aldol reactions catalyzed by triazolium tagged organocatalysts **1** and **2** (Scheme 3)[a]

Entry	Product **13**	Catalyst **1a**			Catalyst **1b**			Catalyst **1c**			Catalyst **2**		
		Yield (%)/time [h]	*anti*/*syn*	ee %	Yield (%)/time [h]	*anti*/*syn*	ee %		*anti*/*syn*	Yield (%)/time [h] ee %	ee %	*anti*/*syn*	Yield (%) /time [h]
1	 **13a**	91/25	80/20	12	92/24	90/10	54	97/24	80/20	79	98	98/2	95/24
2	 **13b**	96/21	97/3	30	98/22	98/2	42	99/22	98/2	52	94	99/1	98/23
3	 **13c**	94/29	98/2	59	95/21	99/1	54	96/27	99/1	72	93	99/1	99/26
4	 **13d**	89/23	99/1	48	91/20	99/1	49	95/18	99/1	50	92	99/1	93/20
5	 **13e**	90/29	65/35	34	28	65/35	94/27	76	65/35	91/33	92	65/35	90/29
6	 **13f**	84/33	—	34	41	—	92/30	28	—	90/31	82	—	87/28

[a] **11** (2.5 mmol), **12** (0.5 mmol), organocatalyst (20 mol %), rt, *syn*/*anti* ratios determined by ^{1}H NMR-spectroscopy, ee of the *anti* isomer determined by chiral HPLC and comparison of the retention times with literature data.[33]

Table 2
Performance of the organocatalyst **2** and the non-methylated precursor **9** in further aldol reactions[a] according to Scheme 3

Entry	Product	Conditions	ee [%]	*anti*/*syn*	Yield [%]
1	 **13a**	20 mol % **2**, 24 h	98	98/2	95
2		10 mol % **2**, 27 h	90	98/2	89
3		05 mol % **2**, 25 h	90	97/3	81
4		01 mol % **2**, 30 h	08	[b]	[b]
5		20 mol % **2**, 48 h	96	80/20	88
6		20 mol % **2**, 96 h	90	70/30	72
7		20 mol % **2**, 26 h, 10 equiv H_2O	98	92/8	79
8		20 mol % **2**, 27 h, 50 equiv H_2O	98	97/3	64
9	 **13g**	20 mol % **9**, 31 h	52	60/40	83
10		20 mol % **2**, 40 h	46	99/1	77
11	 **13h**	20 mol % **2**, 27 h	97	98/2	74
12	 **13i**	20 mol % **2**, 38 h	34	95/5	57

[a] **11** (2.5 mmol), **12** (0.5 mmol), rt, *syn*/*anti* ratios determined by ^{1}H NMR-spectroscopy, ee of the *anti* isomer determined by chiral HPLC and comparison of the retention times with literature data.
[b] Not determined.

Table 3
Recycling of IL-tagged organocatalyst **2** in aldol reaction of 4-nitrobenzaldehyde with cyclohexanone[a]

Run	ee [%]	*anti*/*syn*	Yield (%)/time [h]
First	98	98/2	95/24
Second	98	94/6	92/29
Third	96	85/15	89/32
Fourth	92	80/20	88/37
Fifth	90	80/20	83/41

[a] **11** (2.5 mmol), **12** (0.5 mmol), organocatalyst **2** (20 mol %), rt, reaction mixture was extracted with Et_2O (3×15 ml) after each run and the remainder was used for the next run without further purification, *syn*/*anti* ratios were determined by ^1H NMR-spectroscopy, ee of the *anti* isomer determined by chiral HPLC and comparison of the retention times with literature data.

extension of the reaction time and the reversibility of the aldol reaction as found before just by the extension of reaction times (compare Table 2, entry 5 and Table 3, entry 5).

The results obtained in the recycling experiments are likely affected by leaching of the organocatalyst during the extraction of the reaction mixture with diethyl ether. We are presently perusing structural analogues of **2**, which lack longer alkyl chains and thus should be more polar and less soluble in diethyl ether.

In conclusion, new IL-tagged organocatalysts **1** and **2** based on 1,2,3-triazolium tags were synthesized and investigated in aldol reactions. Remarkably, the lysine-derived 1,2,3-triazolium tetrafluoroborate **2** performed much better than organocatalysts with (*S*)-proline moieties **1** affording high yields and stereoselectivities. Acetone performed comparatively well with this IL-tagged organocatalyst **2**. Recycling and re-usage of **2** was possible by extraction of the products with diethyl ether giving ee higher than 90% till the fifth run.

3. Experimental

3.1. General

^1H 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. 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 optical rotation with literature data.

3.2. Preparation of 1,2,3-triazoles 5a–c, 9, general procedures

To a solution of corresponding azide (1 mmol) in MeOH (5 ml), sodium ascorbate (40 mg, 20 mol %), $CuSO_4$ (24 mg, 15 mol %) and alkyne **4** (1 mmol) were added. The solution was stirred at rt for 2–3 days (TLC check, see Tables 1, 2). After completion of the reaction water (25 ml) was added and the mixture was extracted with ethyl acetate (3×25 ml). The combined organic layers were washed with brine (25 ml) and then dried over Na_2SO_4. Evaporation of the solvent in vacuo gave an oily residue, which was purified by column chromatography.

*3.2.1. 2-(4-(((3R,5R)-1,5-Bis(benzyloxycarbonyl)pyrrolidin-3-yloxy) methyl)-1H-1,2,3-triazol-1-yl)acetic acid (**5a**).* Yellow oil, yield 99%. $[\alpha]_D^{22}$ −8.5 (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)= 7.28–7.37 (m, 11H, $CH_{aromatic}$+$CH_{triazole}$), 4.89–5.19 (m, 4H, 2*CH_2–Ph), 4.70 (s, 2H, O=C–CH_2–N–N), 4.37–4.61 (m, 2H, CH_2–O–CH), 4.09–4.17 (m, 1H, CH_2–O–*CH*), 3.82 (m, 1H, *CH*–C=O), 3.64–3.68 (m, 2H, CH_2–N–C=O), 1.08–1.14 (m, 2H, CH_2–CH–C=O). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=171.4 (O=*C*–OH), 140.7 ($C_{triazole}$), 136.0 ($C_{aromatic}$), 128.5 ($CH_{aromatic}$), 128.4 ($CH_{aromatic}$), 128.1 ($CH_{aromatic}$), 128.0 ($CH_{aromatic}$), 127.8 ($CH_{aromatic}$), 127.6 ($CH_{aromatic}$), 127.0 ($CH_{triazole}$), 69.0 (CH_2–O–*CH*), 67.3 (CH_2–Ph), 67.2(CH_2–Ph), 65.1 (*CH*–C=O), 60.5 (CH_2–O–CH), 57.8 (O=C–CH_2–N–N), 52.1 (CH_2–N–C=O), 36.4 (CH_2–CH–C=O). HRMS (ESI): *m*/*z* $[M+H^+]^+$ calcd for $C_{25}H_{26}N_4O_7$: 495.1880; found: 495.1833.

*3.2.2. (2R,4R)-Dibenzyl 4-((1-(2-methoxy-2-oxoethyl)-1**H**-1,2,3-triazol-4-yl)methoxy)pyrrolidine-1,2-dicarboxylate (**5b**).* Light yellow sticky oil, yield 96%. $[\alpha]_D^{22}$ −7.1 (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.29–7.37 (m, 11H, $CH_{triazole}$+$CH_{aromatic}$), 5.11–5.21 (m, 4H, 2*CH_2–Ph), 5.01–5.09 (m, 2H, CH_2–N–N), 4.10–4.17 (m, 2H, CH_2– $C_{triazole}$), 3.85 (s, 3H, CH_3–O), 3.80–3.81 (m, 2H, CH_2–O–*CH*+N–*CH*–C=O), 3.65–3.68 (m, 2H, CH_2–N–C=O), 1.21–1.30 (m, 2H, CH_2–CH–C=O). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=166.7 (CH_3–O–*C*=O), 154.6 (N–*C*=O), 140.9 ($C_{triazole}$), 136.2 ($C_{aromatic}$), 128.6 ($CH_{aromatic}$), 128.5 ($CH_{aromatic}$), 128.4 ($CH_{aromatic}$), 128.0 ($CH_{aromatic}$), 127.8 ($CH_{aromatic}$), 127.6 ($CH_{aromatic}$), 127.0 ($CH_{triazole}$), 79.2 (CH_2–O–*CH*), 74.9 (CH_2–Ph), 68.9 (CH_2–Ph), 67.3 (CH_2–$C_{triazole}$), 65.2 (N–*CH*–C=O), 56.7 (CH_3–O), 53.1 (CH_2–N–N), 51.8 (N–CH_2–CH–O), 36.5 (CH_2–CH–N). HRMS (ESI): *m*/*z* $[M+H^+]^+$ calcd for $C_{26}H_{28}N_4O_7$: 509.2036; found: 509.2072.

*3.2.3. (R)-2-(Benzyloxycarbonylamino)-6-(4-(((3R,5S)-1,5-bis(benzyloxycarbonyl)pyrrolidin-3-yloxy)methyl)-1H-1,2,3-triazol-1-yl) hexanoic acid (**5c**).* Yellow oil, yield 97%. $[\alpha]_D^{22}$ −9.0 (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.50 (s, 1H, CH–*NH*), 7.28–7.35 (m, 16H, $CH_{aromatic}$+$CH_{triazole}$), 4.98–5.08 (m, 6H, 3* CH_2–Ph), 4.68 (s, 2H, CH_2–$C_{triazole}$), 4.59 (t, *J*=7.08 Hz, 1H, *CH*–NH), 4.37 (m, 1H, CH–CH_2–*CH*–C=O), 4.29(m, 2H, CH_2–N–N), 4.21 (m, 1H, CH_2–N–C=O), 3.60–3.65 (m, 1H, CH_2–N–C=O), 2.28–2.39 (m, 1H, *CH*–O–CH_2), 1.88 (m, 2H, CH–CH_2–CH–C=O), 1.23–1.27 (m, 2H, CH_2–CH–NH), 1.17–1.21 (m, 2H, CH_2–CH_2–N–N), 1.04–1.11 (m, 2H, CH_2–CH_2–CH_2–N–N). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=174.3 (O=*C*–OH), 160.4 (O=*C*–O–CH_2), 156.3 (O=*C*–O–CH_2), 141.1 ($C_{triazole}$), 136.5 ($C_{aromatic}$), 128.8 ($CH_{aromatic}$), 128.4 ($CH_{aromatic}$), 128.1 ($CH_{aromatic}$), 127.3 ($CH_{triazole}$), 76.5 (*CH*–O–CH_2), 67.3 (CH_2–Ph), 67.2 (CH_2–Ph), 65.5 (CH_2–$C_{triazole}$), 62.7 (CH_2–Ph), 58.3 (*CH*–NH), 53.8 (CH–CH_2–*CH*–C=O), 52.6 (CH_2–N–C=O), 50.3 (CH_2–N–N), 35.7 (CH–CH_2–CH–C=O), 31.9 (CH_2–CH–NH), 29.8 (CH_2–CH_2–N–N), 21.8 (CH_2–CH_2–CH_2–N–N). HRMS (ESI): *m*/*z* $[M+H^+]^+$ calcd for $C_{37}H_{41}N_5O_9$: 700.2983; found: 700.2955.

*3.2.4. (R)-2-(Benzyloxycarbonylamino)-6-(4-decyl-1H-1,2,3-triazol-1-yl)hexanoic acid (**9**).* Azide **8** (1 g, 3.2 mmol) and 1-dodecyne **7** 0.69 ml (3.2 ml) were dissolved in a mixture of *t*-BuOH (2 ml) and water (1 ml). With vigorous stirring, sodium ascorbate (43 mg, 20 mol %) was added followed by copper sulfate (17 mg, 10 mol %) solution in water (1 ml). The mixtures were stirred at rt for 24 h. The solvents were then evaporated to dryness and the residue taken up in AcOEt (100 ml). The suspension was washed 2–3 times with 5 ml of 0.5 N HCl (copper removal), and then with water (100 ml). Drying with Na_2SO_4, evaporation of the solvent yielded the pure compound.

Yellow oil, yield 96%. $[\alpha]_D^{22}$ −3.9 (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.31–7.33 (m, 6H, $CH_{aromatic}$+$CH_{triazole}$), 5.1 (s, 2H, CH_2–Ph), 4.38 (m, 1H, *CH*–NH), 4.30 (m, 2H, CH_2–N–N), 2.69 (s, 2H, CH_2–$C_{triazole}$), 2.05 (s, 2H, CH_2–CH_2–N–N), 1.91 (m, 2H, CH_2–CH–NH), 1.63 (m, 2H, CH_2–CH_2–$C_{triazole}$), 1.26 (m, 16H, 7*CH_2 $_{(alkyl\ chain)}$+CH_2–CH_2–CH_2–N–N), 0.88 (t, *J*=6.69 Hz, 3H, CH_3–CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=171.3 (O=C–OH), 156.0 (O=*C*–O–CH_2), 136.2 ($C_{aromatic}$), 128.5 ($CH_{aromatic}$), 128.1 ($CH_{aromatic}$), 128.0 ($CH_{aromatic}$), 66.9(CH_2–Ph), 60.4 (*CH*–NH), 50.0 (CH_2–N–N), 31.8 (CH_2–CH–NH_2), 31.7 ($CH_{2(alkyl\ chain)}$) 29.6 ($CH_{2(alkyl\ chain)}$) 29.5 ($CH_{2(alkyl\ chain)}$) 29.3 ($CH_{2(alkyl\ chain)}$) 29.1 ($CH_{2(alkyl\ chain)}$), 28.4 ($CH_{2(alkyl\ chain)}$), 25.3 (CH_2–CH_2–N–N), 22.6 (CH_2–$C_{triazole}$), 21.9 (CH_2–CH_2–CH_2–N–N), 21.0 (CH_2–CH_2–$C_{triazole}$), 18.4 (CH_3–CH_2), 14.1 (CH_3–CH_2). HRMS (ESI): *m*/*z* $[M+H^+]^+$ calcd for $C_{26}H_{40}N_4O_4$: 473.3128; found: 473.3095.

3.3. Preparation of 1,2,3-triazolium salts 1, 2, 6 and 10, general procedure

A solution of the 1, 2, 3-triazole **5a**–**c** or **9** (20 mmol) and 5 equiv of MeI (14,3 g, 100 mmol) in dry MeCN (30 ml) was refluxed for 12 h. All volatile compounds were removed under vacuum with a rotary evaporator leaving behind the ionic liquid as oil or sticky oil that was washed with diethyl ether to remove the traces of impurities. The resulting iodide was transmitted to salt metathesis with $AgBF_4$ using a procedure published before.[29,30]

*3.3.1. 3-(Carboxymethyl)-5-(((3R,5R)-5-carboxypyrrolidin-3-yloxy) methyl)-1-methyl-3H-1,2,3-triazol-1-ium tetrafluoroborate (**1a**).* Light yellow sticky oil, yield 85%. $[\alpha]_D^{22}$ −2.5 (*c* 1, CH_3OH). ^1H NMR (CD_3OD, 300 MHz): δ (ppm)=8.71 (s, 1H, $CH_{triazole}$), 5.61 (s, 2H, CH_2–N–N), 4.59 (m, 1H, *CH*–C=O), 4.54 (m, 1H, CH_2–O–*CH*), 4.36 (s, 2H, CH_2–O–CH), 3.85 (s, 3H, CH_3–N), 3.32 (m, 1H, CH_2–NH), 2.72–2.77 (m, 1H, CH_2–NH), 2.58–2.61 (m, 1H, CH_2–CH–C=O), 2.24–2.32 (m, 1H, CH_2–CH–C=O). ^{13}C NMR (CD_3OD, 75 MHz): δ (ppm)=168.0 (O=*C*–OH), 165.0 (CH_2–C=O), 140.5 ($C_{triazole}$), 130.9 ($CH_{triazole}$), 78.1 (CH_2–O–*CH*), 71.2 (*CH*–C=O), 58.2 (CH_2–O–CH), 53.1 (CH_2–N–C=O), 51.0 (CH_2–NH), 37.7 (CH_3–N), 34.1 (CH_2–CH–C=O). HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{17}N_4O_5^+$: 285.1198; found: 285.1199.

*3.3.2. 5-(((3R,5R)-5-Carboxypyrrolidin-3-yloxy)methyl)-3-(2-methoxy-2-oxoethyl)-1-methyl-3H-1,2,3-triazol-1-ium tetrafluoroborate (**1b**).* Light yellow oil, yield 92%. $[\alpha]_D^{22}$ −2.3 (*c* 1, CH_3OH). ^1H NMR (CD_3OD, 300 MHz): δ (ppm)=8.69 (s, 1H, $CH_{triazole}$), 4.59 (s, 2H, CH_2–N–N), 4.35 (m, 3H, N–*CH*–C=O+N–CH_2–CH–O), 3.84 (s, 3H, CH_3–N), 3.36 (s, 3H, CH_3–O), 3.36 (m, 2H, CH_2–O–CH), 2.91 (s, 1H, CH_2–O–*CH*), 1.31–1.32 (m, 2H, CH_2–CH–N). ^{13}C NMR (CD_3OD, 75 MHz): δ (ppm)=169.7 (OH–*C*=O), 166.8 (CH_3–O–*C*=O), 141.8 ($C_{triazole}$), 129.7 ($CH_{triazole}$), 79.4 (CH_2–O–*CH*), 59.5 (N–*CH*–C=O), 59.4 (CH_2–O–CH), 54.4 (CH_3–O), 54.0 (CH_2–N–N), 45.4 (N–CH_2–CH–O), 39.0 (CH_3–N), 35.4 (CH_2–CH–N). HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{19}N_4O_5^+$: 299.1355; found: 299.1374.

*3.3.3. 3-((R)-5-Amino-5-carboxypentyl)-5-(((3R,5S)-5-carboxypyrrolidin-3-yloxy)methyl)-1-methyl-3H-1,2,3-triazol-1-ium tetrafluoroborate (**1c**).* Colourless solid, yield 67%, mp 104 °C. $[\alpha]_D^{22}$ +5.9 (*c* 1, CH_3OH). ^1H NMR (CD_3OD, 300 MHz): δ (ppm)=8.94 (s, 1H, $CH_{triazole}$), 4.77–4.87 (m, 2H, *CH*–NH_2+CH–CH_2–*CH*–C=O), 4.61 (s, 2H, CH_2–$C_{triazole}$), 4.23 (s, 3H, CH_3–N), 3.32–3.34 (m, 1H, *CH*–O–CH_2), 3.10–3.20 (m, 2H, CH_2–N–N), 2.49–2.51 (m, 2H, CH_2–NH), 1.90 (m, 2H, CH–CH_2–CH), 1.73 (m, 2H, CH_2–CH–NH), 1.16–1.21 (m, 4H, CH_2–CH_2–N–N+CH_2–CH_2–CH_2–N–N). ^{13}C NMR (CD_3OD, 75 MHz): δ (ppm)=171.5 (O=*C*–OH), 140.6 ($C_{triazole}$), 129.5 ($CH_{triazole}$), 79.4 (*CH*–O–CH_2), 58.2 (CH_2–$C_{triazole}$), 57.7 (*CH*–NH_2), 53.2(CH–CH_2–*CH*–C=O), 52.5 (CH_2–NH), 51.0 (CH_2–N–N), 38.0 (CH_3–N), 35.2 (CH–CH_2–CH), 29.4 (CH_2–CH–NH_2), 27.9 (CH_2–CH_2–N–N), 21.4 (CH_2–CH_2–CH_2–N–N). HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{26}N_5O_5^+$: 356.1933; found: 356.1939.

*3.3.4. (R)-3-(5-Amino-5-carboxypentyl)-5-decyl-1-methyl-3H-1,2,3-triazol-1-ium tetrafluoroborate (**2**).* Off white solid, yield 83%, mp 91 °C. $[\alpha]_D^{22}$ +4.6 (*c* 1, CH_3OH). ^1H NMR (CD_3OD, 300 MHz): δ (ppm)= 8.80 (s, 1H, $CH_{triazole}$), 4.59 (t, *J*=6.98 Hz, 2H, CH_2–N–N), 4.20 (s, 3H, CH_3–N), 3.73 (m, 1H, *CH*–NH_2), 2.82–2.89 (m, 2H, CH_2–$C_{triazole}$), 2.01–2.10 (m, 2H, CH_2–CH_2–N–N), 1.87–1.97 (m, 2H, CH_2–CH–NH_2), 1.72.1.82 (m, 2H, CH_2–CH_2–$C_{triazole}$), 1.30–1.52 (m, 16H, 7*$CH_{2(alkyl\ chain)}$+CH_2–CH_2–CH_2–N–N), 0.90 (t, *J*=6.52 Hz, 3H, CH_3–CH_2). ^{13}C NMR (CD_3OD, 75 MHz): δ (ppm)=144.9 ($C_{triazole}$), 127.6 ($CH_{triazole}$), 53.6 (*CH*–NH_2), 52.9 (CH_2–N–N), 36.3 (CH_3–N), 31.6 (CH_2–CH–NH_2), 29.7 ($CH_{2(alkyl\ chain)}$) 29.3 ($CH_{2(alkyl\ chain)}$) 29.2 ($CH_{2(alkyl\ chain)}$) 29.0 ($CH_{2(alkyl\ chain)}$) 28.9 ($CH_{2(alkyl\ chain)}$), 28.7 ($CH_{2(alkyl\ chain)}$), 28.2 (CH_2–CH_2–N–N), 26.4(CH_2–CH_2–CH_2–N–N), 22.7 (CH_2–CH_2–$C_{triazole}$), 22.3 (CH_2–$C_{triazole}$), 21.3 (CH_3–CH_2), 13.0 (CH_3–CH_2). HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{19}H_{37}N_4O_2^+$: 353.2917; found: 353.2927.

*3.3.5. 5-(((3R,5R)-1,5-Bis(benzyloxycarbonyl)pyrrolidin-3-yloxy) methyl)-3-(carboxymethyl)-1-methyl-3H-1,2,3-triazol-1-ium iodide (**6a**).* Brownish yellow oil, yield 94%. $[\alpha]_D^{22}$ −6.6 (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.28–7.36 (m, 11H, $CH_{aromatic}$+$CH_{triazole}$), 5.05–5.13 (m, 4H, 2*CH_2–Ph), 4.91–5.01 (m, 4H, O=C–CH_2–N–N+CH_2–O–CH), 4.67 (m, 1H, CH_2–O–*CH*), 4.09 (m, 1H, *CH*–C=O), 3.81 (s, 3H, CH_3–N), 3.61–3.66 (m, 2H, CH_2–N–C=O), 1.18–1.23 (m, 2H, CH_2–CH–C=O). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=165.6 (O=*C*–OH), 154.6 (O=*C*–O–CH_2), 140.9 ($C_{triazole}$), 136.0 ($C_{aromatic}$), 128.5 ($CH_{aromatic}$), 128.2 ($CH_{aromatic}$), 128.1 ($CH_{aromatic}$), 127.9 ($CH_{aromatic}$), 127.8 ($CH_{aromatic}$), 127.5 ($CH_{aromatic}$), 127.0 ($CH_{triazole}$), 69.0 (CH_2–O–*CH*), 67.4 (CH_2–Ph), 67.3(CH_2–Ph), 64.9 (*CH*–C=O), 59.0 (CH_2–O–CH), 58.2 (O=C–CH_2–N–N), 53.9 (CH_2–N–C=O), 39.5 (CH_3–N), 36.5 (CH_2–CH–C=O). HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{26}H_{29}N_4O_7^+$: 509.2036; found: 509.203.

*3.3.6. 5-(((3R,5R)-1,5-Bis(benzyloxycarbonyl)pyrrolidin-3-yloxy) methyl)-3-(2-methoxy-2-oxoethyl)-1-methyl-3H-1,2,3-triazol-1-ium iodide (**6b**).* Light brown oil, yield 81%. $[\alpha]_D^{22}$ −7.2 (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=9.04 (s, 1H, $CH_{triazole}$), 7.27–7.33 (m, 10H, $CH_{aromatic}$), 4.97–5.13 (m, 4H, 2*CH_2–Ph), 4.84–4.93 (m, 2H, CH_2–N–N), 4.27–4.38 (m, 4H, CH_2–$C_{triazole}$+CH_2–O–*CH*+N–*CH*–C=O), 4.07–4.18 (m, 2H, CH_2–N–C=O), 3.78 (s, 3H, CH_3–N), 3.65 (s, 3H, CH_3–O), 1.22–1.26 (m, 2H, CH_2–CH–C=O). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=171.6 (N–CH–*C*=O), 165.1 (CH_3–O–*C*=O), 154.5 (N–*C*=O), 136.8 ($C_{triazole}$), 132.0 ($C_{aromatic}$), 128.4 ($CH_{aromatic}$), 128.2 ($CH_{aromatic}$), 128.0 ($CH_{aromatic}$), 127.9 ($CH_{aromatic}$), 127.8 ($CH_{aromatic}$), 127.4 ($CH_{aromatic}$), 127.0 ($CH_{triazole}$), 79.1 (CH_2–O–*CH*), 74.9 (CH_2–Ph), 67.2 (CH_2–Ph), 65.8 (CH_2–O–CH), 64.9 (N–*CH*–C=O), 56.4 (CH_3–O), 53.7 (CH_2–N–N), 45.3 (N–CH_2–CH–O), 39.1 (CH_3–N), 36.5 (CH_2–CH–N). HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{27}H_{31}N_4O_7^+$: 523.2193; found: 523.2185.

*3.3.7. 3-((R)-5-(Benzyloxycarbonylamino)-5-carboxypentyl)-5-(((3R,5S)-1,5-bis(benzyloxycarbonyl)-pyrrolidin-3-yloxy)methyl)-1-methyl-3H-1,2,3-triazol-1-ium iodide (**6c**).* Light yellow oil, yield 92%. $[\alpha]_D^{22}$ −3.5 (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)= 9.01 (s, 1H, CH–*NH*), 7.29–7.34 (m, 16H, $CH_{aromatic}$+$CH_{triazole}$), 4.86–5.10 (m, 6H, 3*CH_2–Ph), 4.66 (s, 2H, CH_2–$C_{triazole}$), 4.54 (m, 2H, *CH*–NH+CH–CH_2–*CH*–C=O), 4.37(m, 2H, CH_2–N–N), 4.13 (s, 3H, CH_3–N), 3.56–3.60 (m, 2H, CH_2–N–C=O), 2.29–2.47 (m, 1H, *CH*–O–CH_2), 1.79–1.81 (m, 2H, CH–CH_2–CH–C=O), 1.41 (m, 2H, CH_2–CH–NH), 1.16–1.21 (m, 2H, CH_2–CH_2–N–N), 1.07–1.12 (m, 2H, CH_2–CH_2–CH_2–N–N). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)= 173.7 (O=*C*–OH), 156.3 (O=*C*–O–CH_2), 140.9 ($C_{triazole}$), 136.3 ($C_{aromatic}$), 128.5 ($CH_{aromatic}$), 128.4 ($CH_{aromatic}$), 128.1 ($CH_{aromatic}$), 127.9 ($CH_{aromatic}$), 127.8 ($CH_{aromatic}$), 127.5 ($CH_{aromatic}$), 127.0 ($CH_{triazole}$), 77.8 (*CH*–O–CH_2), 66.8 (CH_2–Ph), 65.8 (CH_2–Ph), 64.9 (CH_2–$C_{triazole}$), 57.7 (*CH*–NH), 53.8 (CH_2–N–C=O), 53.5 (CH–CH_2–*CH*–C=O), 52.1 (CH_2–N–N), 39.3 (CH_3–N), 36.6 (CH–CH_2–CH–C=O), 30.7 (CH_2–CH–NH), 28.5 (CH_2–CH_2–N–N), 21.5 (CH_2–CH_2–CH_2–N–N). HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{38}H_{44}N_5O_9^+$: 714.3139; found: 714.3133.

*3.3.8. (R)-3-(5-(Benzyloxycarbonylamino)-5-carboxypentyl)-5-decyl-1-methyl-3H-1,2,3-triazol-1-ium iodide (**10**).* Brownish yellow oil, yield 93%. $[\alpha]_D^{22}$ −4.3 (*c* 1, CH_3OH). ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm)=8.80 (s, 1H, O=C–*OH*), 8.29 (s, 1H, *NH*–CH), 7.28–7.32 (m, 6H, $CH_{aromatic}$+$CH_{triazole}$), 5.06 (s, 2H, CH_2–Ph), 4.61 (t, *J*=6.66 Hz, 2H, CH_2–N–N), 4.23–4.30 (m, 1H, *CH*–NH), 4.17 (s, 3H, CH_3–N), 2.79–2.86 (m, 2H, CH_2–$C_{triazole}$), 1.79–2.06 (m, 2H, CH_2–CH_2–N–N), 1.76–1.88 (m, 2H, CH_2–CH–NH), 1.66.1.76 (m, 2H, CH_2–CH_2–$C_{triazole}$),

1.24 (m, 16H, 7*$CH_{2(alkyl\ chain)}$+*CH_2*−CH_2−CH_2−N−N), 0.86 (t, *J*=6.70 Hz, 3H, *CH_3*−CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=174.4 (O=*C*−OH), 156.4 (O=*C*−O−CH_2), 144.6 ($C_{triazole}$), 136.2 ($C_{aromatic}$), 128.9 ($CH_{aromatic}$), 128.5 ($CH_{aromatic}$), 128.1 ($CH_{aromatic}$), 127.8 ($CH_{triazole}$), 66.8(*CH_2*−Ph), 53.7 (*CH_2*−N−N), 53.6 (*CH*−NH), 38.4 (*CH_3*−N), 31.8 (*CH_2*−CH−NH), 30.8 ($CH_{2(alkyl\ chain)}$) 29.5 ($CH_{2(alkyl\ chain)}$) 29.4 ($CH_{2(alkyl\ chain)}$) 29.2 ($CH_{2(alkyl\ chain)}$) 29.1 ($CH_{2(alkyl\ chain)}$), 28.6 (*CH_2*−CH_2−N−N), 27.1 (*CH_2*−CH_2−$C_{triazole}$), 23.8 (*CH_2*−$C_{triazole}$), 22.6 (*CH_2*−CH_2−CH_2−N−N), 21.9 (CH_3−*CH_2*), 14.1 (*CH_3*−CH_2). HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{27}H_{43}N_4O_4^+$: 487.3284; found: 487.3263.

3.4. Typical experimental procedure for asymmetric direct aldol reaction (in excess of ketone as solvent) catalyzed by 2

A catalytic amount of catalyst **2** (35 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 rt for 24 h and subsequently extracted with diethyl ether (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 **13** was purified by silica-gel column chromatography (*n*-hexane/AcOEt=4/1) to afford the aldol product as a white solid (118 mg, 95% yield).

*3.4.1. (S)-2-((R)-Hydroxy(4-nitrophenyl)methyl)cyclohexanone **13**.* (R^1/R^2=$(CH_2)_3$, R^3=NO_2). The diastereomeric *anti*/*syn* ratio was determined by ^{1}H 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). ^{1}H NMR (300 MHz, $CDCl_3$): 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) ppm. ^{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 ppm.

3.5. Typical experimental procedure for recycling catalyst 2 in asymmetric aldol reaction

The reaction mixture of 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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