Tetrahedron 67 (2011) 1812–1820

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Ionic-liquid tagged prolines as recyclable organocatalysts for enantioselective α-aminoxylations of carbonyl compounds

Sadaf Sadiq Khan, Jabbar Shah, Jürgen Liebscher *

Institute of Chemistry, Humboldt-University Berlin, Brook-Taylor-Street 1-2, 12489 Berlin, Germany

ARTICLE INFO

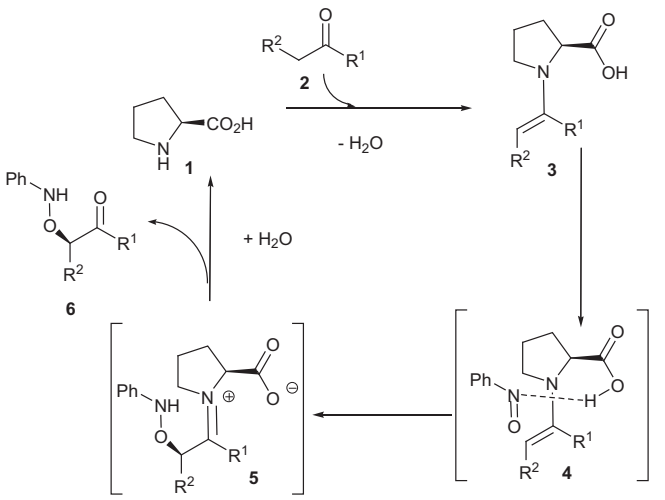
Article history:
Received 16 November 2010
Received in revised form 5 January 2011
Accepted 12 January 2011
Available online 15 January 2011

ABSTRACT

With the aim of improving catalytic performance and recyclability various ionic-liquid-tagged organocatalysts (ILTOCs) based on (*S*)-proline as organocatalysts and triazolium or guanidinium salts as ionic liquid tags were applied in the asymmetric α-aminoxylation of ketones and aldehydes with nitrosobenzene in IL as solvents. Amongst such ILTOC's compounds were found which performed better (ee >99%, yield 97%) than (*S*)-proline in reported cases. Recycling and reusage of ILTOCs were easily possible and yields higher than 80% and ees higher than 90% were obtained until the fifth cycle. Important information about the crucial role of water in recycling of proline-derived organocatalysts in reactions with carbonyl compounds via enamine activation was found to prevent blockade of the organocatalyst by oxazolidinone formation.

1. Introduction

Optically active α-hydroxycarbonyl compounds have gained wide interest as important intermediates in organic synthesis and as building blocks for natural products and bioactive compounds. Among the various synthetic routes to this important class of compounds organocatalyzed α-aminoxylation of carbonyl compounds has become very popular in recent years also from the point of view of Green Chemistry.[1–11] This strategy uses nitrosoarenes as reagents (recently also TEMPO was also successfully employed)[12] and either chiral amines or less often[13] chiral Brønsted acids as organocatalysts (for the mechanism of the proline catalyzed α-aminoxylation see Scheme 1). It results in α-aminoxycarbonyl compounds, which can easily be transformed into α-hydroxy analogues by N–O bond cleavage either by excess of the nitrosoarene[10] or by copper sulfate.[3] Eventually, the carbonyl group was reduced in a final step when sodium borohydride was added[1,3,5,7,14] giving rise to optically active 2-aminoxyalcohols or 1,2-diols as other important classes of building blocks in organic synthesis. α-Aminoxylation can also be involved in other subsequent or tandem reactions, such as formation of oxazines,[8,9,11,15] carbon-chain extended α-hydroxyketones[14,16] or vicinal diols[14] thus providing additional synthetic applications. As compared with the organocatalyzed aldol reaction (in fact the aminoxylation of carbonyl compounds is often termed as nitroso aldol reaction) the α-aminoxylation has some peculiarities. Thus it can result in regioisomeric α-oxamination products, a problem which was solved by applying proper organocatalysts (in fact proline amides derived from 2-aminoalcohols gave preferably the corresponding α-hydroxylamino carbonyl compounds)[17] and conditions. Unlike the aldol reaction, the aminoxylation results in an amine, which itself can also act as an organocatalyst and thus can cause autocatalysis and non-linear asymmetric induction when **6** acts in a similar way as proline **1**.[18]



Scheme 1. Mechanism of (*S*)-proline catalyzed α-aminoxylation of carbonyl compounds with nitrosobenzene.[19]

* Corresponding author. Tel.: +49 30 20937550; fax: +49 30 20937552; e-mail address: liebscher@chemie.hu-berlin.de (J. Liebscher).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.01.031

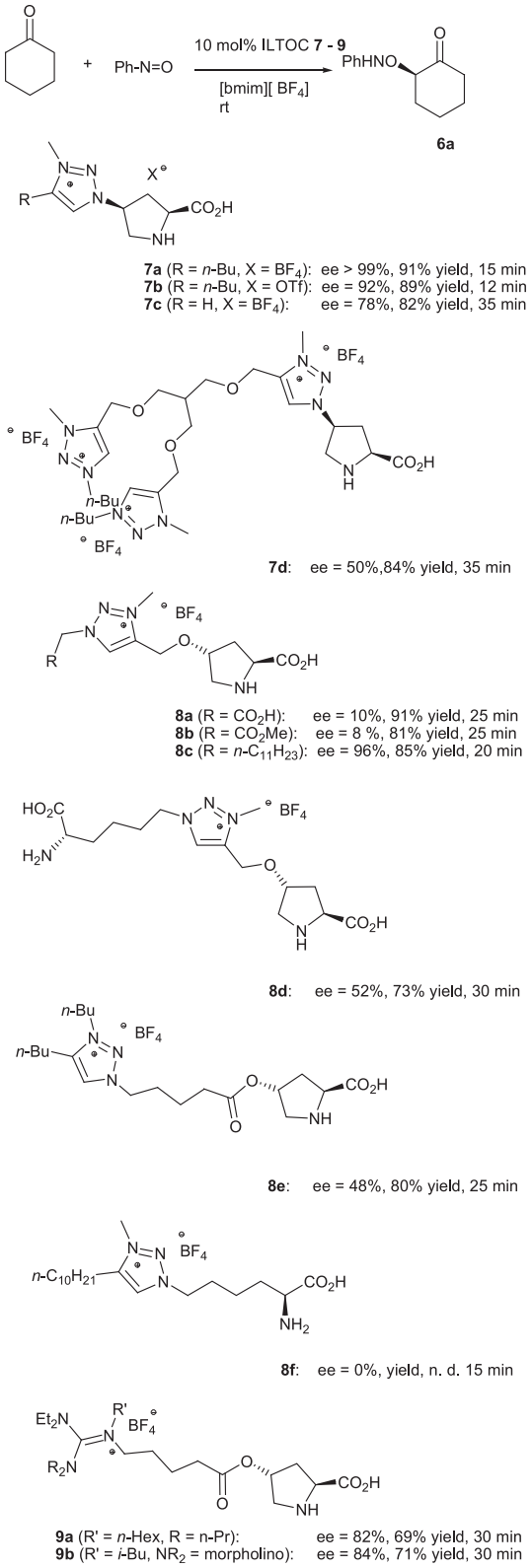
Although (*S*)-proline is most abundant as catalyst in organocatalyzed α-aminoxylation also other chiral secondary amines, such as substituted prolines,[9] binaphthyl-derived amines,[5,20] (*S*)-pyrrolidin-2-yl-tetrazoles,[7,8,10,11,14,15] 2-aminomethylpyrrolidine sulfonamides,[4,11] thioproline,[6] and others[10] were applied with great success. After optimisation, most of these methods provided high yields and excellent stereoselectivities. The catalysts are easily available and environmentally benign in most cases. Recently water could be used as solvent for α-aminoxylation with success.[6] As a general issue in catalysis recycling of the catalyst is an important aspect of Green Chemistry. This aspect was addressed in α-aminoxylation by fixation of the catalyst on polymer supports, where 4-hydroxyproline was linked to Merrifield resin by Cu(I)-catalyzed cycloaddition of alkynes to azides (click chemistry).[21] However, performance of this catalyst in recycling was only demonstrated until the second recycling, where high ees (99%) were maintained while the yield dropped from 81 to 75%. As an alternative for catalyst recycling aminoxylations with (*S*)-proline were carried out in ionic liquids as solvents. Here, the catalyst was retained by the IL during extraction of the products by organic solvents (e.g., diethyl ether) leaving behind a so-called working solution (IL with catalyst), which can be used in the next batch. Although this methodology was reported to work excellently with mere (*S*)-proline,[22] these results are questionable as shown by Guo et al. demonstrating a considerable decrease of yields in each recycling step going down to 50% ee after the fifth recycling.[23] As a recent methodology to improve the solubility in ionic liquids and decreasing solubility in less polar organic solvents so-called ionic-liquid-tagged organocatalysts (ILTOC) were developed wherein an IL-unit is covalently linked to the organocatalytic moiety.[24,25] The aim of this strategy is to reduce leaching during the extraction of products and thus to improve recycling. Sometimes a synergistic catalytic effect is observed when the organocatalyst and the IL are covalently linked. Very recently and parallel to our investigations, this methodology was also applied in α-aminoxylation by using an ILTOC consisting of an imidazolium salts linked to position 4 of (*S*)-proline.[26] Here, high yields (79%) and enantioselectivities (>99%) were maintained in the α-aminoxylation of cyclohexanone with nitrosobenzene until the seventh run.

We have been using 1,2,3-triazolium[25,27,28] and guanidinium salts as IL-tags for organocatalysts in several reactions. Both tags can be easily synthesized and allow a wide structural variation. The 1,2,3-triazolium rings are easily available by Cu-catalyzed 1,3-dipolar cycloaddition of alkynes to azides followed by N-methylation and eventual salt metathesis. Guanidinium salts are easily obtained by alkylation of pentasubstituted guanidines. So far, these types of ILTOCs were applied to aldol reactions, nitro-Michael reactions and Mannich reactions and showed synergistic effects as well as good recyclability in a number of cases.

2. Results and discussion

2.1. Asymmetric α-aminoxylation

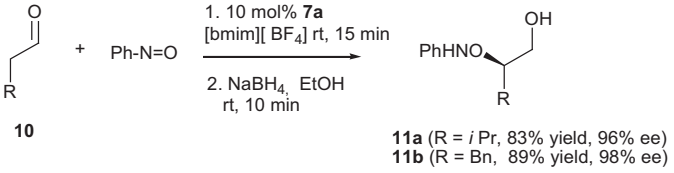
Here, we report the α-aminoxylations of carbonyl compounds with nitrosobenzene using (*S*)-prolines or a lysine derivative tagged with triazolium salts **7a**–**c**, **8a**–**f** or guanidinium salts **9a**,**b** (Scheme 2, see also chapter 2.2.). This collection of ILTOCs (Scheme 2) allowed studying the effect of substituents, anions, linkers, hydrophilicity, and lipophilicity on the catalytic performance. All ILTOCs were first screened in the α-aminoxylation of cyclohexanone with nitrosobenzene using [bmim][BF_4] as IL solvent at room temperature (see Scheme 2). It turned out that the 1,2,3-triazolium tagged proline tetrafluoroborate **7a** gave superior ee (>99%) and yield (91%). These results are better than reported in cases wherein simple (*S*)-proline was used.[11] Exchanging the anion with triflate (ILTOC **7b**) resulted in a somewhat lower ee (92%). Unexpectedly, the triazolium-tagged proline **7c** lacking a substituent in position 4 of the 1,2,3-triazole ring and thus is less lipophilic performed worse resulting in 78% ee and 82% yield after prolonged reaction time. We expected the proline **7d** with three IL-tags to be very promising for recycling because of its highly ionic character. Unfortunately, it provided only 50% ee and thus was not worth to submit to recycling experiments. In the other



Scheme 2. Application of ILTOCs **7**–**9** in α-aminoxylation of cyclohexanone in [bmim][BF_4].

triazolium-tagged prolines **8** the triazolium unit was tethered to the proline as ether or ester and the configuration at position 4 of the proline moiety was opposite. The lipophilic dodecyl derivative **8c** gave a high ee (96%), while the short chain carboxylate **8b** (8% ee) or carboxylic acid **8a** (10% ee) behaved unsatisfactorily. Placing a second α-amino acid moiety in the side chain of the 1,2,3-triazolium salt (**8d**) had a disadvantageous effect resulting in only 52% ee. Unexpectedly, the triazolium ILTOC **8f** where the proline moiety is replaced by a non-cyclic α-amino acid unit failed to give any enantioselectivity. In this context it is worth mentioning that this ILTOC **8f** gave very good results in aldol reactions, which were better than corresponding proline derivatives.[27] Guanidinium-tagged prolines **9a**,**b** performed better than the analogous 1,2,3-triazolium tagged proline **8e** but could not compete with the best ILTOCs **7a**,**b** and **8c** in the triazolium series.

In order to test scope and limitation of our favorite ILTOC **7a** we also investigated α-aminoxylation of aldehydes with nitrosobenzene in [bmim][BF_4]. Since the expected α-phenylaminoxyaldehydes are known to be unstable they were reduced to the corresponding 3-arylaminoxyalcohols by sodium borohydride after isolation (Scheme 3).

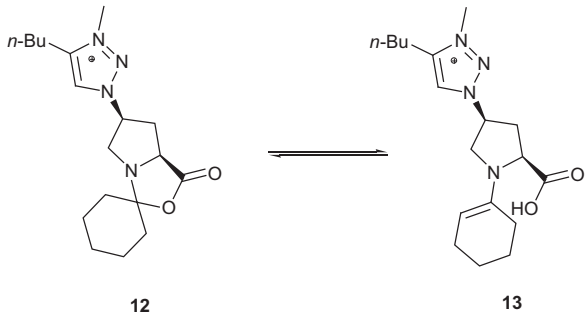


Scheme 3. α-Aminoxylation/reduction of aldehydes with nitrosobenzene catalyzed by **7a**.

Isobutyraldehyde as well as 3-phenylpropionaldehyde gave the α-phenylaminoxyalcohols **11a** and **11b**, respectively, in high yields and very good enantioselectivities thus proving that our methodology is also suitable to the α-aminoxylation of aldehydes.

Since the ILTOC **7a** turned out to be the best ILTOC in the test α-aminoxylation its recyclability was investigated using [bmim][BF_4] or [emim] [BF_4] as solvents and diethyl ether or cyclohexane for extraction of the products from the reaction mixture (see Table 1).

It turned out that in general the enantioselectivities and yields decreased with each recycling. Reaction time had to increase to get complete conversion of the starting material. Extraction with cyclohexane turned out to be advantageous over diethyl ether. [emim] [BF_4] did not work as well as [bmim][BF_4] demonstrating that small differences in the type of IL can have an effect on the recyclability of the ILTOC. The decrease of the performance upon recycling is likely to be caused by leaching. This assumption is in line with the advantage found with cyclohexane as extracting solvent (Table 1), which is less polar than diethyl ether and thus leaches less of the polar ILTOC from the reaction mixture. However, we also detected the hemiacetal **12** (Scheme 4) by HPLC–MS in the working solution (ILTOC and IL) after the product **6a** was extracted from the reaction mixture. Such oxazolidinones are generally found in proline catalyzed reaction of carbonyl compounds[29] and were sometimes applied as soluble 'proline catalysts'. According to recent NMR-investigations they were proposed as intermediates in the catalytic cycle of aldol reactions where they form enamines (in our case **13**), which then are attacked by the nitrosobenzene (Scheme 1). The equilibrium between the oxazolidinone and the enamine (e.g., **12** and **13**) is reported to be dependent on the water content of the medium and the amount of (*S*)-proline. When in our cases starting materials, that is, the carbonyl compound and nitrosobenzene are added to the working solution after recycling from a previous batch, part of the proline catalyst **7** remains captured as **12** or **13** and cannot be liberated by hydrolysis because of the absence of water. Thus the amount of catalyst is reduced. Therefore, we tried to improve the recycling procedure by the addition of a small amount of water after each recycling. Indeed, some improvement could be achieved (Table 1, values in parenthesis, entries 1–5). The improving effect of the addition of water was even more obvious when after the sixth run water was added to the working solution for the first time and the resulting working solution was then used in the seventh run (see entries 6 and 7). As a result, the ee increased from 24% in the sixth run to 54% in the seventh run. Advantageous effect of water in proline catalyzed aldol reactions is known,[30] but it has not been looked at in cases of recycling of proline catalysts, wherein it seems to play an even more important role.



Scheme 4. ILTOC **7a** trapped as oxazolidinone **12**.

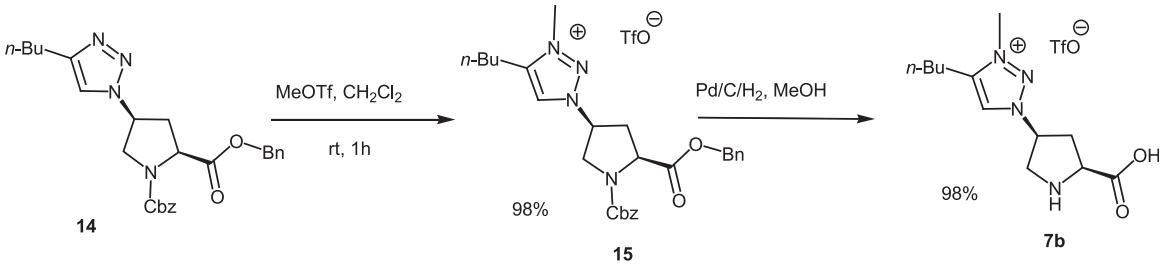
2.2. Synthesis of ionic-liquid-tagged organocatalysts

ILTOCS **7a**,[25] **8a**,[27] **8b**,[27] **8c**,[25] **8d**,[27] **8e**,[25] **8f**,[27] **9a**,[31] and **9b**[31] were published by us before. The other members are new. They were synthesized adopting procedures used for the preparation of the other 1,2,3-triazolium-based ILTOCs ,that is, Cu-catalyzed [3+2] cycloaddition of alkynes to azides followed by N-methylation of the

Table 1
Recycling of ILTOC **7a** in α-aminoxylation of cyclohexanone to **6a** using different IL and different solvents in extraction of the reaction mixture (see also Scheme 2)

Cycle	[bmim][BF_4] extr. Et_2O			[bmim][BF_4] extr. C_6H_{12}			[emim] [BF_4] extr. C_6H_{12}		
	ee[a] %	Yield[a] %	min[b]	ee[a] %	Yield[a] %	min[b]	ee %	Yield %	min[b]
1	>99 (99)	91 (91)	15	99 (>99)	95 (97)	15	98	94	15
2	99 (99)	83 (87)	20	99 (99)	91 (95)	20	96	92	25
3	90 (92)	77 (83)	30	96 (97)	90 (92)	30	92	88	30
4	78 (86)	71 (72)	40	92 (95)	82 (89)	40	88	85	50
5	62 (78)	67 (61)	60	90 (92)	76 (83)	60	82	79	85
6	24	n.d.							
7	54[c]	n.d.							

[a] Values in brackets were obtained if 18 μl H_2O was added after each cycle.
[b] Reaction time.
[c] H_2O (18 μl) was added for the first time after sixth cycle before running this seventh cycle, that is, the performance of working solution improved after sixth cycle by addition of water.

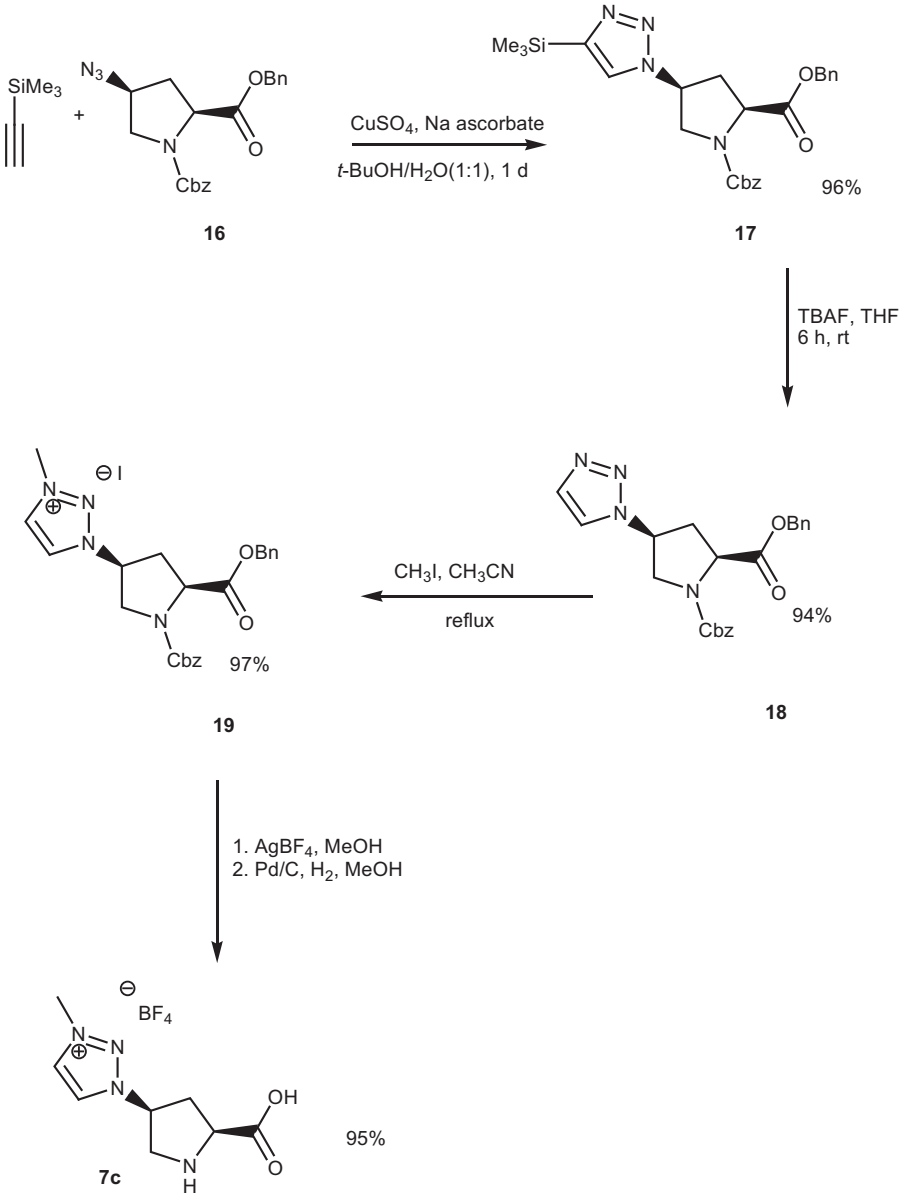


Scheme 5. Synthesis of ILTOC **7b**.

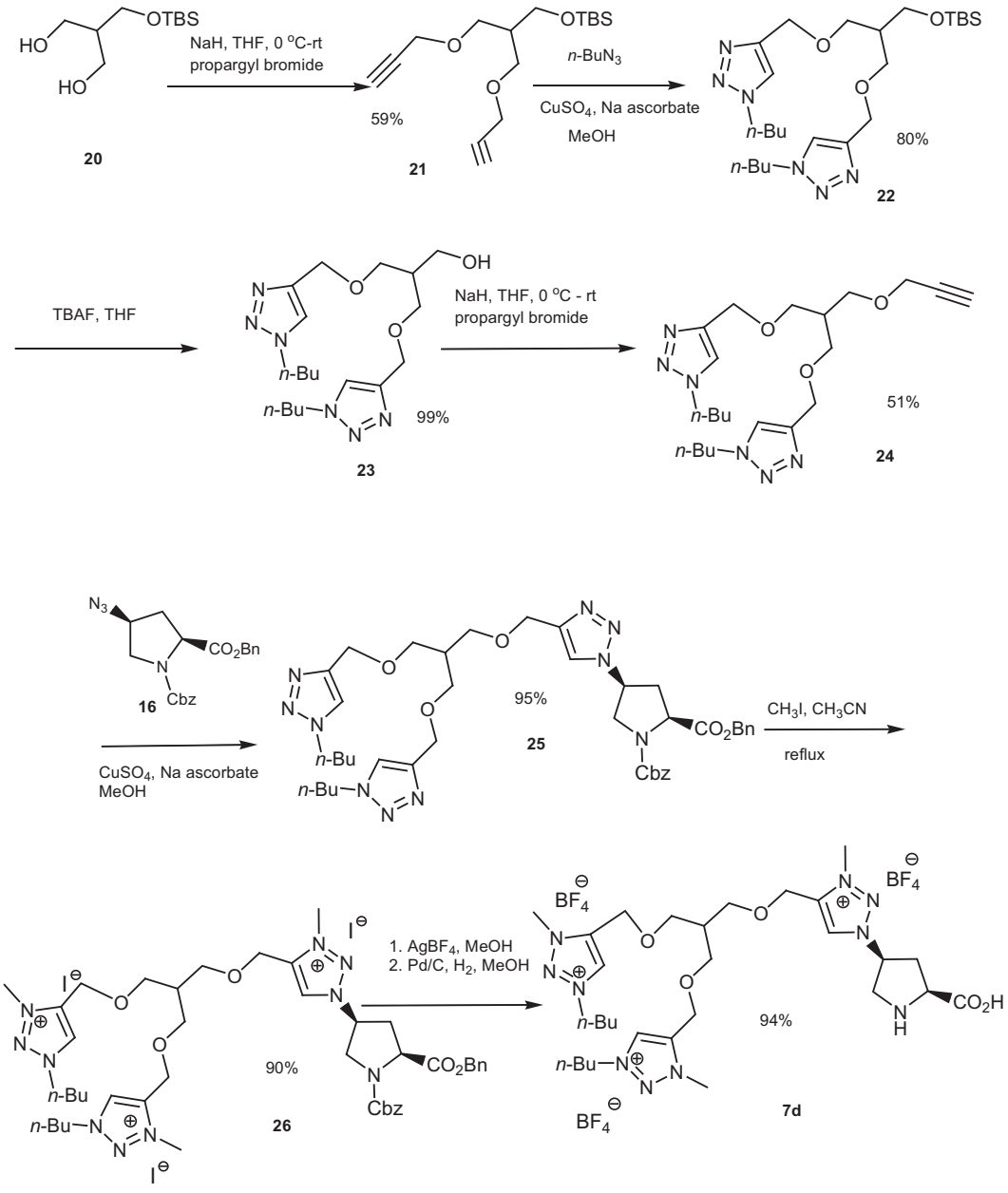
resulting 1,2,3-triazoles and final salt metathesis (Schemes 5–7). All cycloadditions as well as the N-alkylations and salt metatheses provided high yields.

In order to obtain the *C*-unsubstituted 1,2,3-triazolium salt **7c** (Scheme 6) TMS–ethyne was used as alkyne component in the reaction with the 4-azidoproline derivative **16** and the resulting TMS–triazole **17** was desilylated by fluoride. Independently of our work this strategy was recently used by Ryu and Jeong in order to synthesize 1,3-dialkyl-1,2,3-triazolium salts as ionic liquids useful for Baylis–Hillman reactions.[32]

The ILTOC **7d** containing three IL-tags was synthesized via twofold click reaction at the propargyl ether **21**, introducing a further propargyl group (formation of **24**) and another click reaction with the azido-substituted organocatalytic moiety **16**.



Scheme 6. Synthesis of ILTOC **7c**.



Scheme 7. Synthesis of ILTOC **7d**.

3. Conclusion

In summary, (*S*)-proline derivatives (ILTOCs) with covalently linked 1,2,3-triazolium or guanidinium salts as IL-tags were investigated in order to develop new organocatalysts for asymmetric α-aminoxylations, which can be recycled and reused. Although the IL-tag and the corresponding linkers are not directly involved in the reaction but their structure influences the performance of these organocatalyst largely and thus has to be chosen carefully. The most efficient ILTOC **7a** could be used in five subsequent reaction cycles maintaining an ee of 90% and 76% yield. The role of traces of water was addressed in recycling experiments in organocatalyzed reactions of carbonyl compounds via enamine intermediates for the first time where part of the organocatalyst was trapped by undesirable oxazolidinone formation and addition of water improved the performance of the working solution.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with a Bruker AC300 in $CDCl_3$ or CD_3OD with TMS as an internal standard. MS analyses were carried out on Varian MAT 711 and Thermo Finnigan LTQ-FT-ICR-MS. Silica gel (0.04–0.063 mm, Merck) was used for preparative column chromatography. Starting materials **14**,[25] **16**,[33] and **20**[34] were obtained by reported procedures. All the other chemicals were purchased from commercial suppliers.

4.2. General procedure for asymmetric α-aminoxylation of ketones in [bmim][BF_4] catalyzed by ILTOC 7a

To a 10 mL round-bottom flask equipped with a magnetic stirring bar and charged with [bmim][BF_4] (1.5 mL) catalyst **7a** (34 mg,

10 mol %) and cyclohexanone (294 mg, 3 mmol) were added. The mixture was stirred for 2 min, followed by the addition of nitrosobenzene (107 mg, 1 mmol). The resulting solution was stirred at room temperature until the color of the mixture turned yellow from green and the aminoxylation reaction was determined to be complete by TLC. The reaction mixture was then extracted with diethyl ether (6×5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuum. Purification of the crude product was done by column chromatography (silica gel, ethyl acetate/petroleum ether as eluant) to give (2*R*)-2-aminoxy ketone **6a**.

4.3. General experimental procedure for asymmetric α-aminoxylation/reduction of aldehydes 10 to α-phenylaminoxyalcohols 11

To a 10 mL round-bottom flask equipped with a magnetic stirring bar and charged with [bmim][BF_4] (1.5 mL) catalyst **7a** (34 mg, 10 mol %) and 3-phenylpropanal **10b** (402 mg, 3 mmol) or isovaleraldehyde **10a** (258 mg, 3 mmol) were added. The mixture was stirred for 2 min, followed by the addition of nitrosobenzene (107 mg, 1 mmol). The resulting solution was stirred at room temperature until the color of the mixture turned yellow from green and the aminoxylation reaction was determined to be complete by TLC. The reaction mixture was then extracted with ethyl ether (6×5 mL). To the combined ether layers ethanol (10 mL) and sodium borohydride (171 mg, 4.5 mmol) were added. The reaction mixture was stirred for 10 min at room temperature. The reaction was quenched with saturated solution of sodium bicarbonate (10 mL) and the resulting mixture was extracted with ethyl acetate (3×5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuum. Purification of the crude product was done by column chromatography (silica gel, ethyl acetate/petroleum ether as eluant) to give (2*R*)-2-aminoxy alcohol **11a** and **11b**.

4.4. Procedure for recycling and reuse of ILTOC 7a in α-aminoxylation of cyclohexanone in [bmim][BF_4]

To a 10 mL round-bottom flask equipped with a magnetic stirring bar and charged with [bmim][BF_4] (1.5 mL) catalyst **7a** (34 mg, 10 mol %) and cyclohexanone (294 mg, 3 mmol) were added. The mixture was stirred for 2 min, followed by the addition of nitrosobenzene (107 mg, 1 mmol) and the resulting solution was stirred at room temperature for 15 min. The reaction mixture was extracted with diethyl ether (6×5 mL). The residue after was dried under vacuum at 60 °C and reused for the next run of reaction. This procedure was repeated until seventh run as shown in the Table 1.

4.5. α-Aminoxylation products

*4.5.1. (2R)-2-Anilinoxycyclohexanone (**6a**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.68–1.85 (m, 3H), 1.99–2.09 (m, 2H), 2.35–2.55 (m, 3H), 4.37–4.43(m, 1H), 6.92–6.98 (m, 3H), 7.23–7.31 (m, 2H); HPLC (Chiracel AD-H, *i*-propanol/hexane=10:90, flow rate 0.5 mL/min, λ=244 nm): t_{minor}=4.9 min, t_{major}=29.5 min, ee 99%.

*4.5.2. (2R)-3-Phenyl-2-anilinoxypropanol (**11a**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=2.84 (1H, dd), 3.07 (1H, dd),1.40–1.47 (m, 1H), 3.73 (dd, 1H), 3.86 (dd, 1H), 4.16–4.18 (m, 1H), 6.85–6.88 (m, 2H), 6.94–6.99 (m, 1H), 7.20–7.34 (m, 7H); HPLC (Chiracel AD-H, *i*-propanol/hexane=10:90, flow rate 0.5 mL/min, λ=244 nm): t_{minor}=24.7 min, t_{major}=32.1 min, ee 98%.

*4.5.3. (R)-3-Methyl-2-(phenylaminoxy)butan-1-ol (**11b**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=0.99 (d, *J*=6 Hz, 3H), 1.05 (d, *J*=6 Hz, 3H), 2.01–2.07 (m, 1H), 3.73–3.76 (m, 1H), 3.88–3.92 (m, 2H), 6.97–7.02 (m, 3H), 7.25–7.31 (m, 2H); HPLC (Chiracel AD-H, *i*-propanol/hexane=5:95, flow rate 0.5 mL/min, λ=244 nm): t_{minor}=25.5 min, t_{major}=29.5 min, ee 96%.

4.6. Synthesis of ILTOCs

*4.6.1. 3-((3S,5S)-1,5-Bis(benzyloxycarbonyl)pyrrolidin-3-yl)-5-butyl-1-methyl-3H-1,2,3-triazol-1-ium trifluoromethanesulfonate (**15**).* To a solution of triazole **14** (0.584 g, 1.26 mmol) in dry CH_2Cl_2 (2 mL) MeOTf (0.14 mL, 1.26 mmol) was added and the mixture was stirred at room temperature for 1 h under an argon atmosphere. Evaporation of the solvent in vacuo gave oil that was washed with Et_2O (2×15 mL) and finally kept under vacuum for several hours to afford the pure product. Light yellow oil, yield 98%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.47 (s, 1H, $CH_{triazole}$), 7.28–7.36 (m, 10H, CH_{arom}), 5.48 (m, 1H, N–*CH*–CH_2–N), 4.98–5.16 (m, 4H, 2×CH_2–Ph), 4.57 (m, 1H, N–*CH*–CO_2), 4.16–4.18 (m, 2H, N–CH_2–CH–N), 4.13 (m, 1H, N–CH–CH_2–CH), 3.99 (s, 3H, CH_3–N), 3.05 (m, 1H, N–CH–CH_2–CH), 2.67–2.75 (m, 2H, C–CH_2–CH_2), 1.60–1.67 (m, 2H, CH_3–CH_2–CH_2), 1.35–1.47 (m, 2H, CH_3–CH_2), 0.95 (t, 3H, CH_3–CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=170.9 (O=*C*–O), 154.0 (O=*C*–N), 145.1 ($C_{triazole}$), 135.7 (C_{arom}), 135.0 (C_{arom}), 129.4 (CH_{arom}), 128.6 (CH_{arom}), 128.6 (CH_{arom}), 128.5 (CH_{arom}), 128.2 (CH_{arom}), 128.0 (CH_{arom}), 127.8 ($CH_{triazole}$), 67.7 (CH_2–Ph), 67.2 (CH_2–Ph), 61.4 (N–*CH*–CO_2), 57.3 (N–*CH*–CH_2–N), 51.2 (N–CH_2–CH–N), 37.4 (CH_3–N), 35.2 (N–CH–CH_2–CH), 28.6 (CH_3–CH_2–CH_2), 22.9 (C–CH_2–CH_2), 22.0 (CH_3–CH_2), 13.4 (CH_3–CH_2). HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{27}H_{34}N_4O_4^+$: 478.257; found: 478.255.

*4.6.2. 5-Butyl-3-((3S,5S)-5-carboxypyrrolidin-3-yl)-1-methyl-3H-1,2,3-triazol-1-ium trifluoromethanesulfonate (**7b**).* To a solution of the protected triazolium triflate **15** (0.78 g, 1.24 mmol) in anhydrous MeOH (10 mL), Pd/C (180 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 the desired product **7b**. Light yellow oil, yield 98%. ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm)=8.69 (s, 1H, $CH_{triazole}$), 5.71–5.72 (m, 1H, N–*CH*–CH_2–N), 4.57 (m, 1H, N–*CH*–CO_2), 4.24 (s, 3H, CH_3–N), 4.00–4.04 (m, 2H, N–CH_2–CH–N), 3.32–3.36 (m, 1H, N–CH–CH_2–CH), 3.19 (m, 1H, N–CH–CH_2–CH), 2.86–2.91 (m, 2H, C–CH_2–CH_2), 1.72–1.82 (m, 2H, CH_3–CH_2–CH_2), 1.47–1.57 (m, 2H, CH_3–CH_2), 1.02 (t, 3H, CH_3–CH_2). ^{13}C NMR (CD_3OD, 75 MHz): δ (ppm)=145.5 ($C_{triazole}$), 127.9 ($CH_{triazole}$), 62.1 (N–*CH*–CO_2), 59.4 (N–*CH*–CH_2-N), 49.7 (N–CH_2–CH–N), 36.9 (CH_3–N), 33.8 (N–CH–CH_2–CH), 28.3 (CH_3–CH_2–CH_2), 22.4 (C–CH_2–CH_2), 21.7 (CH_3–CH_2), 12.5 (CH_3–CH_2). HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{12}H_{22}N_4O_2^+$: 254.173; found: 254.171.

*4.6.3. (2S,4S)-Dibenzyl 4-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl) pyrrolidine-1,2-dicarboxylate (**17**).* Azide **16** (1 g, 2.63 mmol), trimethylsilylacetylene (0.31 g, 3.16 mmol), $CuSO_4$ (0.082 g, 20 mol %), and sodium ascorbate (0.21 g, 40 mol %) were suspended in a mixed solution of *tert*-butanol/water (4 mL, 1/1) at room temperature. After the mixture was stirred for 24 h, water (10 mL) was added and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL) and then dried over Na_2SO_4. Evaporation of the solvent in vacuo gave yellow oil that was used in the next step without further purification. Yellow oil, yield 96%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.87 (s, 1H, CH–*CH*–N–CH), 7.21–7.32 (m, 10H, 10×CH_{arom}), 5.01–5.27 (m, 4H, 2×CH_2–Ph), 4.57–4.60 (m, 1H, *CH*–C=O), 4.27–4.31 (m, 1H, *CH*–$N_{triazole}$), 3.94–4.02 (m, 1H, CH_2–CH–C=O), 2.96–2.98 (m, 1H, CH_2–CH–C=O), 2.67–2.77 (m, 1H, CH_2–N–C=O), 2.42–2.48 (m, 1H, CH_2–N–C=O), 0.29 (s, 9H, 3×CH_3–Si). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=171.1 (CH–*C*=O), 154.7 (NH–*C*=O), 151.4 (CH–*C*–Si), 136.0 (C_{arom}), 129.9 (CH–*CH*–N–CH), 128.6 (CH_{arom}), 128.5 (CH_{arom}), 128.4 (CH_{arom}), 128.3 (CH_{arom}), 128.1 (CH_{arom}), 128.0 (CH_{arom}), 67.8

(CH_2–Ph), 67.7 (CH_2–Ph), 65.4 (*CH*–C=O), 57.9 (*CH*–$N_{triazole}$), 52.1 (CH_2–N–C=O), 30.0 (CH_2–CH–C=O), 0.67 (CH_3–Si). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{30}N_4O_4Si$: 479.2115; found: 479.2066.

*4.6.4. (2S,4S)-Dibenzyl 4-(1H-1,2,3-triazol-1-yl)pyrrolidine-1,2-dicarboxylate (**18**).* To a solution of triazole **17** (1.20 g, 2.51 mmol) in anhydrous THF (10 mL) TBAF (1 M in THF, 1.02 mL, 2.51 mmol) was added dropwise. The reaction was monitored for the disappearance of starting materials by TLC. After 6 h at room temperature, the reaction mixture was concentrated in vacuo. The remaining **17** was purified by column chromatography (silica gel, 2:1 chloroform/acetone, R_f=0.68). Light yellow oil, yield 94%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.83 (s, 1H, CH–*CH*–N–CH), 7.20–7.37 (m, 11H, *CH*–CH–N–CH+10×CH_{arom}), 5.01–5.24 (m, 4H, 2×*CH*$_2$–Ph), 4.54–4.58 (m, 1H, *CH*–C=O), 4.21–4.25 (m, 1H, *CH*–$N_{triazole}$), 3.94–4.01 (m, 1H, CH_2–CH–C=O), 2.94–2.96 (m, 1H, *CH*$_2$–CH–C=O), 2.62–2.75 (m, 1H, *CH*$_2$–N–C=O), 2.43–2.46 (m, 1H, CH_2–N–C=O). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=171.0 (CH–*C*=O), 154.4 (NH–*C*=O), 141.1 (*CH*–CH–N–CH), 135.9 (C_{arom}), 128.6 (CH_{arom}), 128.5 (CH_{arom}), 128.5 (CH_{arom}), 128.3 (CH_{arom}), 128.0 (CH_{arom}), 127.5 (CH_{arom}), 126.9 (CH–*CH*–N–CH), 67.7 (*CH*$_2$–Ph), 67.4 (*CH*$_2$–Ph), 65.1 (*CH*–C=O), 57.9 (*CH*–$N_{triazole}$), 51.5 (CH_2–N–C=O), 29.7 (CH_2–CH–C=O). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{22}N_4O_4$: 407.1719; found: 407.1682.

*4.6.5. 3-((3S,5S)-1,5-Bis(benzyloxycarbonyl)pyrrolidin-3-yl)-1-methyl-3H-1,2,3-triazol-1-ium iodide (**19**).* To a solution of the triazole **18** (1 g, 2.46 mmol) in MeCN (50 mL), MeI (0.76 mL, 12.3 mmol, 5 equiv) was added. The reaction mixture was refluxed under an argon atmosphere overnight. After completion of the reaction, the solvent was removed to obtain the product, which was purified by washing with diethyl ether (3×20 mL). Brown-yellow oil, yield 97%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=9.18 (s, 1H, *CH*–N–CH_3), 9.03 (s, 1H, *CH*–CH–N–CH_3), 7.21–7.31 (m, 10H, 10×CH_{arom}), 4.97–5.14 (m, 4H, 2×*CH*$_2$–Ph), 4.57–4.66 (m, 1H, *CH*–C=O), 4.21–4.26 (m, 4H, CH_3–N+*CH*–$N_{triazole}$), 3.92–4.00 (m, 1H, CH_2–CH–C=O), 3.14–3.19 (m, 1H, CH_2–CH–C=O), 2.77–2.81 (m, 1H, *CH*$_2$–N–C=O), 2.27–2.28 (m, 1H, *CH*$_2$–N–C=O). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=170.9 (CH–*C*=O), 153.8 (NH–*C*=O), 135.8 (C_{arom}), 132.2 (*CH*–N–CH_3), 129.5 (CH_{arom}), 128.7 (CH_{arom}), 128.6 (CH_{arom}), 128.2 (CH_{arom}), 128.0 (CH_{arom}), 127.7 (CH_{arom}), 127.0 (*CH*–CH–N–CH_3), 67.6 (*CH*$_2$–Ph), 67.3 (*CH*$_2$–Ph), 61.9 (*CH*–C=O), 57.3 (*CH*–$N_{triazole}$), 51.4 (CH_2–N–C=O), 41.4 (CH_3–N), 35.8 (CH_2–CH–C=O). HRMS (ESI): m/z $[M]^+$ calcd for $C_{23}H_{25}N_4O_4^+$: 421.1876; found: 421.1886.

*4.6.6. 3-((3S,5S)-5-Carboxypyrrolidin-3-yl)-1-methyl-3H-1,2,3-triazol-1-ium tetrafluoroborate (**7c**).* In a 50 mL round-bottom flask the triazolium iodide **19** (1.09 g, 1.98 mmol) was dissolved in anhydrous MeOH (20 mL). In a second flask (which was either brown colored or wrapped in aluminum foil to exclude light), $AgBF_4$ (0.39 g, 1.98 mmol) was dissolved in anhydrous MeOH (20 mL). The $AgBF_4$ solution was added dropwise to the solution of the triazolium iodide **19** 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 the protected triazolium tetrafluoroborate as yellow oil. To a solution of this tetrafluoroborate (1.00 g, 1.97 mmol) in anhydrous MeOH (20 mL), Pd/C (180 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 the final product **7c**. Light yellow oil, yield 95%. ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm)=8.73 (s, 1H, *CH*–N–CH_3), 7.95 (s, 1H, *CH*–CH–N–CH_3), 4.41–4.48 (m, 1H, *CH*–C=O), 4.32–4.36 (m, 1H, *CH*–$N_{triazole}$), 4.14 (s, 3H, CH_3–N), 3.95–4.08 (m, 2H, CH_2–NH), 3.12–3.23 (m, 1H, CH_2–CH–C=O), 2.87–2.96 (m, 1H, *CH*$_2$–CH–C=O). ^{13}C NMR (CD_3OD, 75 MHz): δ (ppm)=131.8 (*CH*–CH–N–CH_3), 130.4 (*CH*–N–CH_3), 62.5 (*CH*–C=O), 59.7 (*CH*–$N_{triazole}$), 49.6 (CH_2–NH), 39.4 (CH_3–N), 34.2 (CH_2–CH–C=O). HRMS (ESI): m/z $[M]^+$ calcd for $C_8H_{13}N_4O_2^+$: 197.1039; found: 197.1007.

*4.6.7. (2,3-Bis(prop-2-ynyloxy)propoxy)(tert-butyl)dimethylsilane (**21**).* To a solution of 3-(*tert*-butyldimethylsilyloxy)propane-1,2-diol **20** (0.8 g, 3.9 mmol) in anhydrous THF (37 mL), sodium hydride (0.28 g, 11.7 mmol) was added. The suspension was stirred for 30 min and cooled with an ice bath. With vigorous stirring propargyl bromide (0.9 mL, 9.75 mmol) was added over 1 h, and the reaction mixture was stirred for 3 days at room temperature. MeOH was added carefully until gas formation ceased (destruction of excess sodium hydride). The solvent was removed under vacuo and the residue was taken up in CH_2Cl_2 (25 mL) and water (15 mL). After phase separation the organic phase was carefully washed with water and dried with magnesium sulfate. The solvent was removed and the raw product was purified by column chromatography (silica gel, 9:1 hexane/EtOAc, R_f=0.53). Light yellow liquid, yield 59%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)= 4.28–4.31 (m, 2H, C–*CH*$_2$–O–CH), 4.14–4.17 (m, 2H, C–*CH*$_2$–O–CH_2), 3.56–3.76 (m, 5H, *CH*$_2$–*CH*–*CH*$_2$), 2.39 (m, 2H, 2×*CH*≡C), 0.87 (s, 9H, 3×*CH*$_3$–C–Si), 0.049 (s, 6H, 2×*CH*$_3$–Si). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=80.2 (CH≡*C*), 79.6 (CH≡*C*), 78.1 (CH_2–CH–CH_2), 74.6 (*CH*≡C), 74.2 (*CH*≡C), 69.6 (*CH*$_2$–O–CH_2), 62.8 (*CH*$_2$–O–Si), 58.6 (C–*CH*$_2$–O–CH), 57.7 (C–*CH*$_2$–O–CH_2), 25.9 (CH_3–C–Si), 18.3 (CH_3–C–Si), −5.3 (*CH*$_3$–Si). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{26}O_3Si$: 283.1721; found: 283.1672.

*4.6.8. 4,4′-(3-(tert-Butyldimethylsilyloxy)propane-1,2-diyl)bis(oxy)bis(methylene)bis(1-butyl-1H-1,2,3-triazole) (**22**).* To a solution of *n*-butyl azide 0.3 g (2.84 mmol, 2 equiv) in MeOH (10 mL) sodium ascorbate (0.11 g, 40 mol %), $CuSO_4$ (0.07 g, 30 mol %), and the alkyne **21** (0.4 g, 1.42 mmol, 1 equiv) were added. The solution was stirred at room temperture for 2–3 days (TLC check). After completion of the reaction, water (20 mL) was added and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (20 mL) and then dried over Na_2SO_4. Evaporation of the solvent in vacuo gave a colorless liquid that was used in the next step without further purification. Colorless liquid, yield 80%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.58 (s, 2H, 2×*CH*$_{triazole}$), 4.61–4.76 (m, 4H, 2×*CH*$_2$–$C_{triazole}$), 4.30–4.32 (m, 4H, *CH*$_2$–$N_{triazole}$), 3.54–3.66 (m, 5H, *CH*$_2$–*CH*–*CH*$_2$), 1.84–1.85 (m, 4H, 2×*CH*$_2$–CH_2–CH_3), 1.30–1.33 (m, 4H, 2×*CH*$_2$–CH_3), 0.89–0.93 (m, 6H, 2×*CH*$_3$–CH_2), 0.84–0.86 (s, 9H, 3×*CH*$_3$–C–Si), 0.01 (s, 6H, 2×*CH*$_3$–Si). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=122.2 (*CH*$_{triazole}$), 79.0 (CH_2–*CH*–CH_2), 70.4 (*CH*$_2$–CH–CH_2–O–Si), 64.0 (*CH*$_2$–O–Si), 63.9 (*CH*$_2$–$C_{triazole}$), 62.7 (*CH*$_2$–$C_{triazole}$), 50.0 (*CH*$_2$–$N_{triazole}$), 32.1 (CH_2–CH_2–CH_3), 25.8 (*CH*$_3$–C–Si), 19.6 (*CH*$_2$–CH_3), 18.2 (CH_3–*C*–Si), 13.4 (*CH*$_3$–CH_2), −5.4 (*CH*$_3$–Si). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{44}N_6O_3Si$: 481.3211; found: 481.3164.

*4.6.9. 2,3-Bis((1-butyl-1H-1,2,3-triazol-4-yl)methoxy)propan-1-ol (**23**).* To a solution of the triazole **22** (0.473 g, 1 mmol) in anhydrous THF (15 mL) TBAF (1 M in THF, 0.5 mL, 1 mmol) was dropwise added. The reaction was monitored for the disappearance of starting materials by TLC. After 6 h at room temperature, the reaction mixture was concentrated in vacuo. Column chromatography on silica gel (2:1 hexane/EtOAc, R_f=0.11) afforded the unprotected alcohol **23** (0.36 g, 99%) as a colorless liquid. Colorless liquid, yield 99%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.58 (s, 1H, *CH*$_{triazole}$), 7.54 (s, 1H, *CH*$_{triazole}$), 4.69 (m, 2H, *CH*$_2$–$C_{triazole}$), 4.58 (m, 2H, *CH*$_2$–$C_{triazole}$), 4.26–4.28 (m, 4H, 2×*CH*$_2$–$N_{triazole}$), 3.61–3.69 (m, 5H, *CH*$_2$–*CH*–*CH*$_2$), 1.79–1.82 (m, 4H, 2×*CH*$_2$–CH_2–CH_3), 1.24–1.31 (m, 4H, 2×*CH*$_2$–CH_3), 0.85–0.89 (m, 6H, 2×*CH*$_3$–CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=145.2 ($C_{triazole}$), 144.7 ($C_{triazole}$), 122.4 (*CH*$_{triazole}$), 78.9 (CH_2–CH–CH_2), 70.3 (*CH*$_2$–CH–CH_2–OH), 64.7 (*CH*$_2$–OH), 62.0 (*CH*$_2$–$C_{triazole}$), 58.8 (*CH*$_2$–$C_{triazole}$), 50.0 (*CH*$_2$–$N_{triazole}$), 32.1

(CH_2–CH_2–CH_3), 19.6 (CH_2–CH_3), 13.4 (CH_3–CH_2). HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{30}N_6O_3$: 367.2405; found: 367.2356.

*4.6.10. 4,4′-(3-(Prop-2-ynyloxy)propane-1,2-diyl)bis(oxy)bis(methylene)bis(1-butyl-1H-1,2,3-triazole) (**24**).* To a solution of 2,3-bis((1-butyl-1*H*-1,2,3-triazol-4-yl)methoxy)propan-1-ol **23** (0.4 g, 1.1 mmol) in anhydrous THF (10 mL) sodium hydride (0.042 g, 1.76 mmol) was added. The suspension was stirred for 30 min and cooled with an ice bath. With vigorous stirring propargyl bromide (0.16 mL, 1.76 mmol) was added over 1 h, and the reaction mixture was stirred for 3 days at room temperature. MeOH was added carefully until gas formation ceased (destruction of excess sodium hydride). The solvent was removed in vacuo and the residue was taken up in CH_2Cl_2 (5 mL) and water (5 mL). After phase separation the organic phase was carefully washed with water and dried with magnesium sulfate. The solvent was removed and the raw product **24** was purified by column chromatography (silica gel, 1:1 hexane/EtOAc and then only EtOAc, R_f=0.10). Colorless liquid, yield 51%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.59 (s, 1H, $CH_{triazole}$), 7.55 (s, 1H, $CH_{triazole}$), 4.77 (s, 2H, CH_2–$C_{triazole}$), 4.63 (s, 2H, CH_2–$C_{triazole}$), 4.27–4.34 (m, 4H, 2×CH_2–$N_{triazole}$), 4.12–4.13 (m, 2H, CH_2–C≡CH), 3.79 (m, 1H, CH_2–CH–CH_2), 3.60–3.63 (m, 4H, CH_2–CH–CH_2), 2.39–2.41 (m, 1H, CH_2–C≡CH), 1.81–1.85 (m, 4H, 2×CH_2–CH_2–CH_3), 1.28–1.36 (m, 4H, 2×CH_2–CH_3), 0.89–0.94 (m, 6H, 2×CH_3–CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=145.3 ($C_{triazole}$), 144.9 ($C_{triazole}$), 122.5 ($CH_{triazole}$), 122.3 ($CH_{triazole}$), 79.5 (CH_2–CH–CH_2), 74.6 (CH_2–CH–CH_2–O–CH_2–C≡CH), 70.2 (C≡CH), 69.6 (CH_2–O–CH_2–C≡CH), 64.9 (CH_2–$C_{triazole}$), 63.8 (CH_2–$C_{triazole}$), 58.5 (CH_2–C≡CH), 50.0 (CH_2–$N_{triazole}$), 32.2 (CH_2–CH_2–CH_3), 19.6 (CH_2–CH_3), 13.4 (CH_3–CH_2). HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{32}N_6O_3$: 405.2501; found: 405.2459.

*4.6.11. (2S,4S)-Dibenzyl 4-(4-((2,3-bis((1-butyl-1H-1,2,3-triazol-4-yl)methoxy)propoxy)methyl)-1H-1,2,3-triazol-1-yl)pyrrolidine-1,2-dicarboxylate (**25**).* To a solution of azide **16** (0.19 g, 0.5 mmol) in MeOH (5 mL) sodium ascorbate (0.02 g, 20 mol %), $CuSO_4$ (0.012 g, 15 mol %), and alkyne **24** (0.2 g, 0.5 mmol) were added. The solution was stirred at room temperature for 2–3 days (TLC check). After completion of the reaction, water (10 mL) was added and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL) and then dried over Na_2SO_4. Evaporation of the solvent in vacuo gave **25** as colorless liquid that was used in the next step without further purification. Light yellow oil, yield 95%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.76 (s, 1H, $CH_{triazole}$), 7.64 (s, 1H, $CH_{triazole}$), 7.59 (s, 1H, $CH_{triazole}$), 7.30–7.35 (m, 10H, 2×CH_{arom}), 5.08–5.26 (m, 4H, 2×CH_2–Ph), 4.95–5.06 (m, 2H, CH–C=O+CH–$N_{triazole}$), 4.78 (s, 2H, CH_2–$C_{triazole}$), 4.60–4.63 (m, 4H, 2×CH_2–$C_{triazole}$), 4.29–4.36 (m, 4H, 2×CH_2–$N_{triazole}$), 3.94–3.97 (m, 1H, O–CH_2–CH–CH_2–O), 3.76–3.82 (m, 2H, CH_2–N–C=O), 3.60–3.64 (m, 4H, O–CH_2–CH–CH_2–O), 2.91–2.96 (m, 1H, CH_2–CH–C=O), 2.64–2.78 (m, 1H, CH_2–CH–C=O), 1.81–1.93 (m, 4H, 2×CH_2–CH_2–CH_3), 1.30–1.40 (m, 4H, 2×CH_2–CH_3), 0.91–0.97 (m, 6H, 2×CH_3–CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=171.1 (CH–C=O), 154.4 (N–C=O), 145.5 ($C_{triazole}$), 136.0 (C_{arom}), 128.6 (CH_{arom}), 128.6 (CH_{arom}), 128.2 (CH_{arom}), 128.1 (CH_{arom}), 128.0 (CH_{arom}), 127.9 (CH_{arom}), 121.9 ($CH_{triazole}$), 121.9 ($CH_{triazole}$), 121.8 ($CH_{triazole}$), 77.2 (O–CH_2–CH–CH_2–O), 70.2 (O–CH_2–CH–CH_2–O), 67.5 (CH_2–Ph), 67.3 (CH_2–Ph), 64.7 (CH_2–$C_{triazole}$), 63.8 (CH_2–$C_{triazole}$), 60.4 (CH_2–$C_{triazole}$), 57.9 (CH–C=O), 57.6 (CH–$N_{triazole}$), 50.1 (CH_2–$N_{triazole}$), 50.0 (CH_2–N–C=O), 35.1 (CH_2–CH–C=O), 32.2 (CH_2–CH_2–CH_3), 19.7 (CH_2–CH_3), 13.5 (CH_3–CH_2). HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{52}N_{10}O_7$: 785.4001; found: 785.3981.

*4.6.12. 5,5′-(3-((1-((3S,5S)-1,5-Bis(benzyloxycarbonyl)pyrrolidin-3-yl)-3-methyl-1H-1,2,3-triazol-3-ium-4-yl)methoxy)propane-1,2-diyl) bis(oxy)bis(methylene)-bis-(3-butyl-1-methyl-3H-1,2,3-triazol-1-ium) iodide (**26**).* To a solution of the triazole **25** (0.35 g, 0.44 mmol) in MeCN (10 mL), MeI (0.55 mL, 8.8 mmol, 20 equiv) was added. The reaction mixture was refluxed under an argon atmosphere overnight. After completion of the reaction, the solvent was removed to obtain the product **26**, which was purified by washing with diethyl ether (3×10 mL). Brown-yellow oil, yield 90%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=9.40 (s, 1H, $CH_{triazole}$), 9.32–9.33 (s, 2H, $CH_{triazole}$), 7.24–7.30 (m, 10H, 2×CH_{arom}), 5.20–5.32 (m, 4H, 2×CH_2–Ph), 5.04–5.11 (m, 4H, CH–C=O+CH–$N_{triazole}$+CH_2–N–C=O), 4.97–5.02 (m, 2H, CH_2–$C_{triazole}$), 4.58–4.63 (m, 4H, 2×CH_2–$C_{triazole}$), 4.38 (s, 3H, CH_3–N), 4.35 (s, 3H, CH_3–N), 4.23 (s, 3H, CH_3–N), 4.14–4.19 (m, 4H, 2×CH_2–$N_{triazole}$), 3.93–4.08 (m, 5H, O–CH_2–CH–CH_2–O), 3.09–3.14 (m, 1H, CH_2–CH–C=O), 2.83–2.84 (m, 1H, CH_2–CH–C=O), 1.92–1.98 (m, 4H, 2×CH_2–CH_2–CH_3), 1.30–1.42 (m, 4H, 2×CH_2–CH_3), 0.89–0.94 (m, 6H, 2×CH_3–CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm)=170.9 (CH–C=O), 153.6 (N–C=O), 141.3 ($C_{triazole}$), 140.9 ($C_{triazole}$), 138.3 (C_{arom}), 128.6 (CH_{arom}), 128.5 (CH_{arom}), 128.4 (CH_{arom}), 128.2 (CH_{arom}), 128.1 (CH_{arom}), 128.0 (CH_{arom}), 78.2 (O–CH_2–CH–CH_2–O), 70.9 (O–CH_2–CH–CH_2–O), 67.6 (CH_2–Ph), 67.2 (CH_2–Ph), 62.0 (CH_2–$C_{triazole}$), 61.2 (CH_2–$C_{triazole}$), 57.6 (CH–C=O), 54.0 (CH–$N_{triazole}$), 51.3 (CH_2–$N_{triazole}$), 51.2 (CH_2–N–C=O), 40.3 (CH_3–N), 40.2 (CH_3–N), 40.1 (CH_3–N), 35.5 (CH_2–CH–C=O), 31.2 (CH_2–CH_2–CH_3), 19.3 (CH_2–CH_3), 13.3 (CH_3–CH_2). HRMS (ESI): *m/z* $[M]^{3+}$ calcd for $C_{43}H_{61}N_{10}O_7^{3+}$: 276.4901; found: 276.4854.

*4.6.13. 5,5′-(3-((1-((3S,5S)-5-Carboxypyrrolidin-3-yl)-3-methyl-1H-1,2,3-triazol-3-ium-4-yl)methoxy)propane-1,2-diyl)-bis-(oxy)-bis-(methylene)-bis-(3-butyl-1-methyl-3H-1,2,3-triazol-1-ium) tetrafluoroborate (**7d**).* In a 50 mL dry, round-bottom flask triazolium iodide **26** (0.4 g, 0.33 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), $AgBF_4$ (0.32 g, 1.65 mmol, 5 equiv) was dissolved in anhydrous MeOH (20 mL). The $AgBF_4$ solution was added dropwise to the solution of iodide **26** 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 the tetrafluoroborate as yellow oil. To a solution of this tetrafluoroborate (0.35 g, 0.32 mmol) in anhydrous MeOH (5 mL), Pd/C (40 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 desire product **7d**.

Colorless oil, yield 94%. ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm)= 8.70 (s, 1H, $CH_{triazole}$), 8.59 (s, 1H, $CH_{triazole}$), 8.58 (s, 1H, $CH_{triazole}$), 4.88–4.90 (m, 8H, CH–C=O+CH–$N_{triazole}$+CH_2–N–C=O+2×CH_2–$C_{triazole}$), 4.86 (s, 2H, CH_2–$C_{triazole}$), 4.28 (s, 3H, CH_3–N), 4.27 (s, 3H, CH_3–N), 4.26 (s, 3H, CH_3–N), 4.58–4.62 (m, 4H, 2×CH_2–$N_{triazole}$), 4.01–4.05 (m, 2H, O–CH_2–CH–CH_2–O), 3.80 (m, 3H, O–CH_2–CH–CH_2–O), 3.31–3.36 (m, 2H, CH_2–CH–C=O), 1.97–2.02 (m, 4H, 2×CH_2–CH_2–CH_3), 1.38–1.44 (m, 4H, 2×CH_2–CH_3), 0.97–1.02 (m, 6H, 2×CH_3–CH_2). ^{13}C NMR (CD_3OD, 75 MHz): δ (ppm)=141.3 ($C_{triazole}$), 141.0 ($C_{triazole}$), 140.6 ($C_{triazole}$), 129.6 ($CH_{triazole}$), 129.0 ($CH_{triazole}$), 128.9 ($CH_{triazole}$), 78.1 (O–CH_2–CH–CH_2–O), 70.5 (O–CH_2–CH–CH_2–O), 70.4 (O–CH_2–CH–CH_2–O), 61.8 (CH_2–$C_{triazole}$), 60.5 (CH_2–$C_{triazole}$), 59.7 (CH_2–$C_{triazole}$), 58.7 (CH–C=O), 53.2 (CH–$N_{triazole}$), 50.0 (CH_2–$N_{triazole}$), 47.2 (CH_2–N–C=O), 37.8 (CH_3–N), 37.4 (CH_3–N), 37.3 (CH_3–N), 33.3 (CH_2–CH–C=O), 30.7 (CH_2–CH_2–CH_3), 18.9 (CH_2–CH_3), 12.2 (CH_3–CH_2). HRMS (ESI): *m/z* $[M]^{3+}$ calcd for $C_{28}H_{49}N_{10}O_5^{3+}$: 201.7966; found: 201.7917.

Acknowledgements

We gratefully acknowledge financial support by Deutsche Forschungsgemeinschaft (DFG). Priority Programme Organocatalysis

(SPP 1179). We thank Prof. Dr. Willi Kantlehner, Fachhochschule Aalen for providing pentasubstituted guanidines. We further acknowledge donation of chemicals from Saltigo GmbH, Bayer Services GmbH & Co. OHG, BASF AG, and Sasol GmbH.

Supplementary data

Supplementary data includes NMR spectra of the products obtained. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.01.031.

References and notes

1. Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809; Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293–8296; Cordova, A.; Sunden, H.; Bogevig, A.; Johansson, M.; Himo, F. *Chem.—Eur. J.* **2004**, *10*, 3673–3684; Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* **2004**, *69*, 5966–5973.
2. Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995–2997; Janey, J. M. –; Angew. Chem., Int. Ed. **2005**, *44*, 4292–4300; Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112–1115.
3. Bogevig, A.; Sunden, H.; Cordova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109–1112.
4. Wang, W.; Wang, J.; Li, H.; Liao, L. X. *Tetrahedron Lett.* **2004**, *45*, 7235–7238.
5. Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046–6047; Kano, T.; Yamamoto, A.; Maruoka, K. *Tetrahedron Lett.* **2008**, *49*, 5369–5371; Kano, T.; Yamamoto, A.; Shirozu, F.; Maruoka, K. *Synthesis* **2009**, 1557–1563.
6. Chua, P. J.; Tan, B.; Zhong, G. F. *Green Chem.* **2009**, *11*, 543–547.
7. Kim, S.-G.; Park, T.-H. *Tetrahedron Lett.* **2006**, *47*, 9067–9071.
8. Lu, M.; Zhu, D.; Lu, Y. P.; Hou, Y. X.; Tan, B.; Zhong, G. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 10187–10191.
9. Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435–1439.
10. Ramachary, D. B.; Barbas, C. F. *Org. Lett.* **2005**, *7*, 1577–1580.
11. Sunden, H.; Dahlin, N.; Ibrahem, I.; Adolfsson, H.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 3385–3389.
12. Kano, T.; Mii, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 1–5.
13. Lu, M.; Zhu, D.; Lu, Y. P.; Zeng, X. F.; Tan, B.; Xu, Z. J.; Zhong, G. F. *J. Am. Chem. Soc.* **2009**, *131*, 4562–4563; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080–1081; Lu, M.; Lu, Y.; Zhu, D.; Zeng, X.; Zhong, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 1–5.
14. Jiao, P.; Kawasaki, M.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3333–3336.
15. Kumarn, S.; Shaw, D. M.; Longbottom, D. A.; Ley, S. V. *Org. Lett.* **2005**, *7*, 4189–4191; Kumarn, S.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2006**, 3211–3213.
16. Yang, L.; Liu, R. H.; Wang, B.; Weng, L. L.; Zheng, H. *Tetrahedron Lett.* **2009**, *50*, 2628–2631.
17. Guo, H. M.; Cheng, L.; Cun, L. F.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z. *Chem. Commun.* **2006**, 429–431.
18. Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317–3321; Mathew, S. P.; Klussmann, M.; Iwamura, H.; Wells, D. H.; Armstrong, A.; Blackmond, D. G. *Chem. Commun.* **2006**, 4291–4293.
19. Cheong, P. H. Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912–13913.
20. Kano, T.; Yamamoto, A.; Mii, H.; Takai, J.; Shirakawa, S.; Maruoka, K. *Chem. Lett.* **2008**, *37*, 250–251.
21. Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2007**, *9*, 1943–1946.
22. Huang, K.; Huang, Z.-Z.; Li, X.-L. *J. Org. Chem.* **2006**, *71*, 8320–8323.
23. Guo, H. M.; Niu, H. Y.; Xue, M. X.; Guo, Q. X.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Wang, J. J. *Green Chem.* **2006**, *8*, 682–684.
24. Sebesta, R.; Kmentova, I.; Toma, S. *Green Chem.* **2008**, *10*, 484–496; Yang, S. D.; Shi, Y.; Sun, Z. H.; Zhao, Y. B.; Liang, Y. M. *Tetrahedron: Asymmetry* **2006**, *17*, 1895–1900; Lombardo, M.; Easwar, S.; Pasi, F.; Trombinia, C. *Adv. Synth. Catal.* **2009**, *351*, 276–282; Lombardo, M.; Pasi, F.; Easwar, S.; Trombini, C. *Synlett* **2008**, 2471–2474; Lombardo, M.; Pasi, F.; Easwar, S.; Trombini, C. *Adv. Synth. Catal.* **2007**, *349*, 2061–2065.
25. Shah, J.; Khan, S. S.; Blumenthal, H.; Liebscher, J. *Synthesis* **2009**, 3975–3982.
26. Ding, X.; Tang, W. M.; Zhu, C. J.; Cheng, Y. X. *Adv. Synth. Catal.* **2010**, *352*, 108–112.
27. Khan, S. S.; Shah, J.; Liebscher, J. *Tetrahedron* **2010**, *66*, 5082–5088.
28. Yacob, Z.; Shah, J.; Leistner, J.; Liebscher, J. *Synlett* **2008**, 2342–2344; Shah, J.; Liebscher, J. *Synthesis* **2008**, 917–920.
29. Schmid, M. B.; Zeitler, K.; Gschwind, R. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4997–5003.
30. Hayashi, Y.; Aratake, S.; Itoh, T.; Okano, T.; Sumiya, T.; Shoji, M. *Chem. Commun.* **2007**, 957–959.
31. Shah, J.; Liebscher, J. *Z. Naturforsch. B* **2011**, *66b*, 88–94.
32. Jeong, Y.; Ryu, J. S. *J. Org. Chem.* **2010**, *75*, 4183–4191.
33. Tamaki, M.; Han, G. X.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1038–1042.
34. Konosu, T.; Oida, S. *Chem. Pharm. Bull.* **1991**, *39*, 2212–2215.