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α,α-Diarylprolinol-derived chiral ionic liquids: recoverable organocatalysts for the domino reaction between α,β-enals and N-protected hydroxylamines

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ABSTRACT

Chiral ionic liquids bearing α,α-diarylprolinol units were synthesized and applied for the first time as organocatalysts for the domino reaction between α,β-enals and N-protected hydroxylamines involving aza-Michael and intramolecular acetalization steps. Corresponding 5-hydroxy-3-arylisoxazolidines with either an (*S*)- or (*R*)-configuration at C-3 were obtained in excellent yields (up to 94%) and with moderate to high enantioselectivities (64 to >99% ee). The ionic liquid supported catalyst can be easily recycled and reused for at least four times without a significant loss of chemical yield or enantioselectivity.

1. Introduction

Asymmetric organocatalysis is a rapidly developing area of modern organic chemistry.[1] Some chiral compounds of natural or synthetic origin such as amino acids,[2] alkaloids,[3] thiourea[4] derivatives, compounds containing pyrrolidines, and imidazolin-4-one fragments,[5] among others[6] are known to have organocatalytic properties. Among them, α,α-diarylprolinol derivatives (Jørgensen–Hayashi-type catalysts) have gained considerable attention;[7] they activate carbonyl compounds via an enamine[7e,7f,8] or iminium[7e,f,9] ion formation and, therefore, catalyze a broad range of reactions, including the reaction sequences where these intermediates are involved in cascade, tandem, or domino processes[10] affording complex molecular scaffolds in an efficient one-pot route from readily available starting materials.

However, industrial applications[11] of the prolinol-type catalysts as well as of a majority of other modern organocatalysts with rather complicated structures demand developing their immobilized versions that can be easily separated from products and reused.[12] Only a few approaches to the immobilization of prolinol-type catalysts have been described. Recently, immobilized prolinol derivatives containing polymeric,[13] dendritic,[14] perfluoroalkyl,[15] or ionic groups[16] have been synthesized. The compounds with ionic groups have some advantages:[12d,e] their catalytic properties are readily tunable by varying the cation and/or anion, their synthesis does not require expensive reagents or special conditions and they can be easily monitored by NMR spectroscopy during all steps.

Chiral ionic liquids bearing the *O*-TMS-α,α-diarylprolinol fragment appeared to be efficient recoverable organocatalysts for the asymmetric Michael reactions between α,β-enals and CH-acids.[16a,b] However, to the best of our knowledge, neither chiral ionic liquids nor other types of immobilized organocatalysts have been successfully applied to domino or cascade reactions. Moreover, polystyrene-supported *O*-TMS-α,α-diarylprolinols became inactive after the first regeneration in the three-component Michael/Michael/aldol cascade reaction.[13b,f]

Herein, we report for the first time that *O*-TMS-α,α-diarylprolinols modified with ionic groups can be used as efficient recoverable catalysts for the asymmetric domino reaction between α,β-enals and N-protected hydroxylamines[17] via the Michael addition stage. We have found that the nature of the substituents in the aromatic rings and the presence of a linker between the chiral inductor and the cation unit are crucial for the catalyst activity and selectivity (Fig. 1). The reaction products, 5-hydroxyisoxazolidines, are valuable intermediates in the organic synthesis,[18] in particular they are used for the preparation of β-amino acids,[19,20] which are precursors of antibiotics[21] and β-peptides.[22]

2. Results and discussion

2.1. Synthesis of catalysts

Initially, we synthesized chiral ionic liquids **1**, **2a–c**, and *cis*-**2a** which differed by the nature of substituents R^1 and R^2 in the α,α-diarylprolinol fragment and by the configuration of the pyrrolidine C-5 atom (Fig. 2).

Compounds **1** and **2a** with a (5*S*)-configuration and catalyst *cis*-**2a** with a (5*R*)-configuration were prepared according to the earlier developed methods.[16a,b] Unknown chiral ionic liquids **2b** and **2c** were synthesized by the synthetic scheme to include reactions of (2*S*,4*R*)-methyl 1-benzyl-4-hydroxypyrrolidine-2-carboxylate **3**

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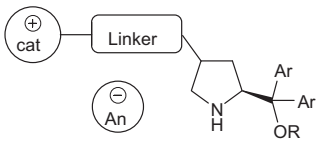
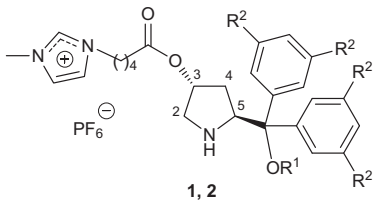


Figure 1. The constitution of the studied ionic liquid-immobilized organocatalysts.



1 $R^1 = R^2 = H$,
2 R^1 = TMS, R^2 = H (**a**), CH_3 (**b**), CF_3 (**c**)

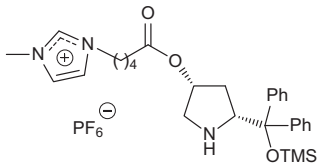


Figure 2. Prolinol/imidazolium derived chiral ionic liquids.

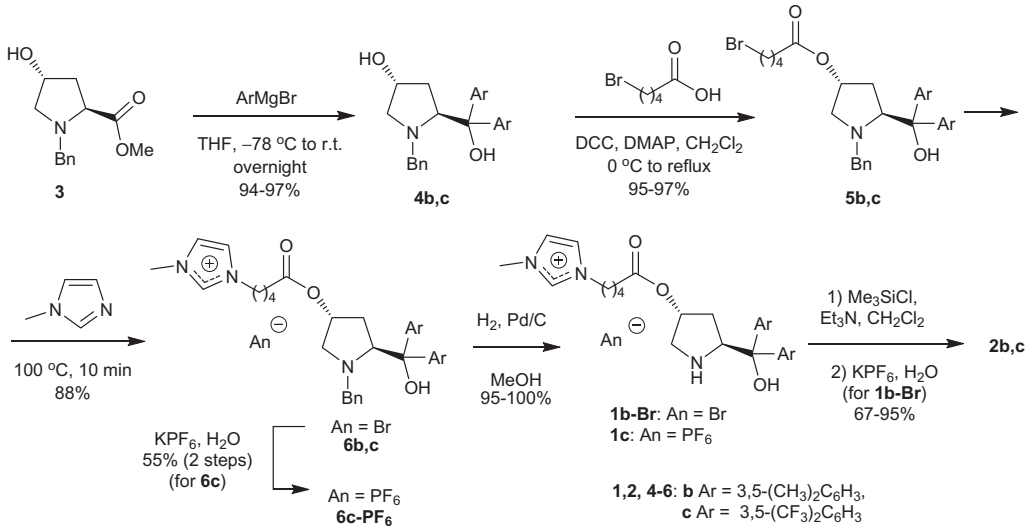
with the respective Grignard reagents, esterification of the corresponding 3-hydroxy-α,α-diarylprolinols **4b**,**c** with 5-bromopentanoic acid, and subsequent reactions of esters **5b**,**c** with 1-methyl-1*H*-imidazole (Scheme 1).

A sequence of further operations depended on the lipophilic properties of imidazolium salts **6b** and **6c**. Bromide **6b**, which was poorly soluble in Et_2O, was easily separated from an excess of 1-methylimidazole by washing with Et_2O and converted into the desired catalyst **2b** by a sequence of hydrogenation, O-silylation, and anion metathesis reactions. On the other hand, bromide **6c**, which is soluble in Et_2O and in 1-methyl-1*H*-imidazole, was directly transformed into hydrophobic hexafluorophosphate **6c-PF$_6$** by the anion exchange reaction. The salt **6c-PF$_6$** after washing with water to remove 1-methyl-1*H*-imidazole-derived impurities was converted into chiral ionic liquid **2c** by successive catalytic hydrogenation and O-silylation reactions. The overall yields of compounds **2b** and **2c** with respect to starting ester **3** were 54% and 46%, respectively.

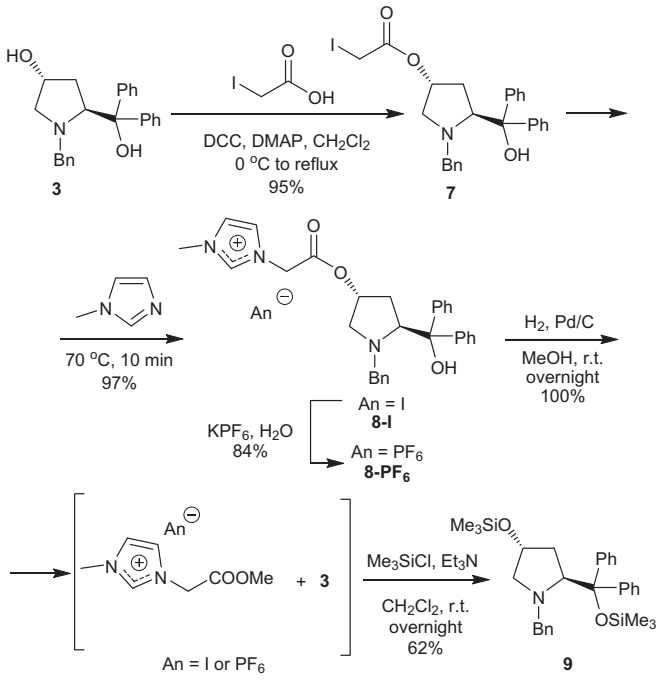
Next, we attempted to apply this strategy to the preparation of α,α-diarylprolinol derivatives bearing a shorter acetic acid-derived linker between the imidazolium cation and the prolinol unit. The esterification of compound **3** with iodoacetic acid in the presence of DCC/DMAP and a subsequent reaction of ester **7** with 1-methyl-1*H*-imidazole afforded iodide **8-I**. However our attempts to deprotect this imidazolium salt failed. The hydrogenation of iodide **8-I** or hexafluorophosphate **8-PF$_6$**, having been prepared from salt **8-I** by an anion exchange reaction, led to prolinol **3**, which was isolated and characterized as bis-TMS-ether **9**, rather than to a corresponding debenzylation product (Scheme 2). This result was unexpected, since respective Cbz-protected proline derivatives had smoothly undergone Pd-catalyzed deprotection under the conditions studied.[23] Apparently, the presence of the α,α-diarylprolinol fragment instead of the amino acid unit enhances the ester group reactivity and makes this immobilization strategy unsuitable.

Recently, stable chiral ionic liquids containing directly linked ionic and proline fragments have been prepared and studied in asymmetric aldol, Michael,[24a] and α-aminoxylation[24b] reactions, however, this strategy has never been applied to the immobilization of Jørgensen–Hayashi-type catalysts. To introduce a good leaving group at the 3-position of the pyrrolidine ring we studied a reaction of compound **3** with the Tf_2O/pyridine mixture under the conditions that had been previously used for the preparation of 4-triflyloxyprolines.[25] However, instead of the expected compound **10**, two major products were obtained; then assigned to isomeric pyrrolines **11a** and **11b** according to HRMS ($[M+H]^+$ m/z = 342.19) and ^{1}H NMR data. The triflate **10** generated in situ was unstable and readily eliminated as triflic acid under the reaction conditions (Scheme 3). Similar elimination products were reported for the reactions of 4-OTf-proline derivatives with some nucleophiles.[25a]

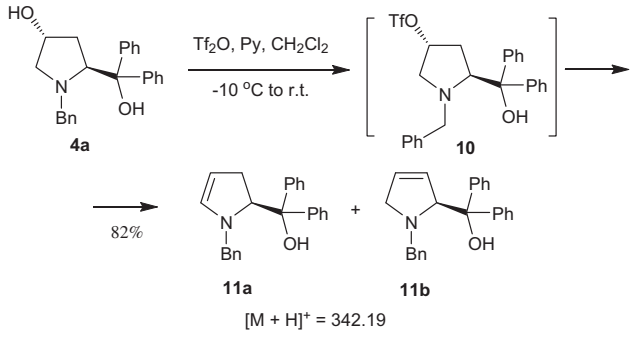
In some cases, less active tosylates can also react with imidazole derivatives to afford the corresponding substitution products.[26] Hence, we prepared tosylate **12** via reaction of prolinol **3** with TsCl/Py.[14d] However compound **12** did not react with 1-methyl-1*H*-imidazole under the conditions proposed for (2*S*,4*R*)-dibenzyl 4-OTf-pyrrolidine-1,2-dicarboxylate.[24b,27] On the other hand, a complex mixture of products was formed under more vigorous conditions (100 °C) (Scheme 4).



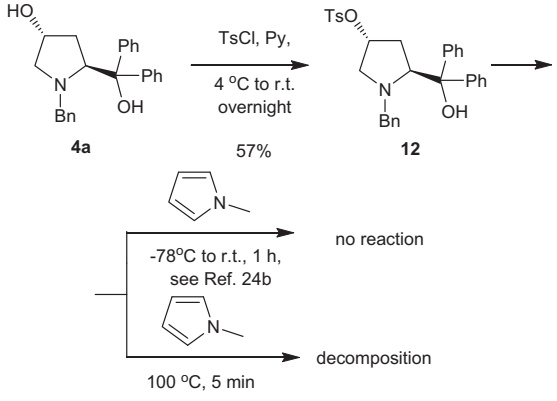
Scheme 1. The preparation of chiral ionic liquids **2b** and **2c**.



Scheme 2. Attempted synthesis of the chiral ionic liquids with the acetic acid-derived linker.



Scheme 3. Attempted synthesis of prolinol triflate **10**.



Scheme 4. Synthesis and reactions of tosylate **12**.

Therefore, for the preparation of a 'linker-free' α,α-diarylprolinol derived chiral ionic liquids we applied an alternative approach resembling the Liebscher's synthesis of 1,2,3-triazolium proline derivatives.[24a] The synthetic route included a reaction of tosylate **12** with sodium azide,[14d] cycloaddition of azide **13** having a reverse configuration of the C-3 atom to 1-heptyne followed by the alkylation of triazole **14** with methyliodide (Scheme 5). Iodide **15-I** did not undergo the catalytic hydrogenation, apparently, due to catalyst poisoning by the iodide anion.[28] We solved this problem by the transformation of iodide **15-I** into hexafluorophosphate **15-PF$_6$**, which was easily deprotected with the formation of pyrrolidine **16**. The subsequent O-silylation of compound **16** in the presence of TMSOTf/2,6-lutidine[16b] afforded target compound **17**.

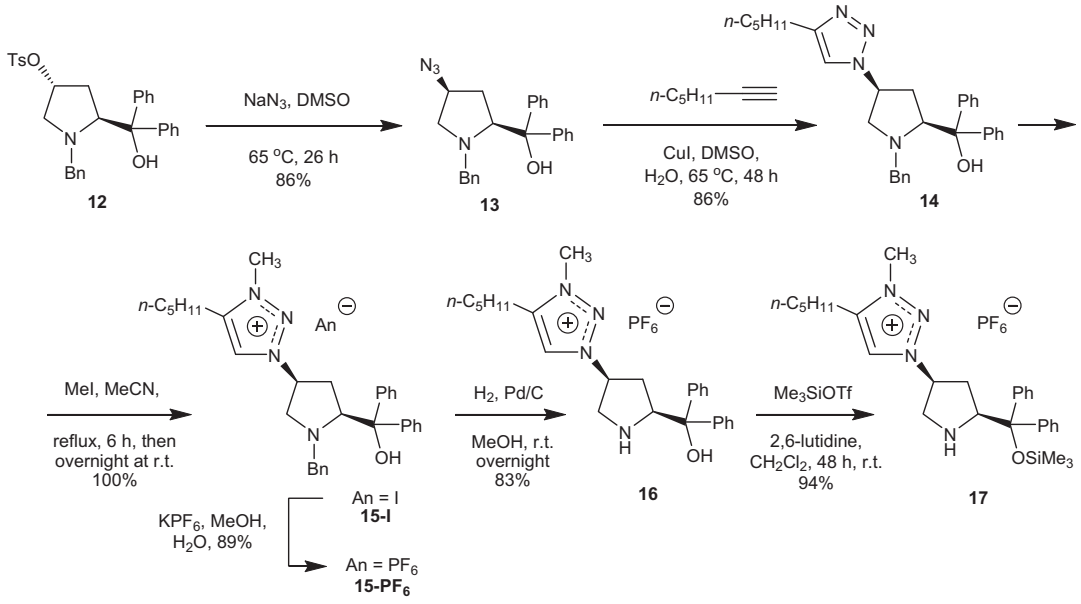
Salts **2b**, **2c**, and **17** as well as known compounds **1**, **2a**, and *cis*-**2a** melt below 150 °C and can be described as ionic liquids.

2.2. Ionic liquid-catalyzed asymmetric domino reaction

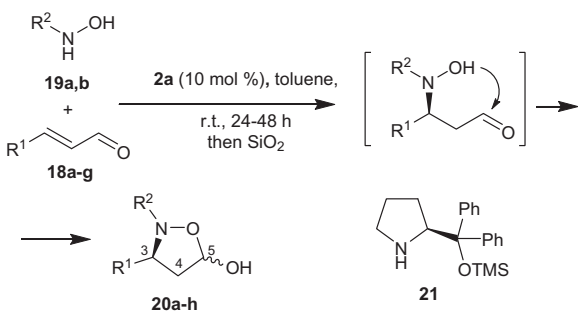
First, we compared the catalytic properties of chiral ionic liquids **1**, **2a–c**, and **17** in the model reaction between *trans*-cinnamaldehyde **18a** and *N*-Cbz-hydroxylamine **19a** to afford chiral 5-hydroxyisoxazolidine **20a** via a tandem sequence of the aza-Michael addition and intramolecular acetalization[17] (Scheme 6, R^1 = Ph, R^2 = Cbz). The experiments were carried out under similar conditions (toluene, rt) until complete cinnamaldehyde conversion was achieved (TLC and NMR monitoring). It was found that enantioselectivity was poor when chiral ionic liquid **1** (10 mol %) bearing the free hydroxyl group had been used as a catalyst (Table 1, entry 1). On the other hand, O-TMS-protected chiral ionic liquid **2a** showed much better results: the ee value of product **20a** was similar to the enantioselectivity obtained using Jørgensen–Hayashi catalyst **21**, though it was lower than that reported before (Table 1, entry 2).[17] Evidently, the presence of the TMS-group was crucial for the stereochemical outcome of the reaction.[29] Catalysts **2b** and **2c** bearing the electron-donating (CH_3) or electron-withdrawing (CF_3) groups in the aromatic rings or "linker-free" chiral ionic liquid **17** were inferior to catalyst **2a** in terms of enantioselectivity. Moreover, chiral ionic liquids **2c** and **17** were considerably less active under the conditions studied (Table 1, entries 3–5).

Next, we studied the chiral ionic liquid **2a** (10 mol %)-catalyzed reaction of *trans*-cinnamaldehyde **18a** with *N*-Cbz-hydroxylamine **19a** in various solvents with a focus on the catalyst regeneration. Therefore, after the reaction had been completed and the product **20a** had been isolated, fresh portions of the starting compounds and corresponding solvent were added to the remaining chiral ionic liquid **2a** and the reaction was repeated. The reaction was found to proceed in CH_3OH, 96%-EtOH, H_2O, Et_2O, and $CHCl_3$ (Table 2, entries 1–5) in a less selective manner than in toluene (Table 2, entry 7). The ee value of the product **20a** was slightly higher in MeCN (90–92% ee), however, the catalyst's activity in this solvent dropped in the third cycle (Table 2, entry 6), whereas in toluene the conversion remained extremely high (99%) for three successive cycles and became just slightly lower (90%) after the third regeneration of the catalyst (Table 2, entry 7). A temperature decrease to 4 °C did not influence the ee value (Table 2, entry 8) but the ee decreased slightly (88% ee) in the experiment where the catalyst loading was 20 mol % (Table 2, entry 9).

Catalyst **2a** was then examined in the reactions between substituted α,β-enals **18a–g** and N-protected hydroxylamines **19a**,**b** under the optimal conditions (Scheme 6, Table 3). In all cases, crude 5-hydroxyisoxazolidines **20a–h** were obtained as single diastereomers (^{1}H NMR data). However, compounds **20a–h** underwent epimerization during purification by column chromatography on silica gel, probably, via a reversible cleavage of the C^5–O bond.[17] The ^{1}H NMR spectra of the purified products contained two sets of signals; the original diastereomer signals representing the major set (dr 9:1–2:1). The epimerization process occurred during HPLC analysis as well, however, it did not interfere with the determination of the enantiomeric composition at C-3 because



Scheme 5. Synthesis of 'linker-free' α,α-diarylprolinol-derived chiral ionic liquid **17**.



Scheme 6. Domino reaction between α,β-enals **18a–g** and N-protected hydroxylamines **19a**,**b**.

Table 1
The reaction between *trans*-cinnamaldehyde **18a** and *N*-Cbz hydroxylamine **19a** in the presence of chiral ionic liquids **1**, **2a–c** and **17**[a]

Entry	Solvent	Catalyst	Time (h)	Conversion[b] (%)	ee[c] (%)
1	Toluene	**1**	48	99	29
2	Toluene	**2a**	24	99 (99[d], 94[e])	90 (90[d], 99[e])
3	Toluene	**2b**	24	99	83
4	Toluene	**2c**	96	99	69
5	Toluene	**17**	96	92	74

[a] All reactions were carried out using *trans*-cinnamaldehyde **18a** (20 mg, 0.15 mmol), *N*-Cbz-hydroxylamine **19a** (32 mg, 0.19 mmol) in toluene (0.3 mL) in the presence of the indicated catalyst (10 mol %) at room temperature.
[b] Estimated by ^{1}H NMR.
[c] Estimated by a chiral HPLC for the isolated products.
[d] Yield and ee values obtained by us in the presence of catalyst **21** (20 mol %) under the conditions of Ref. 17 for 24 h.
[e] Yield and ee values according to Ref. 17.

the diastereomers having opposite configurations at C-5 were indistinguishable under the HPLC conditions.

We established that the ee values of compounds **20a–h** depended on the structure of α,β-enals **18a–g**. The reactions of cinnamaldehyde derivatives **18b–d** containing halogen atoms (F or Cl) or a methoxy group at the *para*-position of the aromatic ring afforded the corresponding 5-hydroxyisoxazolidines **20b–d** with moderate enantioselectivity (64–77% ee) (Table 3, entries 2–4), whereas in the cases of aldehydes **18e** [R^1 = 4-OMe-3-($OC_5H_{11}^{cyclo}$)C_6H_3] and **18f** (R^1 = 4-$NO_2C_6H_4$), it increased to 88% ee and to more than 99% ee, respectively (Table 3, entries 5 and 6). In the presence of *O*-TMS-α,α-diarylprolinol *cis*-**2a** with an (*R*)-configuration at the carbon atom next to the nitrogen atom (see Fig. 2), the corresponding 5-hydroxyisoxazolidine **20g** was obtained with excellent enantioselectivity (>99% ee).

Compounds **20f** and **20g** had an opposite configurations at C-3 (Table 3, entries 6 and 7): their specific rotations were −21.7 and +27.1 (*c* 1.0, $CHCl_3$), respectively. A difference in absolute magnitudes of the measured specific rotations between compounds **20f** and **20g** could be explained by the different ratios of C-5 centered epimers (5:1 and 7:1, respectively, according to ^{1}H NMR) formed during the final products purification by column chromatography on silica gel.

The chiral ionic liquid **2a**-catalyzed reaction of α,β-enal **18a** with *N*-Boc-hydroxylamine **19b** also took place under the conditions studied, yet the enantioselectivity was only moderate (Table 3, entry 8).

Compounds **20** are valuable intermediates in the synthesis of chiral β-amino acids (Scheme 7), which serve as key motifs of natural compounds[19,20] and precursors for the preparation of β-lactam antibiotics,[21] and β-peptides.[22] In this context, the availability of (*S*)- and (*R*)-enantiomers of β-amino acids creates novel opportunities for their application in the synthesis of practically useful chiral compounds. The partial racemization of the C-5 atom during the isolation and purification of heterocycles **20** does not influence the enantiomeric purity of the **20**-derived products, in particular β-amino acids, where this atom acquires an sp^2-configuration.[17]

3. Conclusion

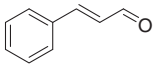
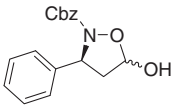
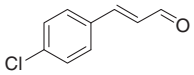
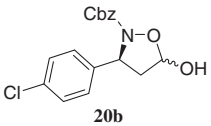
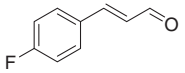
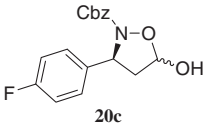
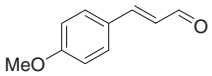
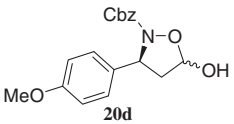
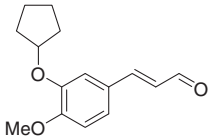
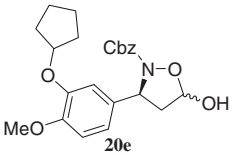
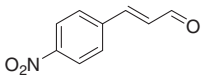
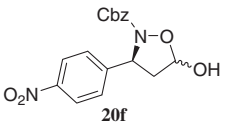
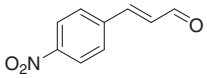
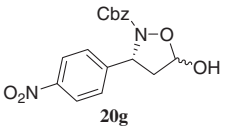
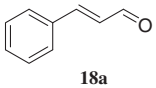
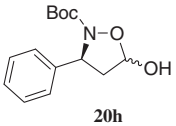
It has been found for the first time that chiral ionic liquids bearing α,α-diarylprolinol units were able to act as efficient recoverable organocatalysts in domino reactions between α,β-enals and N-protected hydroxylamines involving aza-Michael and intramolecular acetalization steps. Novel chiral ionic liquids of this type, different in the nature of the substituents on the aromatic rings and in the mode of linkage between ionic and catalytic sites, were synthesized and their catalytic properties were studied. Chiral 5-hydroxyisoxazolidines with an (*S*)- or (*R*)-config-

Table 2
The chiral ionic liquid **2a** catalyzed reaction of *trans*-cinnamaldehyde **18a** with *N*-Cbz-hydroxylamine **19a** in various solvents[a]

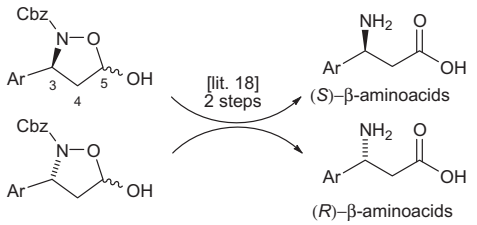
Entry	Solvent	Temp (°C)	Conversion[b] (%) (cycle)	ee[c] (%) (cycle)
1	MeOH	rt	88 (1) 73 (2)	77 (1) 77 (2)
2	96%-EtOH	rt	98 (1) 88 (2)	87 (1) 87 (2)
3	H_2O	rt	97 (1) 91 (2) 75 (3)	87 (1) 86 (2) 87 (3)
4	Et_2O	rt	99 (1) 99 (2) 93 (3) 50 (4)	70 (1) 69 (2) 70 (3) 69 (4)
5	$CHCl_3$	rt	99 (1) 98 (2) 96 (3) 86 (4)	86 (1) 86 (2) 85 (3) 86 (4)
6	MeCN	rt	98 (1) 95 (2) 77 (3)	92 (1) 90 (2) 91 (3)
7	**Toluene**	**rt**	**99 (1) 99 (2) 99 (3) 93 (4)**	**90 (1) 90 (2) 90 (3) 90 (4)**
8	Toluene	4	99 (1) 98 (2) 95 (3)	90 (1) 90 (2) 90 (3)
9[d]	Toluene	4	99 (1) 99 (2) 99 (3)	88 (1) 88 (2) 88 (3)

[a] Unless specified otherwise, all reactions were carried out using *trans*-cinnamaldehyde **18a** (20 mg, 0.15 mmol), *N*-Cbz-hydroxylamine **19a** (32 mg, 0.19 mmol) in the indicated solvent (0.3 mL) in the presence of catalyst **2a** (10 mg, 10 mol %) for 24 h.
[b] Estimated by ^{1}H NMR.
[c] Estimated by a chiral HPLC for the isolated products.
[d] The reaction was carried out in the presence of 20 mol % of catalyst **2a**.

Table 3
Scope and limitations of the domino reaction between α,β-enals **18a–g** and N-protected hydroxylamines **19a–b** in the presence of catalyst **2a**[a]

Entry	Aldehyde, **18**	Hydroxylamine, **19**	Product, **20**	Time (h)	Yield[b] (%) (lit.)	ee[c] (%) (lit.)
1	 **18a**	CbzNHOH **19a**	 **20a**	24	90 (94[d])	90 (99[d])
2	 **18b**	CbzNHOH **19a**	 **20b**	24	91	75
3	 **18c**	CbzNHOH **19a**	 **20c**	24	91	64
4	 **18d**	CbzNHOH **19a**	 **20d**	48	79	77
5	 **18e**	CbzNHOH **19a**	 **20e**	48	73	88
6	 **18f**	CbzNHOH **19a**	 **20f**	24	94	>99
7[e]	 **18f**	CbzNHOH **19a**	 **20g**	24	87	>99
8	 **18a**	BocNHOH **19b**	 **20h**	24	78 (80[d])	67 (99[d])

[a] Unless specified otherwise, all reactions were carried out using the respective *trans*-cinnamaldehyde **18** (0.35 mmol) and N-protected hydroxylamine **19** (0.44 mmol) in toluene (0.7 mL) in the presence of catalyst **2a** (10 mol %, 23 mg) at room temperature.
[b] Isolated yield.
[c] Estimated by a chiral HPLC of the isolated products.
[d] Yield and enantioselectivity according to Ref. 17.
[e] The reaction was carried out in the presence of catalyst *cis*-**2a** (10 mol %, 23 mg).



Scheme 7. 5-Hydroxyisoxazolidines as intermediates in the synthesis of β-aminoacids.

uration at the C-3 atom were obtained in the presence of catalysts **2a** and *cis*-**2a** in excellent yields (up to 94%) and with moderate to high enantioselectivities (up to >99%) retained over four cycles.

4. Experimental

4.1. General

The reagents were used as purchased from commercial suppliers without further purification if otherwise is not indicated. The p.a. quality solvents were pre-dried by standard procedures, if appropriate. DMSO and DMF were distilled over CaH_2 and THF was distilled over $LiAlH_4$ before usage.

The NMR spectra were recorded on a Bruker AM300 NMR spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C, 282 MHz for ^{19}F, 121 MHz for ^{31}P) at 25 °C. Chemical shifts are given in δ ppm referenced to an internal TMS standard for ^{1}H NMR, $CDCl_3$ for ^{13}C NMR, $CFCl_3$ for ^{19}F NMR, and H_3PO_4 for ^{31}P NMR. High resolution mass spectra (HR MS) were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI).[30] The measurements were carried out in a positive ion mode (interface capillary voltage −4500 V); mass range from *m/z* 50 to *m/z* 3000 Da; external or internal calibration was done with Electrospray Calibrant Solution (Fluka). A syringe injection was used for solutions in acetonitrile or MeOH (flow rate 3 μL/min). Nitrogen was applied as a dry gas; the interface temperature was set at 180 °C. Specific optical rotations $[\alpha]_D^{t,°C}$ were measured on a Jasco DIP–D360 instrument at 589 nm. The IR spectrum of **13** (KBr pellets) was recorded on a Specord M82 instrument. Analytical high performance liquid chromatography (HPLC) was performed on a Stayer chromatograph equipped with an UV detector (λ = 254 nm), using a DAICEL Chiralpak® AD–H column and eluent: *n*-hexane/*i*PrOH = 70/30, flow rate: 0.7 mL/min. Melting points were measured with a Franz Küstner Nachf. KG, Dresden HMK (Germany) apparatus and were uncorrected. Silica gels (0.060–0.200 nm and 0.035–0.070 (Acros)) were used for column chromatography with the indicated eluents. The reactions were monitored by TLC (silufol plates; visualization by I_2, UV, and for carbonyl compounds—by 0.5% 2,4-dinitrophenylhydrazine in 2 M HCl) with the indicated eluents. Air and/or moisture sensitive compounds were kept under inert atmosphere at −14 °C.

Compounds **1**, **2a**,[16a] *cis*-**2a**,[16b] **3**,[31] **19a**,[32] and **19b**[33] were prepared according to the literature procedures. (*E*)-Cinnamaldehyde **18a** was obtained from commercial sources and purified by vacuum distillation before usage. 4-Chloro- **18b**, 4-fluoro- **18c**, 4-methoxy- **18d**, 4-nitro- **18f** (*E*)-cinnamaldehydes were prepared according to the Battistuzzi's procedure[34] and purified by recrystallization or distillation under reduced pressure. 3-Cyclopentyloxy-4-methoxy-(*E*)-cinnamaldehyde **18e** was prepared according to Palomo's procedure.[35] Catalyst **21** was prepared according to Ref. 36. Racemic compounds **20a**–**h** were prepared using a racemic catalyst *rac*-**21**[36] according to Ref. 17. All Grignard reagents were prepared by a general procedure.[37] Trimethylsilyl trifluoromethane-sulfonate (TMSOTf) was prepared by the method reported for *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf).[38]

4.2. Synthesis of the catalysts

4.2.1. (3*R*,5*S*)-1-Benzyl-5-(*bis*(3,5-dimethylphenyl)-(hydroxy)methyl)pyrrolidin-3-ol 4b

(3,5-Dimethylphenyl)magnesium bromide ($Me_2C_6H_3MgBr$) prepared from Mg (0.46 g, 19.1 mmol), 1-bromo-3,5-dimethylbenzene (3.37 g, 18.2 mmol), and THF (20 ml) was added to a solution of methyl (2*S*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate **3** (0.54 g, 2.28 mmol) in freshly distilled THF (10 ml) at −78 °C. Then the reaction mixture was stirred overnight at room temperature. Saturated aqueous NH_4Cl (10 ml) was added. The organic layer was separated and the water phase was extracted with Et_2O (3 × 15 ml). The combined organic extracts were washed with saturated aqueous NH_4Cl (2 × 15 ml) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure. The residue was purified by column chromatography (*l* = 17 cm, *d* = 2 cm) using a mixture of *n*-hexane/EtOAc (from 5:1 to 2:1) to afford 0.89 g (94%) of **4b** as a pale yellow oil. R_f 0.18 (*n*-hexane/EtOAc, 5:1). $[\alpha]_D^{21} = +58.8$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.91 (m, 2H, 4-H), 2.28 (m, 12H, CH_3), 2.53 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 3.3 Hz; 1H, 2-H), 3.09 (dd, $^2J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 4.4 Hz; 1H, 2-H), 3.27 (s, 2H, CH_2Ph), 4.30 (m, 2H, 5-H, OH), 4,81 (s, 1H, 3-H), 6.73 (s, 1H, Ar-H), 6.80 (s, 1H, Ar-H), 7.04 (m, 2H, Ph-H), 7.23 (m, 5H, Ph-H, Ar-H), 7.34 (s, 2H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ 21.6, 21.7, 38.8, 61.3, 62.2, 70.8, 71.0, 77.1, 123.4, 123.6, 127.0, 128.1, 128.3, 128.7, 137.4, 137.6, 139.9, 145.9, 147.7 ppm. Anal. Calcd for $C_{28}H_{33}NO_2$ (415.57): C, 80.93; H, 8.00; N, 3.37. Found: C, 80.59; H, 8.34; N, 3.30.

4.2.2. (3*R*,5*S*)-1-Benzyl-5-(*bis*(3,5-*bis*(trifluoromethyl)-phenyl)(hydroxy)methyl)pyrrolidin-3-ol 4c

The title compound was prepared according to the procedure for **4b** from a solution of (3,5-*bis*(trifluoromethyl)phenyl)magnesium bromide ($(CF_3)_2C_6H_3MgBr$) prepared from Mg (0.36 g, 14.7 mmol), 1-bromo-3,5-*bis*(trifluoromethyl)benzene (4.1 g, 14.0 mmol), and THF (16 ml) and a solution of **3** (0.48 g, 2.0 mmol) in freshly distilled THF (10 ml).

Product **4c** was purified by column chromatography (*l* = 20 cm, *d* = 2 cm) using a mixture of *n*-hexane/EtOAc (6:1) to afford 1.25 g (97%) of **6c** as a pale yellow oil. R_f 0.13 (*n*-hexane/EtOAc, 6:1). $[\alpha]_D^{25} = +7.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.75 (m, 2H, 4-H), 2.72 (d, $^3J_{H,H}$ = 11.7 Hz; 1H, 2-H), 3.20 (m, 2H, 2-H, CH_2Ph), 3.52 (d, $^3J_{H,H}$ = 12.8 Hz; 1H, CH_2Ph), 4.33 (m, 1H, 3-H), 4.52 (t, $^3J_{H,H}$ = 8.0 Hz; 1H, 5-H), 5,56 (s, 1H, OH), 6.96 (m, 2H, Ph-H), 7.23 (m, 3H, Ph-H), 7.75 (m, 2H, Ar-H), 8.06 (s, 2H, Ar-H), 8.24 (s, 2H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ 38.9, 61.8, 62.7, 70.8, 71.1, 76.2, 121.5, 121.6, 121.7, 125.1 (d, $^3J_{C,F}$ = 3.3 Hz), 125.7 (d, $^3J_{C,F}$ = 3.3 Hz), 126.1 (d, $^3J_{C,F}$ = 3.3 Hz), 127.6, 128.2, 128.7, 132.1 (q, $^2J_{C,F}$ = 33.7 Hz), 132.2 (q, $^2J_{C,F}$ = 33.2 Hz), 138.5, 147.2, 149.5 ppm. Anal. Calcd for $C_{28}H_{21}F_{12}NO_2$ (631.45): C, 53.26; H, 3.35; N 2.22. Found: C, 53.05; H, 3.19; N, 2.06.

4.2.3. (3*R*,5*S*)-1-Benzyl-5-(*bis*(3,5-dimethylphenyl)-(hydroxy)methyl)pyrrolidin-3-yl 5-bromopentanoate 5b

5-Bromopentanoic acid (0.48 g, 2.7 mmol) was added to a solution of DCC (0.55 g, 2.7 mmol) and DMAP (0.03 g, 0.2 mmol) in CH_2Cl_2 (20 ml) at 0 °C and compound **4b** (0,89 g, 2.1 mmol) was added in 10 min. The reaction mixture was stirred at 0 °C for 1 h. Then DCC (0.27 g, 1.3 mmol) and 5-bromopentanoic acid (0.24 g, 1.3 mmol) were added and the reaction mixture was refluxed for 30 min. The reaction progress was monitored by TLC (*n*-hexane/EtOAc, 6:1, $R_{f\ prod}$ 0.32). The precipitate was filtered off and washed

with CH_2Cl_2 (3 × 15 ml). The organic filtrate was washed with conc. HCl (1 ml), saturated aqueous $NaHCO_3$ (2 × 10 ml), water (15 ml), and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the product was isolated by column chromatography (l = 17 cm, d = 2 cm) using a mixture of n-hexane/EtOAc (from 10:1 to 4:1) to afford 1.19 g (97%) of **5b** as colorless oil. $[\alpha]_D^{25} = +20.4$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.87 (m, 6H, 4-H, $CH_2CH_2CH_2CO$), 2.31 (m, 14H, CH_3, CH_2COO), 2.60 (dd, $^2J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 3.3 Hz; 1H, 2-H), 3.24 (m, 3H, 2-H, CH_2Ph), 3.43 (t, $^3J_{H,H}$ = 6.2 Hz; 2H, $BrCH_2$), 4.26 (t, $^3J_{H,H}$ = 7.7 Hz; 1H, 5-H), 4.70 (s, 1H, OH), 5.05 (m, 1H, 3-H), 6.74 (s, 1H, Ar-H), 6.80 (s, 1H, Ar-H), 7.00 (m, 2H, Ph-H), 7.22 (m, 5H, Ph-H, Ar-H), 7.34 (s, 2H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ 21.6, 21.7, 23.7, 32.1, 33.1, 33.6, 35.7, 59.5, 61.1, 70.7, 74.0, 76.9, 123.3, 123.6, 127.1, 128.3, 128.4, 128.7, 137.5, 137.6, 139.5, 145.6, 147.4, 172.6 ppm. Anal. Calcd for $C_{33}H_{40}BrNO_3$ (578.58): C, 68.50; H, 6.97; N, 2.42. Found: C, 68.27; H, 7.12; N, 2.22.

4.2.4. (3*R*,5*S*)-1-Benzyl-5-(*bis*(3,5-*bis*(trifluoromethyl)-phenyl)-(hydroxy)methyl)pyrrolidin-3-yl 5-bromopentanoate 5c

The title compound was prepared according to the procedure for **5b** from 5-bromopentanoic acid (0.66 g, 3.68 mmol), DCC (0.75 g, 3.68 mmol), DMAP (24 mg, 0.20 mmol), **4c** (1.24 g, 1.96 mmol), and CH_2Cl_2 (16 ml).

Product **5c** was purified by column chromatography (l = 19 cm, d = 2 cm) using a mixture of n-hexane/EtOAc (6:1) to afford 1.48 g (95%) of **7c** as a pale yellow oil. R_f 0.36 (n-hexane/EtOAc, 6:1). $[\alpha]_D^{25} = -3.9$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.87 (m, 6H, 4-H, $CH_2CH_2CH_2COO$), 2.36 (m, 2H, CH_2COO), 2.81 (m, 1H, 2-H), 3.38 (m, 5H, 2′-H, CH_2Ph, $BrCH_2$), 4.45 (m, 1H, 5-H), 5.12 (m, 1H, 3-H), 5.38 (s, 1H, OH), 6.95 (m, 2H, Ph-H), 7.25 (m, 3H, Ph-H), 7.77 (m, 2H, Ar-H), 8.05 (s, 2H, Ar-H), 8.24 (s, 2H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ 23.6, 32.1, 33.1, 33.6, 36.0, 60.0, 61.4, 70.6, 73.4, 76.3, 121.5, 121.7, 121.8, 125.1 (d, $^3J_{C,F}$ = 2.5 Hz), 125.6 (d, $^3J_{C,F}$ = 2.5 Hz), 126.1 (d, $^3J_{C,F}$ = 2.5 Hz), 127.9, 128.3, 128.8, 132.3 (q, $^2J_{C,F}$ = 33.2 Hz), 132.4 (q, $^2J_{C,F}$ = 33.7 Hz), 138.7, 146.9, 149.0, 172.5 ppm. Anal. Calcd for $C_{33}H_{28}BrF_{12}NO_3$ (794.47): C, 49.89; H, 3.55; N, 1.76. Found: C, 50.01; H, 3.79; N, 1.67.

4.2.5. 1-(5-((3*R*,5*S*)-1-Benzyl-5-(*bis*(3,5-dimethyl-phenyl)(hydroxy)methyl)pyrrolidin-3-yloxy)-5-oxopentyl)-3-methyl-1*H*-imidazol-3-ium bromide 6b

A mixture of compound **5b** (1.17 g, 2 mmol) and 1-methyl-1H-imidazole (0.41 g, 5 mmol) was heated at 100 °C for 10 min, cooled to room temperature and washed with Et_2O (5 × 4 ml) to separate an excess of 1-methyl-1H-imidazole. The residue was dissolved in MeOH (1 ml), and Et_2O (20 ml) was added to the solution. The ether layer was separated and the residue was washed with Et_2O (5 × 4 ml). The obtained product was dried under reduced pressure (2 barr) to afford 1.17 g (88%) **6b** as a colorless hydroscopic solid. $[\alpha]_D^{26} = +19.5$ (c 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.64 (m, 2H, 4-H), 2.00 (m, 4H, $CH_2CH_2CH_2COO$), 2.32 (m, 14H, CH_2COO, $(CH_3)_2C_6H_3$), 2.66 (m, 1H, 2-H), 3.21 (m, 3H, 2-H, CH_2Ph), 4.04 (s, 3H, CH_3), 4.37 (m, 3H, 5-H, NCH_2), 5.03 (m, 1H, 3-H), 6.76 (m, 2H, Ar-H), 7.03 (m, 2H, Ar-H), 7.27 (m, 9H, Ar-H, NCHCHN), 10.62 (s, 1H, NCHN) ppm. ^{13}C NMR ($CDCl_3$): δ 21.2, 21.5, 21.6, 29.5, 33.2, 35.5, 36.7, 49.6, 59.2, 60.9, 70.4, 73.6, 77.0, 122.2, 123.2, 123.4, 127.0, 128.1, 128.3, 128.6, 137.4, 137.6, 139.1, 145.5, 147.1, 172.5 ppm. Anal. Calcd for $C_{37}H_{46}BrN_3O_3$ (660.68): C, 67.26; H, 7.02; N, 6.36. Found: C, 67.02; H, 7.35; N, 6.52.

4.2.6. 1-(5-((3*R*,5*S*)-1-Benzyl-5-(*bis*(3,5-*bis*(trifluoromethyl)-phenyl)(hydroxy)methyl)pyrrolidin-3-yloxy)-5-oxopentyl)-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate 6c-PF_6

A mixture of compound **5c** (0.49 g, 0.62 mmol) and 1-methyl-1H-imidazole (0.26 g, 3.1 mmol) was heated at 100 °C for 10 min and then cooled to room temperature. The product was dissolved in a mixture of water (15 ml) and MeOH (5 ml). A solution of KPF_6 (0.34 g, 1.85 mmol) in water (10 ml) was added. MeOH was removed under reduced pressure. When transparent solution was formed, aqueous phase was decanted, and the residue was washed with water (3 × 5 ml) to remove an excess of 1-methyl-1H-imidazole. Then the residue was dissolved in CH_2Cl_2 (30 ml), washed with 0.1 M solution of KPF_6 (2 × 10 ml), and dried over $MgSO_4$. The solvent was evaporated, and the residue was dried under reduced pressure (2 barr) to afford 0.32 g (55%) **6c-PF_6** as a colorless solid. $[\alpha]_D^{23} = -3.3$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.64 (m, 2H, 4-H), 1.92 (m, 4H, $CH_2CH_2CH_2COO$), 2.41 (m, 2H, CH_2COO), 2.82 (m, 1H, 2-H), 3.35 (m, 3H, 2-H, CH_2Ph), 3.91 (s, 3H, CH_3), 4.18 (m, 2H, NCH_2), 4.56 (m, 1H, 5-H), 5.06 (m, 1H, 3-H), 6.94 (br s, 2H, Ph-H), 7.21 (br s, 5H, Ph-H, NCHCHN), 7.73 (s, 2H, Ar-H), 8.09 (s, 2H, Ar-H), 8.28 (s, 2H, Ar-H), 8.63 (s, 1H, NCHN) ppm. ^{13}C NMR ($CDCl_3$): δ 21.1, 29.1, 33.1, 35.9, 36.3, 49.7, 59.7, 61.2, 70.2, 73.6, 76.6, 121.5, 121.6, 122.3, 123.7, 125.1 (d, $^3J_{C,F}$ = 3.0 Hz), 125.8 (d, $^3J_{C,F}$ = 3.0 Hz), 126.2 (d, $^3J_{C,F}$ = 3.0 Hz), 127.6, 128.3, 128.7, 132.0 (q, $^2J_{C,F}$ = 33.6 Hz), 132.2 (q, $^2J_{C,F}$ = 33.6 Hz), 136.2, 138.2, 147.1, 149.3, 172.8 ppm. ^{19}F NMR ($CDCl_3$): δ −72.5 (d, $^1J_{P-F}$ = 712 Hz) ppm. ^{31}P NMR ($CDCl_3$): δ −144.0 (heptet, $^1J_{P-F}$ = 712 Hz) ppm. Anal. Calcd for $C_{37}H_{34}F_{18}N_3O_3P$ (941.63): C, 47.19; H, 3.64; N, 4.46. Found: C, 47.02; H, 3.81; N, 4.59.

4.2.7. 1-(5-((3*R*,5*S*)-5-(*bis*(3,5-Dimethylphenyl)-(hydroxy)methyl)pyrrolidin-3-yloxy)-5-oxopentyl)-3-methyl-1*H*-imidazol-3-ium bromide 1b-Br

A mixture of compound **6b** (1.11 g, 1.7 mmol), 5% Pd/C (0.16 g), and MeOH (22 ml) was stirred under a H_2 atmosphere overnight at room temperature. The catalyst was filtered off, the filtrate was evaporated under reduced pressure, and the product obtained was dried under a vacuum pump to give 0.96 g (100%) of **1b-Br** as a white hydroscopic solid. $[\alpha]_D^{28} = -43.7$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.62 (m, 3H, 4-H, $CH_2CH_2CH_2COO$), 2.06 (m, 3H, 4-H, $CH_2CH_2CH_2COO$), 2.34 (m, 14H, CH_2COO, $(CH_3)_2C_6H_3$), 3.22 (d, $^2J_{H,H}$ = 12.1 Hz; 1H, 2-H), 3.37 (d, $^2J_{H,H}$ = 12.1 Hz; 1H, 2-H), 4.02 (s, 3H, CH_3), 4.35 (m, 3H, OH, NCH_2), 4.66 (m, 1H, 5-H), 5.15 (m, 1H, 3-H), 6.79 (m, 2H, Ar-H), 7.05 (m, 2H, Ar-H), 7.35 (m, 4H, Ar-H, NCHCHN), 10.28 (s, 1H, NCHN) ppm. ^{13}C NMR ($CDCl_3$): δ 21.1, 21.4, 21.5, 29.4, 33.1, 33.2, 36.7, 49.5, 52.6, 63.7, 75.3, 76.9, 122.3, 123.0, 123.5, 123.6, 123.8, 128.2, 128.5, 137.2, 137.4, 137.7, 144.5, 146.9, 172.7 ppm. Anal. Calcd for $C_{30}H_{40}BrN_3O_3$ (570.56): C, 63.15; H, 7.07; N, 7.36. Found: C, 63.00; H, 7.30; N, 7.19.

4.2.8. 1-(5-((3*R*,5*S*)-5-(*bis*(3,5-*bis*(Trifluoromethyl)-phenyl)(hydroxy)methyl)pyrrolidin-3-yloxy)-5-oxo-pentyl)-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate 1c

The title compound was prepared according to the procedure for **1b-Br** from **6c-PF_6** (0.30 g, 0.32 mmol), 5% Pd/C (100 mg), and MeOH (5 ml). Yield 259 mg (95%). White solid. Mp 49–51 °C. $[\alpha]_D^{24} = -27.5$ (c 1.0, $CHCl_3$). ^{1}H NMR (DMSO-d_6): δ 1.50 (m, 2H, 4-H), 1.90 (m, 4H, $CH_2CH_2CH_2COO$), 2.37 (t, ^3J = 7.0 Hz; 2H, CH_2COO), 3.13 (m, 2H, 2-H), 3.84 (s, 3H, CH_3), 4.14 (m, 4H, OH, NCH_2, 5-H), 5.15 (m, 1H, 3-H), 7.70 (s, 1H, NCHCHN), 7.75 (s, 1H, NCHCHN), 8.03 (s, 2H, Ar-H), 8.31 (s, 2H, Ar-H), 8.40 (s, 2H, Ar-H), 9.12 (s, 1H, NCHN) ppm. ^{13}C NMR (CD_3OD): δ 22.2, 30.3, 34.0, 34.3, 36.4, 50.4, 53.6, 65.0, 76.0, 78.6, 122.8, 122.9, 123.6, 124.9, 126.4, 126.5, 127.5 (d, $^3J_{C,F}$ = 2.8 Hz), 128.1 (d, $^3J_{C,F}$ = 2.8 Hz), 133.2 (q, $^2J_{C,F}$ = 32.6 Hz), 137.8, 148.3, 148.7, 174.4 ppm. ^{19}F NMR (CD_3OD): δ −71.0 (d, $^1J_{P-F}$ = 710 Hz), −61.2, −61.1 ppm. ^{31}P NMR (CD_3OD): δ −139.7 (heptet, $^1J_{P-F}$ = 710 Hz) ppm. Anal. Calcd for $C_{30}H_{28}F_{18}N_3O_3P$ (851.51): C, 42.32; H, 3.31; N, 4.93. Found: C, 42.17; H, 3.50; N, 4.76.

4.2.9. 1-(5-((3*R*,5*S*)-5-(*bis*(3,5-Dimethylphenyl)-(trimethylsilyloxy)methyl)pyrrolidin-3-yloxy)-5-oxopentyl)-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate 2b

At first, Me_3SiCl (98 μl, 87 mg, 0.8 mmol) was added to an ice-cooled solution of **1b-Br** (228 mg, 0.4 mmol) and Et_3N (169 μl, 121 mg, 1.2 mmol) in CH_2Cl_2 (1.2 ml) for 15 min. The reaction mixture was stirred at room temperature for 20 h under Ar. The solvent was evaporated and the residue dissolved in a mixture of water (2 ml) and Et_2O (1 ml). Next, Et_2O was evaporated (<50 °C), and MeOH (0.3 ml) was added to the remaining aqueous suspension. A solution of KPF_6 (368 mg, 2.0 mmol) in water (4 ml) was gradually added and the mixture was stirred for 10 min. The aqueous layer was decanted from the resulting oil, after which the residue was dissolved in CH_2Cl_2 (40 ml) and the solution was washed with 0.1 M KPF_6 (2 × 10 ml), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was dried in vacuo (2 barr) to afford **2b** (189 mg, 67%) as a reddish hydroscopic solid. Mp 47–49 °C. $[\alpha]_D^{28} = -19.5$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ −0.10 (s, 9H, Si(C*H*$_3$)$_3$), 1.77 (m, 6H, 4-H, C*H*$_2$C*H*$_2$CH$_2$COO), 2.34 (m, 14H, C*H*$_2$COO, (C*H*$_3$)$_2$C$_6$H$_3$), 2.95 (m, 2H, 2-H), 3.90 (s, 3H, C*H*$_3$), 4.16 (m, 2H, NC*H*$_2$), 4.36 (t, $^3J_{H,H}$ = 7.0 Hz; 1H, 5-H), 4.98 (m, 1H, 3-H), 7.01 (m, 8H, Ar-H, NC*H*C*H*N), 8.65 (s, 1H, NC*H*N) ppm. ^{13}C NMR ($CDCl_3$): δ 2.3, 21.2, 21.5, 21.6, 29.1, 33.3, 34.7, 36.3, 49.7, 53.0, 64.4, 75.4, 83.0, 122.2, 123.7, 125.4, 126.1, 128.8, 128.9, 136.1, 137.1, 137.2, 144.9, 145.8, 173.0 ppm. ^{19}F NMR ($CDCl_3$): δ −71.9 (d, $^1J_{P-F}$ = 714 Hz) ppm. ^{31}P NMR ($CDCl_3$): δ −144.0 (heptet, $^1J_{P-F}$ = 714 Hz) ppm. Anal. Calcd for $C_{33}H_{48}F_6N_3O_3PSi$ (707.80): C, 56.00; H, 6.84; N, 5.94. Found: C, 55.82; H, 6.99; N, 5.68.

4.2.10. 1-(5-((3*R*,5*S*)-5-(*bis*(3,5-*bis*(Trifluoromethyl)phenyl)-(trimethylsilyloxy)methyl)pyrrolidin-3-yloxy)-5-oxopentyl)-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate 2c

At first, Me_3SiCl (26 μl, 22 mg, 0.2 mmol) was added to an ice-cooled (0 °C) solution of **1c** (85 mg, 0.1 mmol) and Et_3N (40 μl, 30 mg, 0.3 mmol) in CH_2Cl_2 (0.4 ml). The reaction mixture was stirred at room temperature for 20 h under Ar. The solvent was evaporated and the residue was dissolved in a mixture of water (2 ml) and Et_2O (1 ml). Next, Et_2O was evaporated (<50 °C). The aqueous layer was decanted from the separated oil, and the residue was dissolved in CH_2Cl_2 (20 ml), washed with 0.1 M KPF_6 (2 × 10 ml), dried over $MgSO_4$, and evaporated. The residue was dried in vacuo (2 barr) to afford **2c** (87 mg, 95%) as a reddish hydroscopic solid. Mp 43–45 °C. $[\alpha]_D^{24} = -2.9$ (*c* 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ −0.07 (s, 9H, Si(C*H*$_3$)$_3$), 1.77 (m, 6H, 4-H, C*H*$_2$C*H*$_2$CH$_2$COO), 2.47 (m, 3H, C*H*$_2$COO, NH), 3.07 (m, 2H, 2-H), 3.90 (s, 3H, C*H*$_3$), 4.17 (m, 2H, NC*H*$_2$), 4.55 (m, 1H, 5-H), 4.94 (m, 1H, 3-H), 7.23 (m, 2H, NC*H*C*H*N), 7.77 (s, 2H, Ar-H), 7.85 (s, 2H, Ar-H), 8.00 (s, 2H, Ar-H), 8.62 (s, 1H, NC*H*N) ppm. ^{13}C NMR ($CDCl_3$): δ 1.9, 21.2, 29.1, 33.2, 34.8, 36.3, 49.7, 53.3, 63.3, 75.7, 82.2, 121.5, 121.6, 122.3, 123.7, 125.1, 125.2, 128.2 (m), 128.8 (m), 130.5, 131.0, 131.6, 132.1, 136.2, 146.1, 148.1, 172.9 ppm. ^{19}F NMR ($CDCl_3$): δ −72.9 (d, $^1J_{P-F}$ = 712 Hz), −63.7, −63.6 ppm. ^{31}P NMR ($CDCl_3$): δ −144.9 (heptet, $^1J_{P-F}$ = 712 Hz) ppm. Anal. Calcd for $C_{33}H_{36}F_{18}N_3O_3PSi$ (923.69): C, 42.91; H, 3.93; N, 4.55. Found: C, 42.76; H, 4.08; N, 4.38.

4.2.11. (3*R*,5*S*)-1-Benzyl-5-(hydroxydiphenylmethyl)-pyrrolidin-3-yl 2-iodoacetate 7

The title compound was prepared according to the procedure for **5b** from 2-iodoacetic acid (1.16 g, 6.3 mmol), DCC (1.29 g, 6.3 mmol), DMAP (48 mg, 0.4 mmol), **4a** (1.44 g, 4.0 mmol), and CH_2Cl_2 (31 ml).

Product **7** was purified by column chromatography (*l* = 15 cm, *d* = 2 cm) using a mixture of *n*-hexane/EtOAc (from 10:1 to 3:1) to afford 2.01 g (95%) of **7** as a dark yellow oil. R_f 0.6 (*n*-hexane/EtOAc, 2:1). $[\alpha]_D^{22} = +5.0$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.98 (m, 2H, 4-H), 2.70 (d, $^3J_{H,H}$ = 12.4 Hz; 1H, 2-H), 3.17 (d, $^3J_{H,H}$ = 12.4 Hz; 2H, 2-H), 3.37 (s, 2H, C*H*$_2$Ph), 3.69 (s, 2H, IC*H*$_2$), 4.41 (t, $^3J_{H,H}$ = 8.1 Hz; 1H, 5-H), 4.83 (s, 1H, OH), 5.09 (m, 1H, 3-H), 7.03 (m, 2H, Ph-H), 7.21 (m, 9H, Ph-H), 7.62 (d, $^3J_{H,H}$ = 7.1 Hz; 2H, Ph-H), 7.79 (d, ^3J = 7.1 Hz; 2H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ −4.9, 35.4, 59.0, 61.1, 70.9, 76.0, 76.7, 125.4, 125.7, 126.7, 126.8, 127.3, 128.3, 128.5, 128.7, 145.6, 147.4, 168.2 ppm. Anal. Calcd for $C_{26}H_{26}INO_3$ (527.39): C, 59.21; H, 4.97; N, 2.66. Found: C, 59.00; H, 5.11; N, 2.39.

4.2.12. 1-(2-((3*R*,5*S*)-1-Benzyl-5-(hydroxydiphenylmethyl)pyrrolidin-3-yloxy)-2-oxoethyl)-3-methyl-1*H*-imidazol-3-ium iodide 8-I

The title compound was prepared according to the procedure for **6b** from **7** (0.51 g, 1.0 mmol) and 1-methyl-1*H*-imidazole (0.21 g, 2.5 mmol) at 70 °C. Yield 0.58 g (97%). Pale yellow hydroscopic solid. $[\alpha]_D^{22} = -5.4$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.11 (m, 2H, 4-H), 2.82 (d, $^3J_{H,H}$ = 12.5 Hz; 1H, 2-H), 3.26 (d, $^3J_{H,H}$ = 12.5 Hz; 2H, 2-H), 3.42 (s, 2H, C*H*$_2$Ph), 3.94 (s, 3H, C*H*$_3$), 4.66 (m, 1H, 5-H), 5.13 (m, 1H, 3-H), 5.50 (dd, *J* = 62.0 Hz, *J* = 18.0 Hz; 2H, IC*H*$_2$), 7.17 (m, 12H, Ph-H, NC*H*C*H*N), 7.57 (s, 1H, Ph-H), 7.67 (d, $^3J_{H,H}$ = 7.9 Hz; 2H, Ph-H), 7.83 (d, ^3J = 7.9 Hz; 2H, Ph-H), 9.98 (s, 1H, NC*H*N) ppm. ^{13}C NMR ($CDCl_3$): δ 35.6, 37.0, 50.7, 58.8, 60.7, 70.1, 77.0, 77.4, 123.0, 124.1, 125.7, 125.8, 126.5, 126.7, 127.2, 128.0, 128.2, 128.4, 128.7, 137.5, 138.9, 145.7, 147.3, 165.6 ppm. Anal. Calcd for $C_{30}H_{32}IN_3O_3$ (609.50): C, 59.12; H, 5.29; N, 6.89. Found: C, 59.40; H, 5.25; N, 6.68.

4.2.13. (2*S*,4*R*)-1-Benzyl-2-(diphenyl(trimethylsilyloxy)-methyl)-4-(trimethylsilyloxy)pyrrolidine 9

A mixture of **8-I** (0.57 g, 0.93 mmol), 5% Pd/C (0.23 g), and MeOH (10 ml) was stirred under H_2 for 16 h at room temperature. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was dried under reduced pressure (2 barr) to afford a colorless oil (0.5 g) as a mixture of 1-(2-methoxy-2-oxoethyl)-3-methyl-1*H*-imidazol-3-ium iodide and (3*R*,5*S*)-1-benzyl-5-(hydroxydiphenylmethyl)pyrrolidin-3-ol **3**. ^1H NMR of above mixture ($CDCl_3$): δ 2.14 (m, 2H, 3-H of **3**), 2.89 (d, $^3J_{H,H}$ = 11.2 Hz; 1H, 3-H of **3**), 3.28 (d, $^3J_{H,H}$ = 11.2 Hz; 2H, 5-H of **3**), 3.62 (dd, *J* = 62.0 Hz, *J* = 12.1 Hz; 2H, C*H*$_2$Ph of **3**), 3.83 (s, 3H, COOC*H*$_3$), 4.03 (s, 3H, C*H*$_3$N), 4.40 (m, 1H, 4-H of **3**), 4.73 (t, $^3J_{H,H}$ = 7.7 Hz, 1H, 2-H of **3**), 5.44 (s, 2H, IC*H*$_2$), 7.20 (m, 12H, Ph-H, NC*H*C*H*N), 7.54 (s, 1H, Ph-H of **3**), 7.61 (d, $^3J_{H,H}$ = 8.1 Hz; 2H, Ph-H of **3**), 7.80 (d, $^3J_{H,H}$ = 8.1 Hz; 2H, Ph-H of **3**), 9.93 (s, 1H, NC*H*N) ppm. ^{13}C NMR of above mixture ($CDCl_3$): 37.2, 38.4, 50.6, 53.7, 61.5, 61.9, 70.4, 71.5, 77.2, 123.2, 124.0, 125.5, 125.7, 126.6, 126.8, 127.4, 128.2, 128.3, 128.4, 128.9, 137.6, 138.0, 145.7, 147.0, 166.3 ppm.

The oil was dissolved in CH_2Cl_2 (3.5 ml) and treated with Me_3SiCl (0.31 ml, 2.4 mmol) and Et_3N (0.45 ml, 3.4 mmol) at 0 °C with stirring. The reaction mixture was kept at room temperature for 15 h. Then the solvent was evaporated, and the residue was dissolved in MeOH (20 ml). A solution of KPF_6 (0.84 g, 4.5 mmol) in water (14 ml) was added. After 5 min the water phase was decanted, and the residue was dissolved in CH_2Cl_2 (25 ml), washed with 0.1 M solution of KPF_6 (2 × 5 ml), and dried over $MgSO_4$. The solvent was removed in vacuo. The residue was dried under reduced pressure (2 barr) to afford 0.35 g (62%) of **9** as a colorless oil. $[\alpha]_D^{24} = -41.6$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ −0.19 (s, 9H, Si(C*H*$_3$)$_3$), −0.11 (s, 9H, Si(C*H*$_3$)$_3$), 1.92 (m, 2H, 3-H), 2.12 (t, $^3J_{H,H}$ = 8.0 Hz; 1H, 5-H), 2.53 (t, $^3J_{H,H}$ = 8.0 Hz; 1H, 5-H), 3.04 (m, 1H, 4-H), 3.87 (dd, *J* = 207.1 Hz, *J* = 12.8 Hz; 2H, C*H*$_2$Ph), 4.08 (t, $^3J_{H,H}$ = 7.3 Hz; 1H, 2-H), 7.21 (m, 11H, Ph-H), 7.56 (m, 4H, Ph-H) ppm. ^{13}C NMR and JMOD ($CDCl_3$): δ −0.1 (4-(C*H*$_3$)$_3$SiO), 2.1 ((C*H*$_3$)$_3$SiO), 38.3 (3-C), 61.4, (C*H*$_2$Ph), 62.6 (5-C), 70.1 (2-C), 71.1 (4-C), 84.6 (C(Ph)$_2$OTMS), aromatic carbons: 126.6, 127.2, 127.3, 127.4, 128.1, 128.8, 129.8, 129.9, 143.4, 143.9 ppm. HRMS (ESI)

calcd for $C_{30}H_{42}NO_2Si_2^+$ ([M+H]$^+$): 504.2749, found: 504.2737. Anal. Calcd for $C_{30}H_{41}NO_2Si_2$ (503.82): C, 71.52; H, 8.20; N, 2.78. Found: C, 71.40; H, 8.38; N, 2.59.

4.2.14. (3*R*,5*S*)-1-Benzyl-5-(hydroxydiphenylmethyl)-pyrrolidin-3-yl 4-methylbenzenesulfonate 12

At first, 4-toluenesulfonyl chloride (TsCl) (0.94 g, 4.9 mmol) was added to an ice-cooled solution of **4a** (1.41 g, 3.9 mmol) in pyridine (8 ml). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 25 h (TLC monitoring, *n*-hexane/EtOAc 2.5:1, $R_{f\ prod}$ 0.56). The solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (50 ml), washed with 1 M HCl (2 × 12 ml), water (2 × 15 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The product was purified by column chromatography (*l* = 12 cm, *d* = 2 cm, eluent: a mixture *n*-hexane/EtOAc (from 4:1 to 2:1) and then pure $CHCl_3$). Yield 1.15 g (57%). White solid. Mp 137 °C (decomp.). $[\alpha]_D^{24} = +15.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.84 (m, 1H, 4-H), 2.01 (m, 1H, 4-H), 2.44 (s, 3H, C*H*$_3$), 2.81 (d, $^3J_{H,H}$ = 12.5 Hz, 1H, 2-H), 3.02 (d, $^3J_{H,H}$ = 11.5 Hz, 1H, 2-H), 3.31 (s, 2H, C*H*$_2$Ph), 4.37 (m, 1H, 5-H), 4.70 (br, 1H, O*H*), 4.79 (m, 1H, 3-H), 6.93 (m, 2H, Ar-H), 7.26 (m, 11H, Ar-H), 7.51 (d, $^3J_{H,H}$ = 7.7 Hz; 2H, Ar-H), 7.76 (m, 4H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ 21.7, 36.1, 59.2, 61.2, 70.5, 76.7, 81.7, 125.3, 125.6, 126.6, 126.9, 127.2, 127.8, 128.2, 128.4, 128.5, 128.6, 130.0, 134.1, 139.1, 145.0, 145.4, 147.2 ppm. Anal. Calcd for $C_{31}H_{31}NO_4S$ (513.65): C, 72.49; H, 6.08; N, 2.73. Found: C 72.40, H 6.18, N 2.62.

4.2.15. ((2*S*,4*S*)-4-Azido-1-benzylpyrrolidin-2-yl)-diphenylmethanol 13

A mixture of **12** (0.56 g, 1.1 mmol), NaN_3 (0.21 g, 3.3 mmol), and dry DMSO (4 ml) was stirred under Ar at 65 °C for 26 h. The mixture was diluted with EtOAc (80 ml), washed with water (3 × 15 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford a white solid. A mixture of *n*-hexane/EtOAc (6:1) was added and the solid was filtered off, washed with the same mixture, and dried to afford 0.36 g (86%) of **13** as a white solid. R_f 0.73 (*n*-hexane/EtOAc, 2:1). Mp 198–200 °C. $[\alpha]_D^{22} = +96.1$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): *v* 2108 (N_3), 3324 (OH). ^{1}H NMR ($CDCl_3$): δ 1.88 (m, 1H, 3-H), 2.30 (m, 1H, 3-H), 2.56 (m, 1H, 5-H), 2.92 (m, 3H, 5-H, C*H*$_2$Ph), 3.26 (d, *J* = 13.2 Hz, 1H, C*H*$_2$Ph), 3.89 (m, 1H, 4-H), 4.06 (m, 1H, 2-H), 4.77 (br, 1H, O*H*), 7.19 (m, 11H, Ph-H), 7.60 (d, $^3J_{H,H}$ = 7.6 Hz; 2H, Ph-H), 7.74 (d, $^3J_{H,H}$ = 7.6 Hz; 2H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ 35.6, 58.4, 59.9, 60.1, 70.0, 77.0, 125.5, 125.7, 126.6, 126.8, 127.3, 128.4, 128.5, 138.9, 146.5, 147.4 ppm. Anal. Calcd for $C_{24}H_{24}N_4O$ (384.47): C, 74.97; H, 6.29; N, 14.57. Found: C, 75.15; H, 6.11; N, 14.66.

4.2.16. ((2*S*,4*S*)-1-Benzyl-4-(4-pentyl-1*H*-1,2,3-triazol-1-yl)pyrrolidin-2-yl)diphenylmethanol 14

Hept-1-yne (113 mg, 1.18 mmol) and CuI (27 mg, 0.14 mmol) were added to a suspension of **13** (361 mg, 0.94 mmol) in a mixture of distilled DMSO (3.4 ml) and water (0.4 ml). The reaction mixture was stirred in a Schlenk flask at 65 °C for 48 h. When the reaction was complete (TLC monitoring, *n*-hexane/EtOAc, 2:1, $R_{f\ prod}$ 0.46), the product was dissolved in $CHCl_3$ (100 ml), washed successively with water (2 × 20 ml), and brine (1 × 15 ml), and dried over $MgSO_4$. Then the solvent was removed under reduced pressure. The product was purified by column chromatography (*l* = 10 cm, *d* = 2 cm, eluent: *n*-hexane/EtOAc (from 2:1 to 1:2)) to afford 387 mg (86%) of **14** as a white solid. Mp 166–168 °C. $[\alpha]_D^{21} = +8.0$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.90 (m, 3H, C*H*$_3$), 1.32 (m, 4H, C*H*$_2$C*H*$_2$CH$_3$), 1.61 (m, 2H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 2.14 (m, 1H, 3-H), 2.62 (m, 3H, 3-H, C*H*$_2$(CH$_2$)$_3$CH$_3$), 3.05 (m, 2H, C*H*$_2$Ph), 3.21 (m, 1H, 5-H), 3.45 (m, 1H, 5-H), 4.25 (m, 1H, 2-H), 4.79 (br, 1H, O*H*), 5.00 (m, 1H, 4-H), 7.19 (m, 12H, Ph-H), 7.60 (d, $^3J_{H,H}$ = 7.2 Hz; 2H, Ph-H), 7.78 (d, $^3J_{H,H}$ = 7.2 Hz; 2H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ 14.1, 22.5, 25.8, 29.2, 31.5, 36.7, 56.8, 59.9, 60.3, 70.5, 76.7, 118.7, 125.2, 125.5, 126.8, 127.0, 127.4, 128.4, 128.6, 138.6, 145.9, 147.2, 148.5 ppm. Anal. Calcd for $C_{31}H_{36}N_4O$ (480.64): C, 77.47; H, 7.55; N, 11.66. Found: C, 77.59; H, 7.33; N, 11.88.

4.2.17. 3-((3*S*,5*S*)-1-Benzyl-5-(hydroxydiphenylmethyl)-pyrrolidin-3-yl)-1-methyl-5-pentyl-1*H*-1,2,3-triazol-3-ium iodide 15-I

A solution of **14** (0.39 mg, 0.81 mmol) and MeI (1.61 g, 11.34 mmol) in MeCN (15 ml) was refluxed for 6 h and then stirred overnight at room temperature. The solvent and an excess of MeI were evaporated. The residue was dried under reduced pressure (2 barr) to afford 0.5 g (100%) of **15-I** as a yellow solid. Mp <50 °C. $[\alpha]_D^{25} = +44.1$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.94 (m, 3H, (CH$_2$)$_4$C*H*$_3$), 1.40 (m, 4H, (CH$_2$)$_2$(C*H*$_2$)$_2$CH$_3$), 1.74 (m, 2H, CH$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$), 2.24 (m, 1H, 4-H), 2.84 (m, 3H, 4-H, C*H*$_2$(CH$_2$)$_3$CH$_3$), 3.15 (m, 2H, 2-H, C*H*$_2$Ph), 3.34 (m, 2H, 2-H, C*H*$_2$Ph), 4.17 (s, 3H, CH$_3$), 4.32 (t, $^3J_{H,H}$ = 13.6 Hz; 1H, 5-H), 4.55 (br, 1H, O*H*), 5.80 (m, 1H, 3-H), 7.18 (m, 11H, Ph-H), 7.52 (d, $^3J_{H,H}$ = 7.5 Hz; 2H, Ph-H), 7.71 (d, $^3J_{H,H}$ = 7.5 Hz; 2H, Ph-H), 8.85 (s, 1H, CC*H*N) ppm. ^{13}C NMR ($CDCl_3$): δ 13.9, 22.2, 23.7, 26.7, 30.9, 36.4, 38.7, 58.4, 59.6, 61.9, 69.7, 77.2, 125.2, 125.5, 126.8, 127.0, 127.4, 128.1, 128.4, 128.5, 138.3, 144.3, 145.5, 146.5 ppm. Anal. Calcd for $C_{32}H_{39}IN_4O$ (622.58): C, 61.73; H, 6.31; N, 9.00. Found: C, 61.49; H, 6.60; N, 8.88.

4.2.18. 3-((3*S*,5*S*)-1-Benzyl-5-(hydroxydiphenylmethyl)-pyrrolidin-3-yl)-1-methyl-5-pentyl-1*H*-1,2,3-triazol-3-ium hexafluorophosphate 15-PF$_6$

A solution of KPF_6 (368 mg, 2.0 mmol) in water (4 ml) was added to a solution of **15-I** (500 g, 0.8 mmol) in a mixture of MeOH (12 ml) and water (2 ml). Next, MeOH was evaporated. The residue was extracted with CH_2Cl_2 (20 ml), washed with 0.1 M KPF_6 (2 × 5 ml), and dried over $MgSO_4$. The solvent was evaporated. The residue was dried under reduced pressure (2 barr) to afford 460 mg (89%) of **15-PF$_6$** as a pale yellow solid. Mp 70–72 °C. $[\alpha]_D^{24} = +39.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.93 (m, 3H, (CH$_2$)$_4$C*H*$_3$), 1.38 (m, 4H, (CH$_2$)$_2$(C*H*$_2$)$_2$CH$_3$), 1.69 (m, 2H, CH$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$), 2.20 (m, 1H, 4-H), 2.76 (m, 3H, 4-H, C*H*$_2$(CH$_2$)$_3$CH$_3$), 3.10 (m, 2H, 2-H, C*H*$_2$Ph), 3.37 (m, 2H, 2-H, C*H*$_2$Ph), 4.08 (s, 3H, CH$_3$), 4.31 (m, 2H, 5-H, O*H*), 5.14 (m, 1H, 3-H), 7.03 (m, 2H, Ph-H), 7.21 (m, 9H, Ph-H), 7.51 (d, $^3J_{H,H}$ = 7.7 Hz; 2H, Ph-H), 7.70 (d, $^3J_{H,H}$ = 7.7 Hz; 2H, Ph-H), 7.98 (s, 1H, CC*H*N) ppm. ^{13}C NMR ($CDCl_3$): δ 13.9, 22.2, 23.2, 26.5, 30.9, 36.1, 37.5, 58.3, 59.7, 61.5, 69.8, 77.2, 125.2, 125.5, 126.8, 127.0, 127.1, 127.6, 128.6, 128.7, 138.2, 144.8, 145.5, 146.5 ppm. ^{19}F NMR ($CDCl_3$): δ −74.3 (d, $^1J_{P-F}$ = 712 Hz) ppm. ^{31}P NMR ($CDCl_3$): δ −144.6 (heptet, $^1J_{P-F}$ = 712 Hz) ppm. Anal. Calcd for $C_{32}H_{39}F_6N_4OP$ (640.64): C, 59.99; H, 6.14; N, 8.75. Found: C, 59.76; H, 6.53; N, 8.31.

4.2.19. 3-((3*S*,5*S*)-5-(Hydroxydiphenylmethyl)-pyrroli-din-3-yl)-1-methyl-5-pentyl-1*H*-1,2,3-triazol-3-ium hexafluorophosphate 16

The title compound was prepared according to the procedure for **1b-Br** from **15-PF$_6$** (0.46 g, 0.72 mmol), 5% Pd/C (0.17 g), and MeOH (12 ml). Yield 328 mg (83%). White solid. Mp 86–88 °C. $[\alpha]_D^{30} = -6.9$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (DMSO-d_6): δ 0.90 (m, 3H, (CH$_2$)$_4$C*H*$_3$), 1.37 (m, 4H, (CH$_2$)$_2$(C*H*$_2$)$_2$CH$_3$), 1.67 (m, 2H, CH$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$), 1.84 (m, 1H, 4-H), 2.59 (m, 1H, 4-H), 2.82 (t, $^3J_{H,H}$ = 7.7 Hz; 2H, C*H*$_2$(CH$_2$)$_3$CH$_3$), 3.74 (m, 1H, 2-H), 3.89 (m, 1H, 2-H), 4.21 (m, 4H, 5-H, C*H*$_3$), 5.20 (br, 1H, O*H*), 5.55 (m, 1H, 3-H), 7.29 (m, 6H, Ph-H), 7.52 (d, $^3J_{H,H}$ = 7.5 Hz; 2H, Ph-H), 7.64 (d, $^3J_{H,H}$ = 7.5 Hz; 2H, Ph-H), 8.97 (s, 1H, CC*H*N) ppm. ^{13}C NMR (DMSO-d_6): δ 13.7, 21.7, 22.3, 25.8, 30.3, 32.1, 37.4, 48.4, 60.1, 64.5, 76.6, 125.3, 125.7, 125.8, 127.2, 127.5, 128.2, 128.4, 128.5,

143.7, 144.2 ppm. ^{19}F NMR (DMSO-d_6): δ −74.0 (d, $^1J_{P-F}$ = 711 Hz) ppm. ^{31}P NMR (DMSO-d_6): δ −144.0 (heptet, $^1J_{P-F}$ = 711 Hz) ppm. Anal. Calcd for $C_{25}H_{33}F_6N_4OP$ (550.52): C, 54.54; H, 6.04; N, 10.18. Found: C, 54.35; H, 6.37; N, 10.01.

4.2.20. 3-((3*S*,5*S*)-5-(Diphenyl(trimethylsilyloxy)-methyl)pyrrolidin-3-yl)-1-methyl-5-pentyl-1*H*-1,2,3-triazol-3-ium hexafluorophosphate 17

At first, TMSOTf (109 μL, 133 mg, 0.6 mmol) was added in one portion to an ice-cooled solution of **16** (110 mg, 0.2 mmol) and 2,6-lutidine (107 mg, 1.0 mmol) in dry CH_2Cl_2 (0.5 ml). The reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated under reduced pressure. A mixture of water (1 ml) and Et_2O (1 ml) was added to the residue, then Et_2O was evaporated, and the water phase was decanted. The residue was washed with water (2 × 2 ml) and dissolved in CH_2Cl_2 (20 ml). The organic phase was washed with 0.1 M KPF_6 (2 × 3 ml) and dried over $MgSO_4$. The solvent evaporation afforded 117 mg (94%) of **17** as a yellow oil. $[\alpha]_D^{28} = -23.6$ (*c* 1.0, $CHCl_3$).^{1}H NMR ($CDCl_3$): δ −0.09 (s, 9H, (CH_3)$_3$Si), 0.89 (m, 3H, $(CH_2)_4CH_3$), 1.34 (m, 4H, $(CH_2)_2(CH_2)_2CH_3$), 1.61 (m, 2H, $CH_2CH_2(CH_2)_2CH_3$), 2.38 (m, 1H, 4-H), 2.61 (m, 3H, 4-H, $CH_2(CH_2)_3CH_3$), 3.01 (m, 1H, 2-H), 3.24 (m, 1H, 2-H), 3.85 (m, 1H, 5-H), 3.97 (s, 3H, CH_3), 4.84 (br, 1H, OH), 5.56 (m, 1H, 3-H), 7.37 (m, 10H, Ph-H), 7.79 (s, 1H, CCHN) ppm. ^{13}C NMR ($CDCl_3$): δ 1.8, 13.9, 22.2, 23.2, 26.3, 31.0, 31.1, 37.3, 62.2, 65.9, 76.7, 82.0, 126.1, 127.1, 127.8, 128.3, 128.4, 128.8, 128.9, 129.0, 129.5, 129.8, 130.3, 142.1, 144.9 ppm. ^{19}F NMR ($CDCl_3$): δ −73.8 (d, $^1J_{P-F}$ = 712 Hz) ppm. ^{31}P NMR ($CDCl_3$): δ −144.5 (heptet, $^1J_{P-F}$ = 712 Hz) ppm. Anal. Calcd for $C_{28}H_{41}F_6N_4OPSi$ (622.70): C, 54.01; H, 6.64; N, 9.00. Found: C, 53.78; H, 6.89; N, 9.34.

4.3. General procedure for the domino reaction

A mixture of α,β-unsaturated aldehyde **18** (0.35 mmol, 1 equiv), N-protected hydroxylamine **19** (0.44 mmol, 1.25 equiv), catalyst **2a** or *cis*-**2a** (23 mg, 0.035 mmol, 10 mol %), and toluene (0.7 ml) was stirred at room temperature for indicated time (Table 3). The solvent was removed under reduced pressure, and the product was extracted with Et_2O (2 × 1 ml). The combined extracts were evaporated to afford crude compounds **20**. For analytical purposes compounds **20** were purified by column chromatography with the indicated solvent. If appropriate, the catalyst was reused.

4.3.1. (3*S*)-Benzyl 5-hydroxy-3-phenylisoxazolidine-2-carboxylate 20a

Yield 90%, 90% ee. Mixture of diastereomers, dr = 9:1. Colorless oil. Eluent for column chromatography: *n*-hexane/EtOAc (3:1). All analytical data were in agreement with the literature.[17] HPLC analysis: t_R = 13.8 min (major), 15.5 min (minor).

4.3.2. (3*S*)-Benzyl 3-(4-chlorophenyl)-5-hydroxy-isoxazolidine-2-carboxylate 20b

Yield 91%, 75% ee (major). Mixture of diastereomers, dr = 6:1. Colorless oil. Eluent for column chromatography: *n*-hexane/EtOAc (3:1). $[\alpha]_D^{28} = -20.7$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.25 (m, 1H, 4-H major), 2.49 (m, 1H, 4-H minor), 2.78 (dd, $^3J_{H,H}$ = 12.5 Hz, $^3J_{H,H}$ = 8.2 Hz; 1H, 4-H major), 3.13 (m, 1H, 4-H minor), 5.18 (m, 2H, CH_2Ph mixture of major and minor), 5.35 (t, $^3J_{H,H}$ = 8.2 Hz; 1H, 3-H major), 5.50 (m, 1H, 3-H minor), 5.82 (m, 1H, 5-H major), 6.15 (m, 1H, 5-H minor), 7.30 (m, 9H, Ar-H mixture of major and minor) ppm. ^{13}C NMR ($CDCl_3$): δ 39.8 (minor), 45.3 (major), 60.9 (major), 62.4 (minor), 68.4 (major), 68.6 (minor), 88.7 (minor), 98.8 (major), 127.4, 127.6, 127.9, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 128.9, 133.4, 135.4, 135.6, 140.0, 156.3, 158.8, 159.3 ppm. HPLC analysis: t_R = 16.6 min (major), 18.7 min (minor). Anal. Calcd for $C_{17}H_{16}ClNO_4$ (333.77): C, 61.18; H, 4.83; N, 4.20. Found: C, 61.00; H, 5.02; N, 4.03.

4.3.3. (3*S*)-Benzyl 3-(4-fluorophenyl)-5-hydroxy-isoxazolidine-2-carboxylate 20c

Yield 91%, 68% ee (major). Mixture of diastereomers, dr = 2.5:1. Colorless oil. Eluent for column chromatography: *n*-hexane/EtOAc (3:1). $[\alpha]_D^{28} = +0.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.26 (m, 1H, 4-H major), 2.50 (m, 1H, 4-H minor), 2.77 (dd, $^3J_{H,H}$ = 12.5 Hz, $^3J_{H,H}$ = 8.2 Hz; 1H, 4-H major), 3.12 (m, 1H, 4-H minor), 5.18 (m, 2H, CH_2Ph mixture of major and minor), 5.35 (t, $^3J_{H,H}$ = 8.2 Hz; 1H, 3-H major), 5.51 (m, 1H, 3-H minor), 5.78 (m, 1H, 5-H major), 6.16 (m, 1H, 5-H minor), 7.01 (m, 2H, Ar-H mixture of major and minor), 7.31 (m, 7H, Ar-H mixture of major and minor) ppm. ^{13}C NMR ($CDCl_3$): δ 39.9 (minor), 45.3 (major), 60.9 (major), 62.3 (minor), 68.4 (major), 68.6 (minor), 88.7 (minor), 98.7 (major), 115.6 (m, Ar-H mixture of major and minor), 127.6, 127.8, 127.9, 128.2, 128.3, 128.4, 128.5, 128.6, 135.4, 135.6, 137.2, 156.4, 158.8, 159.3, 159.4, 160.6, 163.9 ppm. HPLC analysis: t_R = 15.8 min (major), 17.7 min (minor). Anal. Calcd for $C_{17}H_{16}FNO_4$ (317.31): C, 64.35; H, 5.08; N, 4.41. Found: C, 64.07; H, 5.29; N, 4.09.

4.3.4. (3*S*)-Benzyl 3-(4-methoxyphenyl)-5-hydroxy-isoxazolidine-2-carboxylate 20d

Yield 79%, 77% ee (major). Mixture of diastereomers, dr = 2:1. Pale yellow oil. Eluent for column chromatography: *n*-hexane/EtOAc (from 3:1 to 2:1). $[\alpha]_D^{28} = -4.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.30 (m, 1H, 4-H major), 2.53 (m, 1H, 4-H minor), 2.74 (dd, $^3J_{H,H}$ = 12.8 Hz, $^3J_{H,H}$ = 8.2 Hz; 1H, 4-H major), 3.09 (m, 1H, 4-H minor), 3.79 (m, 3H, CH_3 mixture of major and minor), 5.18 (m, 2H, CH_2Ph mixture of major and minor), 5.33 (t, $^3J_{H,H}$ = 8.2 Hz; 1H, 3-H major), 5.49 (m, 1H, 3-H minor), 5.78 (m, 1H, 5-H major), 6.18 (m, 1H, 5-H minor), 6.86 (m, 2H, Ar-H mixture of major and minor), 7.30 (m, 7H, Ar-H mixture of major and minor) ppm. ^{13}C NMR ($CDCl_3$): δ 39.7 (minor), 45.3 (major), 55.4 (OCH_3 mixture of major and minor), 61.0 (major), 62.6 (minor), 68.2 (major), 68.5 (minor), 88.8 (minor), 98.8 (major), 114.1, 127.2, 127.5, 127.8, 128.2, 128.3, 128.5, 128.6, 133.5, 135.5, 135.7, 156.3, 158.9, 159.1, 159.4 ppm. HPLC analysis: t_R = 21.7 min (major), 23.2 min (minor). Anal. Calcd for $C_{18}H_{19}NO_5$ (329.35): C, 65.64; H, 5.81; N, 4.25. Found: C, 65.44; H, 5.99; N, 4.02.

4.3.5. (3*S*)-Benzyl 3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-hydroxyisoxazolidine-2-carboxylate 20e

Yield 73%, 88% ee (major). Mixture of diastereomers, dr = 2:1. Pale yellow oil. Eluent for column chromatography: *n*-hexane/EtOAc (from 3:1 to 2:1). $[\alpha]_D^{28} = -5.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.72 (m, 8H, CH_2-cyclopentyl mixture of major and minor), 2.30 (m, 1H, 4-H major), 2.54 (m, 1H, 4-H minor), 2.74 (dd, $^3J_{H,H}$ = 12.8 Hz, $^3J_{H,H}$ = 8.4 Hz; 1H, 4-H major), 3.09 (m, 1H, 4-H minor), 3.83 (m, 3H, CH_3O mixture of major and minor), 4.72 (m, 1H, CH-cyclopentyl mixture of major and minor), 5.19 (m, 2H, CH_2Ph mixture of major and minor), 5.30 (m, 1H, 3-H major), 5.46 (m, 1H, 3-H minor), 5.78 (m, 1H, 5-H major), 6.18 (m, 1H, 5-H minor), 6.85 (m, 2H, Ar-H mixture of major and minor), 7.31 (m, 6H, Ph-H mixture of major and minor) ppm. ^{13}C NMR ($CDCl_3$): δ 24.1, 32.8, 39.7 (minor), 45.3 (major), 56.2, 61.2 (major), 62.8 (minor), 68.2 (major), 68.5 (minor), 80.5, 88.8 (minor), 98.7 (major), 112.2, 122.9, 113.1, 118.1, 118.3, 127.8, 128.1, 128.2, 128.3, 128.5, 128.6, 133.8, 133.9, 135.5, 135.6, 135.7, 148.0, 149.5, 156.3, 158.9, 159.5 ppm. HPLC analysis: t_R = 16.5 min (major), 17.6 min (minor). Anal. Calcd for $C_{23}H_{27}NO_6$ (413.46): C, 66.81; H, 6.58; N, 3.39. Found: C, 66.67; H, 6.87; N, 3.12.

4.3.6. (3*S*)-Benzyl 3-(4-nitrophenyl)-5-hydroxy-isoxazolidine-2-carboxylate (−)-20f

Yield 94%, 99.5% ee (major). Mixture of diastereomers, dr = 5:1. White solid. Eluent for column chromatography: *n*-hexane/EtOAc (from 3:1 to 1:1). Mp 104 °C (decomp.). $[\alpha]_D^{28} = -21.7$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.25 (m, 1H, 4-H major), 2.50 (m, 1H, 4-H minor), 2.86 (dd, $^3J_{H,H}$ = 12.5 Hz, $^3J_{H,H}$ = 8.4 Hz; 1H, 4-H major), 3.22 (m, 1H, 4-H minor), 5.19 (m, 2H, CH_2Ph mixture of major and minor), 5.47 (t, $^3J_{H,H}$ = 8.4 Hz; 1H, 3-H major), 5.62 (m, 1H, 3-H minor), 5.83 (m, 1H, 5-H major), 6.16 (m, 1H, 5-H minor), 7.31 (m, 5H, Ph-H mixture of major and minor), 7.50 (m, 2H, Ar-H mixture of major and minor), 8.19 (m, 2H, Ar-H mixture of major and minor) ppm. ^{13}C NMR ($CDCl_3$): δ 39.9 (minor), 45.1 (major), 61.0 (major), 62.4 (minor), 68.7 (major), 68.8 (minor), 88.7 (minor), 98.8 (major), 123.8, 124.1, 126.9, 127.0, 127.3, 127.9, 128.1, 128.3, 128.5, 128.6, 135.3, 147.4, 148.7, 156.4, 159.3 ppm. HPLC analysis: t_R = 31.8 min (major), 35.9 min (minor). Anal. Calcd for $C_{17}H_{16}N_2O_6$ (344.32): C, 59.30; H, 4.68; N, 8.14. Found: C, 59.16; H, 4.90; N, 7.96.

4.3.7. (3*R*)-Benzyl 3-(4-nitrophenyl)-5-hydroxy-isoxazolidine-2-carboxylate (+)-20g

The title compound was prepared according to the general method using catalyst *cis*-**2a**. Yield 87%, >99% ee (major). Mixture of diastereomers, dr = 7:1. White solid. Eluent for column chromatography: *n*-hexane/EtOAc (from 3:1 to 1:1). Mp 104 °C (decomp.). $[\alpha]_D^{28} = +27.1$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.25 (m, 1H, 4-H major), 2.49 (m, 1H, 4-H minor), 2.86 (dd, $^3J_{H,H}$ = 12.8 Hz, $^3J_{H,H}$ = 8.4 Hz; 1H, 4-H major), 3.22 (m, 1H, 4-H minor), 5.19 (m, 2H, CH_2Ph mixture of major and minor), 5.47 (t, $^3J_{H,H}$ = 8.4 Hz; 1H, 3-H major), 5.61 (m, 1H, 3-H minor), 5.83 (m, 1H, 5-H major), 6.15 (m, 1H, 5-H minor), 7.31 (m, 5H, Ph-H mixture of major and minor), 7.50 (m, 2H, Ar-H mixture of major and minor), 8.19 (m, 2H, Ar-H mixture of major and minor) ppm. ^{13}C NMR ($CDCl_3$): δ 39.9 (minor), 45.1 (major), 61.0 (major), 62.4 (minor), 68.7 (major), 68.8 (minor), 88.7 (minor), 98.8 (major), 123.8, 124.1, 126.9, 127.0, 127.3, 127.9, 128.1, 128.3, 128.5, 128.6, 135.3, 147.4, 148.7, 156.4, 159.3 ppm. HPLC analysis: t_R = 36.05 min (major), n.d. (minor). Anal. Calcd for $C_{17}H_{16}N_2O_6$ (344.32): C, 59.30; H, 4.68; N, 8.14. Found: C, 59.10; H, 4.95; N, 7.90.

4.3.8. (3*S*)-Benzyl 5-hydroxy-3-phenylisoxazolidine-2-carboxylate 20h

Yield 78%, 67% ee (major). Mixture of diastereomers, dr = 9:1. Colorless oil. All analytical data were in agreement with the literature.[17] HPLC analysis: t_R = 8.3 min (major), 10.1 min (minor).

4.4. Catalyst recycling

A mixture of (*E*)-cinnamaldehyde **18a** (20 mg, 0.15 mmol), *N*-Cbz-hydroxylamine **19a** (32 mg, 0.19 mmol), and catalyst **2a** (10 mol %, 10 mg) in the indicated solvent (Tables 1 and 2) (0.3 ml) was stirred for an indicated time (Tables 1 and 2). The solvent was evaporated in vacuo, after which product **20a** was extracted with Et_2O (2 × 1 ml). The combined organic extracts were evaporated to afford product **20a**. The remaining catalyst was dried under reduced pressure (2 barr) and reused in the same reaction without further purification.

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