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The asymmetric organocatalytic 1,3-dipolar cycloaddition of alkyl pyruvate-derived nitrones and α,β-unsaturated aldehydes

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ABSTRACT

The catalytic asymmetric 1,3-dipolar cycloaddition of pyruvate-derived nitrones to α,β-unsaturated aldehydes was investigated in the presence of various chiral amines. Highly functionalized isoxazolidines containing a quaternary stereocenter were obtained in moderate yields with up to 92% ee. To the best of our knowledge, this is the first example of an enantioselective 1,3-dipolar cycloaddition of ketonitrones. The model product was subsequently transformed into a 2-pyrrolidinone derivative in two steps.

1. Introduction

The 1,3-dipolar cycloaddition of nitrones remains a powerful method for the construction of nitrogen-containing heterocyclic products.[1] Among existing asymmetric variants of this reaction,[2] the use of chiral amines as organocatalysts for the activation of α,β-unsaturated aldehydes as dipolarophiles is one of the latest developments in this area.[3] In our laboratory, we have developed a new family of organocatalysts, known as hybrid diamines,[4] and showed that their efficiency in the reaction of aromatic nitrones with α,β-unsaturated aldehydes was comparable to the efficiency of the catalysts reported by other groups.[3g] Recently, we have also reported the first highly enantioselective 1,3-dipolar cycloaddition of alkyl glyoxylate-derived nitrones to (*E*)-crotonaldehyde, catalyzed by hybrid diamines and demonstrated the application of the cycloadducts obtained in the synthesis of functionalized 2-pyrrolidinones.[5] In continuation of our efforts to expand upon the utility of hybrid diamines as organocatalysts, we became interested in the 1,3-dipolar cycloaddition reaction of pyruvate-derived nitrones. These substrates would lead to isoxazolidines possessing a quaternary stereogenic center, the stereocontrolled formation of which is often a challenging task.[6] According to a literature search, this task has not been realized by means of enantioselective catalysis with ketonitrones as dipoles. Some examples of non-asymmetric 1,3-dipolar cycloaddition of pyruvate-derived nitrones have been previously reported.[7,8]

2. Results and discussion

We obtained the model compound (*E*)-*N*-(1-methoxy-1-oxopropan-2-ylidene)(phenyl)methanamine oxide **1a** in a good yield according to a literature procedure, in diastereomerically pure *E*-form (as established by NMR data).[8] At the beginning, we investigated its reaction with (*E*)-crotonaldehyde **2b** under standard conditions used by us[5] in the presence of hybrid diamine salt **C1**·TfOH (Scheme 1, Chart 1). The results are presented in Table 1. We obtained isoxazolidine **3a** in a 75% yield as the sole product; the relative configuration was determined by a NOESY experiment. After its reduction with $NaBH_4$, the corresponding alcohol **4a** was isolated with a moderate 47% ee value (Table 1, entry 1). We also investigated the reaction of other pyruvate-derived nitrones **1b-d** with (*E*)-crotonaldehyde **2b**, since the stereoselective formation of quaternary stereogenic centers is often strongly substrate-dependent.[6] However, in all cases the ee's were in the range of 35–53% ee (entries 2–4), with the highest value obtained for nitrone **1b** (entry 2). The nitrones with a larger alkyl group at the α-position (e.g., *i*-Pr nitrone, see Experimental section) were not reactive. The use of other hybrid diamines **C2** and **C3** (Chart 1) as organocatalysts led to similar results, indicating the small influence of the side chain of the amino acid part of the catalyst on the stereochemical outcome of the reaction (entries 5 and 6). Similarly, a low ee was obtained with the non-hybrid biphenyl analogue of the phenylalanine catalyst (33% ee).[5] Attempts at the modification of previously established experimental conditions were also unsuccessful, for example, reactions conducted in toluene and acetonitrile led to the product **3a** in 30% and 41% ee, respectively. The combination of nitromethane as the solvent and trifluoromethanesulfonic (triflic) acid as the co-catalyst was found to be crucial for the highest level of enantioselectivity, which was still not synthetically useful. Subsequently, we investigated the reaction of nitrone **1b** with various α,β-unsaturated aldehydes (Scheme 1). Using 20 mol % of the hybrid catalyst **C1**∗TfOH in the reaction with (*E*)-pentenal **2c** led after 168 h at 4 °C to a single diastereomer of isoxazolidine **3f** in a 60% yield and with low enantioselectivity (17% ee, Table 1, entry 7). The reaction with acrolein **2a** under similar conditions

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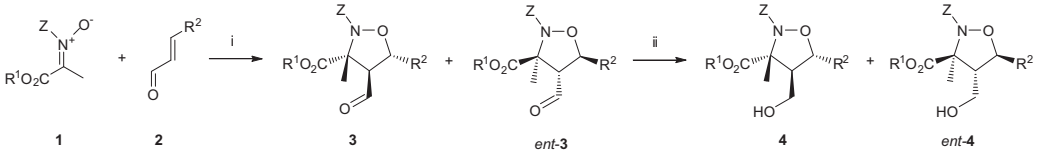


1a: Z=Bn, R^1=Me; **b**: Z=Bn, R^1=Et, **c**: Z=R^1=Bn, **d**: Z=R^1=Me
2a: R^2=H; **b**: R^2=Me; **c**: R^2=Et
3a: Z=Bn, R^1=R^2=Me; **b**: Z=Bn, R^1=Et, R^2=Me; **c**: Z=Bn, R^1=Bn, R^2=Me; **d**: Z=R^1=R^2=Me; **e**: Z=Bn, R^1=Et, R^2=H; **f**: Z=Bn, R^1=R^2=Et
4a: Z=Bn, R^1=R^2=Me; **b**: Z=Bn, R^1=Et, R^2=Me; **c**: Z=Bn, R^1=Bn, R^2=Me; **d**: Z=R^1=R^2=Me; **e**: Z=Bn, R^1=Et, R^2=H; **f**: Z=Bn, R^1=R^2=Et

Scheme 1. Reagents: (i) catalyst (10–20 mol %), $MeNO_2$; (ii) $NaBH_4$, MeOH.

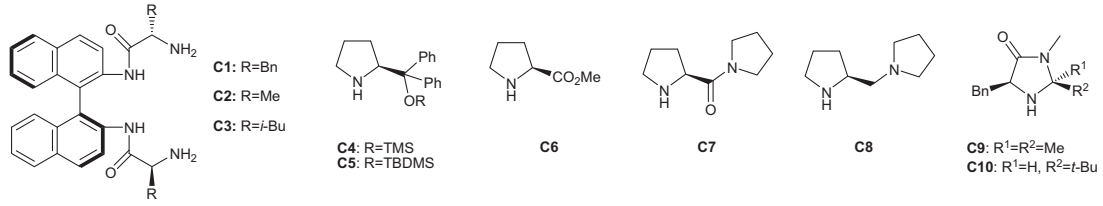


Chart 1.

Table 1
The results of the reaction of nitrones **1a–d** with (*E*)-crotonaldehydes **2a–c**, catalyzed by hybrid diamines **C1–C3**[a]

Entry	Catalyst	Nitrone	Aldehyde	Time (h)	Yield of **3**[b] (%)	ee[c] (%)
1	**C1***TfOH	**1a**	**2b**	72	75	47
2	**C1***TfOH	**1b**	**2b**	72	81	53[d]
3	**C1***TfOH	**1c**	**2b**	72	81	35
4	**C1***TfOH	**1d**	**2b**	72	52	41
5	**C2***TfOH	**1b**	**2b**	72	44	45
6	**C3***TfOH	**1b**	**2b**	72	36	47
7	**C1***TfOH	**1b**	**2c**	168	60	17
8	**C1***TfOH	**1b**	**2a**	80	—[e]	45

[a] Reaction conditions: **1** (0.25 mmol), **2** (1 mmol, then 0.75 mmol after every 24 h), catalyst [0.025 mmol for (*E*)-crotonaldehyde, 0.05 for other dipolarophiles], acid co-catalyst [0.0225 mmol, for (*E*)-crotonaldehyde, 0.045 for other dipolarophiles], $MeNO_2$ (1 ml), H_2O (0.75 mmol), 4 °C.
[b] Isolated yield after flash chromatography.
[c] Determined by chiral HPLC analysis of the corresponding alcohol **4**.
[d] 42% ee with *p*-TsOH as the co-catalyst.
[e] An inseparable mixture of products was obtained.

(80 h, 4 °C) led to a mixture of products, among which the 3,4-*trans*-isoxazolidine **3e** was identified after reduction to the corresponding alcohol **4e**, and its enantioselectivity estimated by HPLC as being up to 45% ee (Table 1, entry 8). Among the other dipolarophiles, cinnamaldehyde or methyl oxobutenoate were not reactive.

Although good yields of the single diastereomeric products were obtained, our catalysts were not efficient enough in the case of ketonitrones as dipoles. Therefore, we decided to investigate the reaction with other catalysts, that were successfully applied for the 1,3-dipolar cycloaddition of nitrones with acyclic dipolarophiles. Among the most efficient and readily available are the diphenyl prolinol silyl ether **C4** triflic acid salt, developed by Nevalainen[3e] and MacMillan's imidazolidinones of type **C6** and **C7** (Chart 1).[9]

We obtained the L-prolinol-derivative **C4**·TfOH according to the described procedure.[3e] When we performed the reaction of ethyl pyruvate-derived nitrone **1b** with (*E*)-crotonaldehyde **2b** in toluene or wet nitromethane at 20 °C, only trace amounts of product formation were observed. In wet nitromethane at 4 °C, the conversion of the nitrone levelled up to 40%, and the enantioselectivity of the corresponding alcohol **4b** was determined to be 85% ee. However, this result was not reproducible, which may be attributed to catalyst deactivation by the silyl ether hydrolysis under the conditions used.[10] Therefore, we turned our attention to more stable catalysts.

We replaced the TMS moiety with a larger and less sensitive TBDMS group of the organocatalyst **C5**.[11] However, this catalyst was also unstable under our conditions, when strong acid cocatalysts (TfOH or *p*-TsOH) were used. However, when we conducted the reaction at room temperature for 3 days in the presence of 10 mol % of TFA salt of **C5**, we were able to isolate 33% of **3b**, with 81% ee. Other pyrrolidine derivatives **C6–C8** were less successful, and we obtained products **3b** in only moderate ee (28% ee for both **C6** and **C7** and 40% ee for **C8**).

Previously, we have shown that the imidazolidinone hydrochloride salt **C9**∗HCl was not an efficient catalyst for the reaction of glyoxylate-derived nitrones.[5] When we applied this catalyst for the model reaction of nitrone **1b** with (*E*)-crotonaldehyde **2b**, we found that after 22 h the isolated yield of **3b** was 43%, while the enantioselectivity was high even at 20 °C (43%, 89% ee, respectively). Other experiments revealed that among the salts tested, similar results could be obtained with some other salts (H_2SO_4, Table 2, entry 4 or with *p*-TsOH, entry 8). The results of the experiments with the use of different salts of **C9** are summarized in Table 2.

Analysis of the crude reaction mixtures revealed the presence of large amounts of ethyl pyruvate, as an outcome of the hydrolysis of nitrone, in addition to other side-products, which resulted in a decrease in the yield of isoxazolidine **3b**. It is noteworthy that only small amounts of these side-products were detected when the hybrid primary diamines **C1–C3** were used as catalysts. We decided to continue our experiments with the commercially available catalyst **C9**·HCl. The results are summarized in Table 3.

The highest yields and ee's were determined for nitrone **1b** (43%, 89% ee, Table 2, entry 1). For nitrones **1a** and **1c**, 60–70% conversions were obtained after 24 h at 20 °C, and the ee values were determined to be 86% and 82%, respectively. The optimal value of the catalyst was 10 mol % (entries 1–3). We found that decreasing the temperature led to slightly enhanced enantioselectivities with similar yields, albeit with prolonged reaction times (entry 2). The presence of water is required for high conversions and enantioselectivities (entries 1, 2 as compared with entries 4,5). We also observed a decrease in the enantioselectivity, when the reaction was performed in the absence of water for a prolonged time (entry 5). This may be attributed to the reversibility of the 1,3-dipolar cycloaddition reaction in the presence of the imidazolidinone catalyst, as shown recently by Tomkinson for the same catalysis of the Diels–Alder reaction.[12] Experiments with other solvents (CH_2Cl_2,

Table 2
The results of the reaction of nitrone **1b** with (*E*)-crotonaldehyde **2b**, catalyzed by the different salts of **C9**[a]

Entry	Acid co-catalyst	Conversion of **1b**[b] (%)	Isolated yield of **3b**[c] (%)	ee[d] (%)
1	HCl	>90	43	89
2	TfOH	>60	—	58
3	$HClO_4$	>70	—	56
4	H_2SO_4	>90	34	91
5	CH_2ClCO_2H	>40	—	67
6	$CHCl_2CO_2H$	>70	—	89
7	CCl_3CO_2H	>40	—	86
8	*p*-TsOH	>70	—	86[e]
9	HBr	>60	—	64

[a] Reaction conditions: **1** (0.25 mmol), **2b** (1 mmol, then 0.75 mmol after every 24 h), catalyst salt (0.025 mmol), $MeNO_2$ (1 ml), H_2O (0.75 mmol), 22 h, 20 °C.
[b] Determined after ^1H NMR integration.
[c] Isolated yield after flash chromatography. Due to the similar R_f values of product **3b** with nitrone **1b**, which led to difficulties in its purification, the yield was determined for conversions higher than 90%.
[d] Determined by chiral HPLC analysis of the alcohol **4b**.
[e] 44% yield and 83% ee for the reaction conducted at 4 °C for 68 h in the presence of 20 mol % of the catalyst.

Table 3
The results of the reaction of nitrone **1b** with (*E*)-crotonaldehyde **2b**, catalyzed by the hydrochloride salt of **C9**[a]

Entry	Time (h)	Temp (°C)	Conversion of **1b**[b] (%)	Isolated yield of **3b**[c] (%)	ee[d] (%)
1	22	20	>90	43	89
2	69	4	>90	45	92
3	48	20	60	—	79[e]
4	22	20	60	—	79[f]
5	94	20	50	—	69[f]

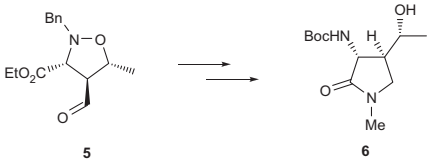
[a] Reaction conditions: **1** (0.25 mmol), **2b** (1 mmol, then 0.75 mmol after every 24 h), **C9**·HCl (0.025 mmol), acid cocatalyst (0.0225 mmol), $MeNO_2$ (1 ml), H_2O (0.75 mmol).
[b] Determined after ^1H NMR integration.
[c] Isolated yield after flash chromatography. Due to the similar R_f values of product **3b** with nitrone **1b**, which led to difficulties in its purification, the yield was determined for conversions higher than 90%.
[d] Determined by chiral HPLC analysis of the alcohol **4b**.
[e] Reaction conducted in the presence of 5 mol % catalyst.
[f] Reaction conducted in anhydrous solvent.

THF, CH_3CN, EtOAc and DMF) instead of nitromethane were unsuccessful.

Next, we performed several experiments with the second generation MacMillan's imidazolidinone **C10**, which was previously shown to be more efficient for many reactions of enals, especially those involving sterically encumbered substrates, by an increased formation rate of the iminium ion intermediate.[9] In our case, we obtained both lower conversions and ee's (both values in the range of 50–60%). The **C10** *trans*-isomer did not promote the reaction, but instead the nearly quantitative hydrolysis of nitrone **1b** was observed. With an increased amount of catalyst **C10** (20 mol %), high conversion was achieved at 20 °C after 24 h, and the product was isolated in a 50% yield with a moderate enantiomeric excess of 54%. Therefore, we did not investigate this catalyst further.

For synthetic purposes, we performed experiments with nitrone **1b** and (*E*)-crotonaldehyde **2b** on a larger (2 mmol) scale with imidazolidinone **C9** hydrochloride salt as the catalyst. However, we found that scaling up the reaction resulted in a further decrease of the yield, with product **3b** being isolated in 18–22% yield. A decrease in the ee was also observed (84% ee as compared with 89% ee for 0.25 mmol scale, see Table 3, entry 1). This is also due to the sensitivity of nitrone, since the use of such substrates often influences the reaction progress, when performed on a preparative scale.

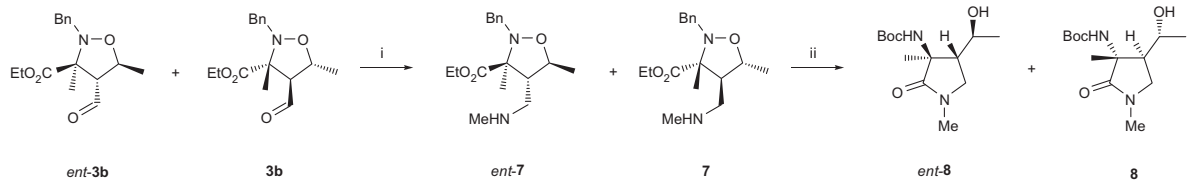
As mentioned earlier, we previously described the preparation of cycloadducts of type **5** (Scheme 2), from the reaction of glyoxylate-derived nitrones with *E*-crotonaldehyde, catalyzed by hybrid diamine **C1**.[5] Their (3*R*,4*S*,5*R*) configuration was unambiguously determined from X-ray crystallographic analysis of the corresponding tosylohydrazones and also confirmed by similar analysis of the derived lactam **6** (Scheme 2).[5] These compounds differ from **3** only at the stereogenic center at C-3, but the relative configuration of all centers, 3,4-*trans*,4,5-*trans*, is retained. In case of products **3**, we were unable to prepare their crystalline derivatives, suitable for similar analysis. However, the functionalized 2-pyrrolidinone *ent*-**8** was prepared according to our described procedure[5] from the obtained cycloadduct *ent*-**3b** (84% ee) (Scheme 3). The relative configuration of compound *ent*-**8** was confirmed by X-ray crystallographic analysis (Fig. 1).[13] As described previously in the synthesis of **6**,[5] no change in the stereochemistry was observed during this transformation. Therefore, we assumed that the configuration of the products of type **3** was also (3*R*,4*S*,5*R*).



Scheme 2. Transformation of the glyoxylate-derived cycloadduct **5** into **6**.[5]

3. Conclusion

We have reported the first enantioselective organocatalytic 1,3-dipolar cycloaddition of ketonitrones to α,β-unsaturated aldehydes, leading to products containing a quaternary stereocenter.



Scheme 3. Reagents and conditions: (i) $MeNH_2$/EtOH, $NaBH_3CN$, AcOH, MeOH, 2 h, rt, 50%; H_2, Pd/C, $Pd(OH)_2$/C, MeOH, 120 h, rt, then Boc_2O, Et_3N, 24 h, rt, 29%.

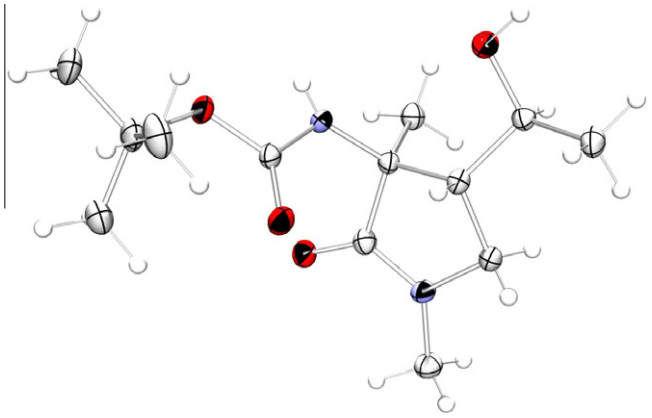


Figure 1. ORTEP projection of the N–Me pyrrolidinone *ent*-**8**.

Although it is possible to obtain high level of asymmetric induction with commercially available organocatalysts (up to 92% ee), the reaction yields are not satisfactory. Hybrid catalysts, developed by us, led only to products with low to moderate enantioselectivity, but the nitrones were stable in their presence, which resulted in good yields of the products. These results show that the solution of the problem possibly lies in the careful optimization of the catalyst's structure which paves the way for further investigation of this reaction. Although the nitrone scope as demonstrated is limited to pyruvic acid derivatives, examples of the reaction with three various dipolarophiles were shown. Moreover, the possibility of transformation of the obtained cycloadduct into a functionalized γ-lactam, containing a quaternary stereogenic center was successfully demonstrated.

4. Experimental section

4.1. General information

Commercially available chemicals were used as received, unless otherwise indicated. THF was dried over sodium in the presence of benzophenone and nitromethane was distilled over CaH_2. Crotonaldehyde, acrolein, and pentenal were freshly distilled before use. (*S*)-1,1′-Binaphthyl-2,2′-diamine [(*S*)-BINAM],[14] *N*-benzylhydroxylamine hydrochloride,[15] benzyl pyruvate,[16] ethyl 3-methyl-2-oxobutyrate,[17] and methyl oxobutenoate[18] were prepared according to the literature procedures. Nitrones were prepared from the corresponding α-ketoesters and *N*-alkylhydroxylamines according to the described procedure.[8] Catalysts **C4**·TfOH,[3e] **C5**,[11] **C6**·HCl,[19] **C7,** and **C8**·2HCl[20] were prepared according to the literature procedures. Analytical TLC was carried out on commercial 0.25 mm plates coated with 0.25 mm of Merck Kieselgel 60 F_{254}. Preparative flash silica chromatography was performed using Merck Kieselgel 60 (230–400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 20 °C. All melting points were measured on a Köfler Boëtius apparatus. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Varian Unity plus spectrometer (200 MHz and 50 MHz, respectively). Chemical shifts of the ^1H NMR and ^{13}C NMR are reported as δ values relative to TMS as the internal standards. The following abbreviations are used to indicate the multiplicity: s—singlet; d—doublet; t—triplet; q—quartet; m—multiplet; b—broad signal. Mass spectra (LRMS and HRMS) were recorded on a Quattro LC Micromass instrument using the ESI technique. Enantiomeric ratios of the products were determined using an HPLC method. HPLC analysis was performed on a Knauer Smartline series HPLC fitted with the diode-array detector (DAD) and Chiracel® AS-H (250 × 4.6 mm, 5 μm) column eluted with 2-propanol (3–5%) in hexane.

4.2. General procedure for synthesis of catalysts C1–C3

To the solution of *N*-Cbz or *N*-Boc protected α-amino acid (7.74 mmol, 2.2 equiv) in dry THF (40 ml), Et_3N (1.08 ml, 7.74 mmol; 2.2 equiv) was added and the mixture was cooled to 0 °C. A solution of ethyl chloroformate (0.74 ml, 7.74 mmol, 2.2 equiv) in dry THF (5 ml) was added over 15 min and the mixture was stirred for 30 min at the same temperature. Then a solution of (*S*)-BINAM (1 g; 3.52 mmol; 1 equiv) in dry THF (50 ml) was added over 15 min at 0 °C and the mixture was stirred overnight with warming up. The reaction mixture was subsequently refluxed for 3 h and after cooling, the precipitate of Et_3N·HCl was filtered off and washed with THF. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to afford the catalyst precursor in 60% (from *N*-Cbz-Phe-OH), 80% (from *N*-Boc-Ala-OH), and 42% (from *N*-Boc-Leu-OH) yields. Cbz protecting group was removed by catalytic hydrogenation (balloon) in MeOH over 48 h in the presence of Pd/C. After filtration of the catalyst and evaporation of the solvent, pure **C1** was obtained in a 92% yield as a colorless foam. The Boc protecting group was removed by stirring the compounds in a 1:1 mixture of CH_2Cl_2/TFA (20–30 equiv) for several hours. After dilution with water and extraction of the impurities with an organic solvent, which was discarded, the remaining mixture was alkalized with 20% NaOH and extracted three times with CH_2Cl_2. The combined extracts were dried over $MgSO_4$. After evaporation of the solvent, pure products **C2**–**C3** were obtained in 74–85% yield as colorless foams.

4.2.1. (2*S*,2′*S*)-*N*,*N*′-((*S*)-1,1′-Binaphthyl-2,2′-diyl)bis(2-amino-3-phenylpropanamide) C1

Colorless foam. $[\alpha]_D = -129$ (*c* 0.7, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): $\delta = 9.24$ (br s, 2H, ArN*H*), 8.42–7.93 (m, 6H, Ar*H*), 7.50–7.02 (m, 16H, Ar*H*), 3.51–3.49 (AB/2, $J = 3.6$, 2H, CH_2), 3.46–3.44 (AB/2, $J = 3.6$, 2H, CH_2), 3.20–3.18 (AB/2, $J = 3.6$, 2H, CH_2), 3.13–3.11 (AB/2, $J = 3.6$, 2H, CH_2), 2.37–2.25 (m, 2H, $C_\alpha H$), 1.18 (b, 4H, NH_2). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 173.7$, 137.6, 134.9, 132.8, 131.4, 129.6, 129.2, 128.8, 128.5, 127.1, 127.0, 125.8, 125.4, 122.1, 121.4, 57.0, 40.5. LR ESI-MS: *m*/*z*: 579.3 for $[M+H]^+$, 601.3 for $[M+Na]^+$. HR ESI-MS: *m*/*z*: calcd for $[C_{38}H_{34}N_4O_2+H]^+$: 579.2760, found: 579.2758.

4.2.2. (2*S*,2′*S*)-*N*,*N*′-((*S*)-1,1′-Binaphthyl-2,2′-diyl)bis(2-aminopropanamide) C2

Colorless powder, mp 166–168 °C (CH_2Cl_2). $[\alpha]_D = -39.0$ (*c* 0.7, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.22 (br s, 2H, ArN*H*), 8.44–7.92 (m, 6H, Ar*H*), 7.48–7.15 (m, 6H, Ar*H*), 3.38–3.28 (q, *J* = 7, 2H, C$_\alpha$*H*), 1.14–1.10 (d, *J* = 7, 10H, overlapped C*H*$_3$ and N*H*$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.0, 135.0, 132.8, 131.3, 129.6, 128.5, 127.0, 125.8, 125.4, 122.0, 121.2, 51.3, 21.3. LR ESI-MS: *m*/*z*: 427.2 for $[M+H]^+$, 449.2 for $[M+H]^+$. HR ESI-MS: *m*/*z*: calcd for $[C_{26}H_{26}N_4O_2+H]^+$: 427.2134, found: 427.2134; calcd for $[C_{26}H_{26}N_4O_2+Na]^+$: 449.1953, found: 449.1960.

4.2.3. (2*S*,2′*S*)-*N*,*N*′-((*S*)-1,1′-Binaphthyl-2,2′-diyl)bis(2-amino-4-methylpentanamide) C3

Colorless foam. $[\alpha]_D = -23.0$ (*c* 0.7, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.26 (br s, 2H, ArN*H*), 8.43–7.92 (m, 6H, Ar*H*), 7.48–7.15 (m, 6H, Ar*H*), 3.30–3.28 (AB/2, *J* = 3.8, 2H, C$_\alpha$*H*), 3.25–3.23 (AB/2, *J* = 3.8, 2H, C$_\alpha$*H*), 1.52–1.50 (AB/2, *J* = 3.4, 2H, C*H*$_2$), 1.48–1.46 (AB/2, *J* = 3.4, 2H, C*H*$_2$), 1.14–1.09 (m, 2H, C*H*(CH$_3$)$_2$), 0.86–0.84 (d, *J* = 6, 6H, C*H*$_3$), 0.83–0.81 (d, *J* = 6, 6H, C*H*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.0, 135.0, 132.9, 131.3, 129.5, 128.5, 127.0, 125.8, 125.3, 122.1, 121.2, 54.1, 43.8, 25.0, 23.5, 21.5. LR ESI-MS: *m*/*z*: 511.3 for $[M+H]^+$, 533.3 for $[M+Na]^+$. HR ESI-MS: *m*/*z*: calcd for $[C_{32}H_{38}N_4O_2+H]^+$: 511.3073, found: 511.3072; calcd for $[C_{32}H_{38}N_4O_2+Na]^+$: 533.2892, found: 533.2892.

4.3. Nitrones 1a–d

4.4.1. (*E*)-*N*-(1-Methoxy-1-oxopropan-2-ylidene)(phenyl)methanamine oxide 1a

On a 10 mmol scale from methyl pyruvate and *N*-benzylhydroxylamine hydrochloride, after purification by flash chromatography (AcOEt/hexane 15%), a colorless oil was obtained (1.5 g, 77%). The spectroscopic data were identical to the literature.[8]

4.4.2. (*E*)-*N*-(1-Ethoxy-1-oxopropan-2-ylidene)(phenyl)methanamine oxide 1b

On a 6 mmol scale from ethyl pyruvate and *N*-benzylhydroxylamine hydrochloride, after purification by flash chromatography (AcOEt/hexane 15%), a colorless oil was obtained (1.25 g, 87%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.52–7.48 (m, 2H, Ar*H*), 7.35–7.32 (m, 3H, Ar*H*), 5.69 (*s*, 2H, NC*H*$_2$Ph), 4.33–4.23 (q, *J* = 7, 2H, OC*H*$_2$CH$_3$), 2.25 (*s*, 3H, C*H*$_3$), 1.36–1.29 (t, *J* = 7, 3H, OCH$_2$C*H*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.7 (C=O), 134.3 (Cq), 129.1 (CH), 128.7 (CH), 128.6 (CH), 67.3 (NCH_2), 62.1 (OCH_2), 15.5 (CH_3), 14.3 (CH_3).

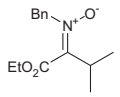
4.4.3. (*E*)-*N*-(1-Benzyloxy-1-oxopropan-2-ylidene)(phenyl)methanamine oxide 1c

On a 10 mmol scale from benzyl pyruvate and *N*-benzylhydroxylamine hydrochloride, after purification by flash chromatography (AcOEt/hexane 15%), a colorless oil was obtained, that solidified upon standing in the refrigerator (1.6 g, 60%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.49–7.44 (m, 2H, Ar*H*), 7.38–7.30 (m, 8H, Ar*H*), 5.69 (s, 2H, NC*H*$_2$Ph), 5.25 (s, 2H, OC*H*$_2$), 2.26 (s, 3H, C*H*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.5 (C=O), 135.2 (Cq), 134.2 (Cq), 129.2 (CH), 128.9 (CH), 128.84 (CH), 128.76 (CH), 128.7 (CH), 128.5 (CH), 67.7 (CH_2), 67.4 (CH_2), 15.6 (CH_3).

4.4.4. (*E*)-*N*-(1-Methoxy-1-oxopropan-2-ylidene)methanamine oxide 1d

On 7 mmol scale methyl pyruvate and *N*-methylhydroxylamine hydrochloride, after purification by flash chromatography (AcOEt/hexane 15%) colorless oil was obtained (0.5 g, 53%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.19 (*s*, 2H, NC*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 2.25 (*s*, 3H, C*H*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 163.2 (C=O), 53.5 (CH_3), 52.8 (CH_3), 15.1 (CH_3).

4.4.5. (*E*)-*N*-(1-Ethoxy-3-methyl-1-oxobutan-2-ylidene)(phenyl)methanamine oxide (*i*-Pr nitrone)



On a 5 mmol scale from ethyl 3-methyl-2-oxobutyrate and *N*-benzylhydroxylamine hydrochloride, after purification by flash chromatography (AcOEt/hexane 10%), a colorless oil was obtained (0.4 g, 32%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.43–7.32 (m, 5H, Ar*H*), 5.24 (s, 2H, NC*H*$_2$), 4.35–4.24 (q, *J* = 7, 2H, OC*H*$_2$CH$_3$), 3.61–3.48 (septet, *J* = 7, 1H, C*H*), 1.35–1.28 (t, *J* = 7, 3H, OCH$_2$C*H*$_3$), 1.18–1.14 (d, *J* = 7, 6H, CH(C*H*$_3$)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 163.7 (C=O), 133.8 (Cq), 128.8 (CH), 128.7 (CH), 67.3 (NCH_2), 62.2 (OCH_2), 28.1 (CH), 17.9 (2xCH_3), 14.2 (CH_3).

4.5. General procedure for the 1,3-dipolar cycloaddition

A solution of nitrone **1** (0.25 mmol, 1 equiv) in nitromethane (1 mL) was placed in a vial, water (13 μl, 0.75 mmol, 3 equiv) and the catalyst (0.025 mmol, 0.1 equiv) were added and the resulting mixture stirred at the indicated temperature for few minutes. Next, freshly distilled dipolarophile was added (1 mmol, 4 equiv, followed by 3 equiv after every 24 h) and the mixture was left to stir for the indicated time, after which it was filtered through a silica gel plug rinsing with EtOAc, and concentrated. The crude mixture was subjected to ^{1}H NMR analysis for determination of the conversion of nitrone. After flash chromatography on silica gel (15–30% EtOAc-hexane), product **3** was isolated as an oil in 34–81% yield.

4.5.1. (3*R*,4*S*,5*R*)-2-Benzyl-4-formyl-3-methoxycarbonyl-3,5-dimethylisoxazolidine 3a

Colorless oil, $[\alpha]_D = -42.1$ (*c* 1, CH_2Cl_2) for 47% ee. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.84–9.82 (d, *J* = 3, 1H, C*H*O), 7.36–7.32 (m, 5H, Ar*H*), 4.56–4.44 (dq, J_1 = 6.2, J_2 = 12.4, 1H, NOC*H*CH$_3$), 4.00–3.93 (d, *J* = 14.4, 1H, NC*H*$_2$Ph), 3.86–3.77 (d, *J* = 14.4, 1H, NC*H*$_2$Ph), 3.82 (s, 3H, OC*H*$_3$), 3.51–3.47 (dd, J_1 = 3, J_2 = 6.4, 1H, C*H*CHO), 1.48 (s, 3H, OC*H*$_3$), 1.35–1.32 (d, *J* = 6, 3H, NOCHC*H*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.1 (CHO), 172.0 (C=O), 137.8 (Cq), 128.5 (CH), 128.4 (CH), 127.4 (CH), 72.42 (NOCH), 72.36 (Cq), 66.6 (*C*HCHO), 55.2 (NC*H*$_2$Ph), 52.8 (OCH_3), 18.7 (CH_3), 16.8 (CH_3). LR ESI-MS: *m*/*z*: 300.1 for $[M+Na]^+$, 332.1 for $[M+MeOH+Na]^+$. HR ESI-MS: *m*/*z*: calcd for $[C_{16}H_{23}NO_5+Na]^+$: 332.1474, found: 332.1438.

4.5.2. (3*R*,4*S*,5*R*)-2-Benzyl-3-ethoxycarbonyl-4-formyl-3,5-dimethylisoxazolidine 3b

Colorless oil, $[\alpha]_D = -48.9$ (*c* 1, CH_2Cl_2) for 53% ee. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.83–9.81 (d, *J* = 3, 1H, C*H*O), 7.39–7.24 (m, 5H, Ar*H*), 4.56–4.44 (dq, J_1 = 6.2, J_2 = 12.4, 1H, NOC*H*CH$_3$), 4.34–4.23 (q, *J* = 7, 2H, OC*H*$_2$CH$_3$), 4.02–3.94 (d, *J* = 14.4, 1H, NC*H*$_2$Ph), 3.89–3.82 (d, *J* = 14.4, 1H, NC*H*$_2$Ph), 3.51–3.47 (dd, J_1 = 3, J_2 = 6.4, 1H, C*H*CHO), 1.48 (s, 3H, C*H*$_3$), 1.38–1.32 (m, 6H, overlapped NOCHC*H*$_3$ and OCH$_2$C*H*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.2 (CHO), 171.4 (C=O), 137.9 (Cq), 128.5 (CH), 128.4 (CH), 127.4 (CH), 72.4 (NOCH), 72.2 (Cq), 66.6 (*C*HCHO), 62.0 (OCH_2), 55.2 (NC*H*$_2$Ph), 18.7 (CH_3), 16.7 (CH_3), 14.7 (OCH$_2$C*H*$_3$). LR ESI-MS: *m*/*z*: 346.2 for $[M+MeOH+Na]^+$. HR ESI-MS: *m*/*z*: calcd for $[C_{17}H_{25}NO_5+Na]^+$: 346.1630, found: 346.1596.

4.5.3. (3*R*,4*S*,5*R*)-2-Benzyl-3-benzyloxycarbonyl-4-formyl-3,5-dimethylisoxazolidine 3c

Colorless oil, $[\alpha]_D = -33.4$ (*c* 1, CH_2Cl_2) for 35% ee. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.80–9.79 (d, *J* = 3, 1H, C*H*O), 7.38–7.25 (m,

10H, Ar*H*), 5.25 (s, 2H, OCH_2Ph), 4.54–4.42 (dq, J_1 = 6.2, J_2 = 12.4, 1H, NOC*H*CH_3), 3.98–3.91 (d, J = 14.4, 1H, NCH_2Ph), 3.83–3.76 (d, J = 14.4, 1H, NCH_2Ph), 3.50–3.45 (dd, J_1 = 3, J_2 = 6.4, 1H, C*H*CHO), 1.48 (s, 3H, CH_3), 1.31–1.28 (d, J = 6, 3H, NOCHCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.1 (CHO), 171.3 (C=O), 137.9 (Cq), 135.4 (Cq), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.4 (CH), 72.4 (NOCH), 72.3 (Cq), 67.7 (OCH_2Ph), 66.5 (*CH*CHO), 55.2 (NCH_2Ph), 18.6 (CH_3), 16.8 (CH_3). LR ESI-MS: m/z: 408.2 for $[M+MeOH+Na]^+$. HR ESI-MS: m/z: calcd for $[C_{22}H_{27}NO_5+Na]^+$: 408.1787, found: 408.1798.

4.5.4. (3*R*,4*S*,5*R*)-4-Formyl-3-methoxycarbonyl-2,3,5-trimethylisoxazolidine 3d

Colorless oil, $[\alpha]_D$ = −36.0 (c 1.5, CH_2Cl_2) for 41% ee. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.82–9.81 (d, J = 3, 1H, C*H*O), 4.67–4.54 (dq, J_1 = 6.2, J_2 = 12.4, 1H, NOC*H*CH_3), 3.82 (s, 3H, OCH_3), 3.57–3.53 (dd, J_1 = 2.4, J_2 = 6.6, 1H, C*H*CHO), 2.63 (s, 3H, NCH_3), 1.42 (s, 3H, CH_3), 1.37–1.32 (d, J = 6.2, 3H, NOCHCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.0 (CHO), 172.3 (C=O), 72.6 (NOCH), 66.1 (*CH*CHO), 53.0 (OCH_3), 38.8 (NCH_3), 18.8 (CH_3), 16.4 (CH_3).

4.5.5. (3*R*,4*S*,5*R*)-2-Benzyl-3-ethoxycarbonyl-5-ethyl-4-formyl-3-methylisoxazolidine 3f

Colorless oil, $[\alpha]_D$ = +7.9 (c = 1.1, CH_2Cl_2) for 17% ee. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.83–9.82 (d, J = 2.6, 1H, C*H*O), 7.39–7.24 (m, 5H, Ar*H*), 4.35–4.22 (m, 3H, overlapped OC$H_2$$CH_3$ and NOC*H*$CH_2$$CH_3$), 3.94 (s, 2H, NC$H_2$Ph), 3.56–3.52 (dd, J_1 = 3, J_2 = 6.2, 1H, C*H*CHO), 1.80–1.54 (m, 2H, NOCHC$H_2$$CH_3$), 1.46 (s, 3H, C$H_3$), 1.37–1.30 (t, J = 7, 3H, OCH$_2$CH_3), 0.92–0.84 (t, J = 7.4, 3H, NOCH-CH$_2$CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.2 (CHO), 171.5 (C=O), 138.0 (Cq), 128.5 (CH), 128.4 (CH), 127.3 (CH), 77.5 (NOCH), 72.1 (Cq), 65.2 (*CH*CHO), 62.0 (OCH_2), 55.2 (NCH_2Ph), 26.6 (NOCH*CH*$_2$$CH_3$), 16.3 ($CH_3$), 14.4 ($CH_3$), 10.3 ($CH_3$).

4.6. General procedure for reduction of the 1,3-dipolar cycloaddition products

Products **3** were reduced to the corresponding alcohols **4** with 1 equiv of $NaBH_4$ in MeOH at 0 °C for 30 min. After aqueous work-up, alcohols **4** were purified by flash chromatography on silica gel (30–40% EtOAc–hexane) and isolated in 60–70% yield. The ee values of the alcohols were determined by chiral HPLC. In the case of product **3d**, the ee was determined from the corresponding **4d**-tosylate, after reduction to alcohol **4d** and its subsequent tosylation (TsCl, Et_3N, CH_2Cl_2, rt, overnight, then purification by chromatography on silica gel).

4.6.1. (3*R*,4*R*,5*R*)-2-Benzyl-4-hydroxymethyl-3-methoxycarbonyl-3,5-dimethylisoxazolidine 4a

Colorless oil, $[\alpha]_D$ = −42.6 (c 1, CH_2Cl_2) for 47% ee. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 5H, Ar*H*), 3.93–3.91 (d, J = 3.8, 2H, CH_2OH), 3.87–3.84 (m, 1H, NOC*H*CH_3), 3.77 (br s, 5H, overlapped NCH_2Ph and OCH_3), 2.68–2.55 (dt, J_1 = 6.4, J_2 = 12.8, 1H, C*H*CH$_2$OH), 2.2 (br s, 1H, O*H*), 1.44 (s, 3H, CH_3), 1.36–1.33 (d, J = 6.2, 3H, NOCHCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.0 (C=O), 138.4 (Cq), 128.4 (CH), 127.2 (CH), 76.1 (NOCH), 71.7 (Cq), 61.8 (CH_2OH), 57.1 (*CH*CH$_2$OH), 55.4 (NCH_2Ph), 52.4 (OCH_3), 19.6 (CH_3), 15.0 (OCH_3). HPLC conditions: DAICEL CHIRALPAK® AS-H, 2-propanol/hexane 3%, 1 ml/min., 35 °C, UV 215 nm, t_{minor} = 15.4 min., t_{major} = 18.1 min. (major for **C1** and **C9**).

4.6.2. (3*R*,4*R*,5*R*)-2-Benzyl-3-ethoxycarbonyl-4-hydroxymethyl-3,5-dimethylisoxazolidine 4b

Colorless oil, $[\alpha]_D$ = −46.9 (c 1.05, CH_2Cl_2) for 47% ee, $[\alpha]_D$ = −59.1° (c = 0.85, $CHCl_3$) for 88% ee. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 5H, Ar*H*), 4.29–4.18 (q, J = 7, 2H, OC$H_2$$CH_3$), 3.94 (s, 2H, NC$H_2$Ph), 3.90–3.83 (m, 1H, NOC*H*CH_3), 3.80–3.67 (m, 2H, CH_2OH), 2.87–2.77 (dt, J_1 = 6.6, J_2 = 13.2, 1H, C*H*CH$_2$OH), 2.4 (br s, 1H, O*H*), 1.43 (s, 3H, CH_3), 1.35–1.28 (m, 6H, overlapped NOCHCH_3 and OCH$_2$CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.2 (C=O), 138.5 (Cq), 128.4 (CH), 127.2 (CH), 76.1 (NOCH), 71.6 (Cq), 61.8 (CH_2), 61.6 (CH_2), 56.9 (*CH*CH$_2$OH), 55.4 (NCH_2Ph), 19.6 (CH_3), 15.0 (CH_3), 14.4 (CH_3). HPLC conditions: DAICEL CHIRALPAK® AS-H, 2-propanol/hexane 3%, 1 ml/min., 35 °C, UV 215 nm, t_{minor} = 12.0 min., t_{major} = 15.4 min. (major for **C1**–**C5** and **C8**–**C10**).

4.6.3. (3*R*,4*R*,5*R*)-2-Benzyl-3-benzyloxycarbonyl-4-hydroxymethyl-3,5-dimethylisoxazolidine 4c

Colorless oil, $[\alpha]_D$ = −30.7 (c 1.35, CH_2Cl_2) for 35% ee. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 10H, Ar*H*), 5.21 (s, OCH_2Ph), 3.98–3.91 (d, J = 14.6, 1H, NCH_2Ph), 3.92–3.80 (m, 1H, NOC*H*CH_3), 3.89–3.82 (d, J = 14.6, 1H, NCH_2Ph), 3.80–3.67 (m, 2H, CH_2OH), 2.88–2.78 (dt, J_1 = 6.2, J_2 = 12.4, 1H, C*H*CH$_2$OH), 2.2 (br s, 1H, O*H*), 1.44 (s, 3H, CH_3), 1.32–1.29 (d, 3H, NOCHCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.9 (C=O), 138.4 (Cq), 135.7 (Cq), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.2 (CH), 76.2 (NOCH), 71.7 (Cq), 67.2 (OCH_2Ph), 61.8 (*CH*$_2$OH), 57.0 (*CH*CH$_2$OH), 55.3 (NCH$_2$Ph), 19.5 (CH_3), 15.0 (CH_3). HPLC conditions: DAICEL CHIRALPAK® AS-H, 2-propanol/hexane 3%, 1 ml/min., 35 °C, UV 215 nm, t_{minor} = 17.5 min., t_{major} = 23.6 min. (major for **C1** and **C9**).

4.6.4. (3*R*,4*R*,5*R*)-2-Benzyl-3-methoxycarbonyl-3,5-dimethyl-4-tosyloxymethylisoxazolidine 4d-tosylate

Colorless oil, $[\alpha]_D$ = −27.0 (c 0.3, CH_2Cl_2) for 41% ee. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.81–7.77 (d, J = 8.2, 2H, Ar*H*), 7.39–7.35 (d, J = 8.2, 2H, Ar*H*), 4.20–4.12 (d, J_1 = 7, J_2 = 9.8, 1H, CH_2OTs), 4.03–3.94 (d, J_1 = 7.6, J_2 = 9.8, 1H, CH_2OTs), 3.77–3.71 (m, 1H, C*H*CH_3), 3.73 (s, 3H, OCH_3), 2.99–2.88 (dt, J_1 = 7.2, J_2 = 14.4, 1H, C*H*CH$_2$OTs), 2.56 (s, 3H, PhCH_3), 2.46 (s, 3H, NCH_3), 2.2 (br s, 1H, O*H*), 1.34–1.30 (d, J = 6.2, 3H, CHCH_3), 1.19 (*s*, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.0 (C=O), 145.4 (Cq), 132.7 (Cq), 130.2 (CH), 128.1 (CH), 76.5 (NOCH), 71.6 (Cq), 68.8 (CH_2OTs), 53.6 (*CH*CH$_2$OTs), 52.4 (OCH_3), 38.3 (NCH_3), 21.9 (CH_3), 18.8 (CH_3). HPLC conditions: DAICEL CHIRAL-PAK® AS-H, 2-propanol/hexane 5%, 1 ml/min., 35 °C, UV 215 nm, t_{major} = 19.2 min. (major for **C1**), t_{minor} = 21.8 min.

4.6.5. (3*R*,4*R*)-2-Benzyl-3-ethoxycarbonyl-4-hydroxymethyl-3-methylisoxazolidine 4e

Colorless oil, could not be purified, 45% ee. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 5H, Ar*H*), 4.30–4.19 (q, J = 7.2, 2H, OC$H_2$$CH_3$), 4.20–4.12 (dd, J_1 = 7.6, J_2 = 9, 1H, NOCH_2), 4.00–3.93 (d, J = 14.4, 1H, NCH_2Ph), 3.91–3.84 (d, J = 14.4, 1H, NCH_2Ph), 3.78–3.75 (d, J = 6.2, 2H, CH_2OH), 3.71–3.65 (dd, J_1 = 5.8, J_2 = 7.6, 1H, NOCH_2), 3.29–3.16 (m, 1H, C*H*CH$_2$OH), 2.7 (br s, 1H, O*H*), 1.48 (s, 3H, CH_3), 1.36–1.29 (t, J = 7, 3H, OCH$_2$CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.5 (C=O), 138.1 (Cq), 128.7 (CH), 128.5 (CH), 127.4 (CH), 71.0 (Cq), 68.5 ($NOCH_2$), 62.0 (CH_2), 61.8 (CH_2), 55.6 (NCH_2Ph), 50.1 (*CH*CH$_2$OH), 14.6 (CH_3), 14.4 (CH_3). LR ESI-MS: m/z: 302.1 for $[M+Na]^+$, 581.3 for $[2M+Na]^+$. HR ESI-MS: m/z: calcd for $[C_{15}H_{21}NO_4+Na]^+$: 302.1368, found: 330.1381. HPLC conditions: DAICEL CHIRALPAK® AS-H, 2-propanol/hexane 3%, 1 ml/min., 35 °C, UV 215 nm, t_{minor} = 20.7 min., t_{major} = 24.4 min. (major for **C1**).

4.6.6. (3*R*,4*R*,5*R*)-2-Benzyl-3-ethoxycarbonyl-5-ethyl-4-hydroxymethyl-3-methylisoxazolidine 4f

Colorless oil, $[\alpha]_D$ = +4.5 (c 2.15, CH_2Cl_2) for 17% ee. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5H, Ar*H*), 4.28–4.17 (q, J = 7,

2H, OCH_2CH_3), 4.07–4.00 (d, J = 14.4, 1H, NCH_2Ph), 3.96–3.88 (d, J = 14.4, 1H, NCH_2Ph), 3.80–3.58 (m, 3H, overlapped $NOCHCH_2CH_3$ and CH_2OH), 2.93–2.84 (m, 1H, $CHCH_2OH$), 2.4 (br s, 1H, O*H*), 1.78–1.55 (m, 2H, $NOCHCH_2CH_3$), 1.46 (s, 3H, CH_3), 1.35–1.28 (t, J = 7, 3H, OCH_2CH_3), 0.95–0.87 (t, J = 7.4, 3H, $NOCHCH_2CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.4 (C=O), 138.5 (Cq), 128.5 (CH), 128.4 (CH), 127.1 (CH), 80.8 (NOCH), 71.7 (Cq), 61.9 (CH_2), 61.7 (CH_2), 55.6 ($CHCH_2OH$), 55.2 (NCH_2Ph), 27.6 ($NOCHCH_2CH_3$), 14.36 (CH_3), 14.32 (CH_3), 10.7 (CH_3). LR ESI-MS: m/z: 330.2 for $[M+Na]^+$, 637.4 for $[2M+Na]^+$. HR ESI-MS: m/z: calcd for $[C_{17}H_{25}NO_4+Na]^+$: 330.1681, found: 330.1670. HPLC conditions: DAICEL CHIRALPAK® AS-H, 2-propanol/hexane 3%, 1 ml/min., 35 °C, UV 215 nm, t_{major} = 9.6 min. (major for **C1**), t_{minor} = 10.8 min.

4.6.7. (3*S*,4*R*,5*S*)-4-(Aminomethyl)methyl-2-benzyl-3-ethoxycarbonyl-3-methylisoxazolidine *ent*-7

To a solution of aldehyde *ent*-**3b** (84% ee, obtained with 10 mol % of *ent*-**C9**·HCl) (0.13 g, 0.45 mmol, 1 equiv) in 20 ml MeOH, an 8.0 M solution of $MeNH_2$/EtOH (1 ml, 15 equiv) was added, followed by 1.64 ml of AcOH, until the pH was acidic. Then $NaBH_3CN$ (28 mg, 1 equiv) was added in one portion and the solution was stirred for 2 h at rt. The mixture was then concentrated, poured into 30 ml aq. $NaHCO_3$ and the whole was extracted with 6x30 ml CH_2Cl_2; the combined extracts were dried over Na_2SO_4, the solids were filtered off, and the solvent was removed. The residual oil was purified by flash chromatography ($MeOH/CH_2Cl_2$ 2–5%), to yield 70 mg (50%) of amine *ent*-**7** as a slightly yellow oil of satisfactory purity. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.22 (m, 5H, Ar*H*), 4.26–4.15 (q, J = 7.2, 2H, OCH_2CH_3), 3.97–3.90 (d, J = 14.6, 1H, NCH_2Ph), 3.88–3.81 (d, J = 14.6, 1H, NCH_2Ph), 3.84–3.78 (m, 1H, $NOCHCH_3$), 2.79–2.76 (d, J = 6.4, 2H, CH_2NHCH_3), 2.73–2.63 (m, 1H, $CHCH_2NHCH_3$), 2.45 (s, 3H, $NHCH_3$), 1.37 (s, 3H, CH_3), 1.37–1.34 (d, J = 6.2, 3H, $NOCHCH_3$), 1.34–1.27 (t, J = 7.2, 3H, OCH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.9 (C=O), 138.6 (Cq), 128.4 (CH), 128.3 (CH), 127.1 (CH), 77.9 (NOCH), 71.7 (Cq), 61.3 (OCH_2), 55.4 (NCH_2Ph), 55.2 ($CHCH_2NHCH_3$), 51.9 ($CHCH_2NHCH_3$), 36.8 ($NHCH_3$), 20.0 (CH_3), 14.6 (CH_3), 14.4 (CH_3).

4.6.8. *tert*-Butyl (3*S*,4*R*,1′*S*)-[4-(1-hydroxyethyl)-1,3-dimethyl-2-oxopyrrolidin-3-yl]-carbamate *ent*-8

Amine *ent*-**7** (70 mg, 0.23 mmol, 1 equiv) was dissolved in 10 ml of MeOH, Pd/C and $Pd(OH)_2$/C were added under an argon atmosphere and the whole was stirred in an atmosphere of hydrogen (balloon) for 120 h at rt. The catalysts were filtered off, washed with methanol, and the filtrate was evaporated. The oil obtained was redissolved in MeOH (3 ml), after which Boc_2O (61 mg, 0.27 mmol, 1.2 equiv) and Et_3N (42 µl, 0.29 mmol, 1.3 equiv) were added and the whole mixture was stirred for 24 h at rt. The volatiles were then evaporated and the residue was purified by flash chromatography ($MeOH/CH_2Cl_2$ 3%), yielding 18 mg (29%) of γ-lactam *ent*-**8** as a colorless solid. Recrystallization from CH_2Cl_2/*n*-hexane afforded crystals (m.p. 173–175 °C), suitable for single crystal X-ray diffraction. $[\alpha]_D$ = +24.0 (*c* 0.85, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.41 (br s, 1H, N*H*), 5.00 (br s, 1H, O*H*), 3.98–3.84 (*m*, 1H, *CH*OH), 3.30–3.21 (m, 1H, CH_2), 2.89 (s, 3H, NCH_3, overlapped with m, 1H, CH_2, 2.89–2.80), 2.60–2.46 (m, 1H, C*H*), 1.43 (s, 9H, $C(CH_3)_3$), 1.42 (*S*, 3H, CH_3), 1.19–1.16 (d, J = 6, 3H, $CHCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.2 (C=O), 156.6 (NHC=O), 80.9 (Cq (*t*-Bu)), 65.5 (CHOH), 60.0 (Cq), 51.8 ($CHCH_2$), 48.8 (CH_2), 30.4 (NCH_3), 28.5 ($C(CH_3)_3$), 21.4 (CH_3), 16.6 (CH_3). LR ESI-MS: m/z: 295.2 for $[M+Na]^+$, 567.3 for $[2M+Na]^+$. HR ESI-MS: m/z: calcd for $[C_{13}H_{24}N_2O_4+Na]^+$: 295.1634, found: 295.1643.

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