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Organocatalysed Asymmetric β-Amination and Multicomponent *syn*-Selective Diamination of α,β-Unsaturated Aldehydes

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Abstract: An easy and affordable route for obtaining chiral β-aminated- and α,β-diaminated aldehydes, 1,3-aminoalcohols, and related compounds by using organocatalysis is presented. The chiral secondary amine (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine is used as the catalyst to activate α,β-unsaturated aldehydes, which allows succinimide to add in a 1,4-regio- and stereoselective fashion thereby forming N-protected 1,3-aminoaldehydes in good yields and enantioselectivities. This is followed by two easy transformations giving rise to optically active 1,3-aminoalcohols, a common motif in many biologically active compounds, for example, fibrinogen receptor antagonists. Furthermore, optically active α,β-*syn*-diaminated aldehydes were obtained by the addition of diethyl azodicarboxylate in a one-pot reaction.

Keywords: amination · asymmetry · multicomponent diamination · organocatalysis

Introduction

Since the start of this decade, great progress has been made in the field of organocatalytic asymmetric reactions.[1] The increasing interest in organocatalysis is mainly due to the possibility of easy and environmentally friendly access to important chiral building blocks, for example, life-science and agriculture. Organocatalysis offers a large number of possibilities which are complementary to, for example, Lewis acid catalysis, such as the possibility of domino reactions.[2]

Among the different catalysts applied in organocatalysis, the use of secondary amines leading to enamine-,[3] iminium-[4] or dienamine[5] intermediates have proven to be a robust tool for stereoselective functionalisations of saturated and unsaturated carbonyl compounds. These reactions now include α-functionalisations leading to, for example, highly selective aldol-,[6] Mannich-,[7] α-amination-,[8] α-hydroxylation-,[9] α-halogenation-[10] and α-sulfenylation[11] reactions of carbonyl compounds. The functionalisation has also been extended to the β-position of α,β-unsaturated aldehydes allowing enantioselective conjugated addition of hydride,[4e,f] sulphur,[4g–j] nitrogen,[4k–m] oxygen[4n] and carbon nucleophiles.[4b–d]

The organocatalytic direct α-amination reaction was developed by using azodicaboxylates as the electrophilic amination reagent and represents an easy approach to the formation of non-natural amino acids and N-protected oxalidinones.[8] Recently, MacMillan et al. introduced a method for the β-amination of α,β-unsaturated aldehydes[4k] by using N-silyloxycarbamates to achieve the 1,4-addition of a nucleophilic nitrogen functionality to the β-position. Subsequently, Cordova et al[4l] used the same nucleophile for the amination, followed by an intramolecular formation of 5-hydroxy isoxazolidine. The latter group has also earlier presented an organocatalytic pathway for asymmetric aziridination.[4m] More recently, it has also been shown that N-heterocycles can add to α,β-unsaturated aldehydes in an enantioselective fashion.[4o]

In recent years, much effort has also been devoted to organocatalysed one-pot, multicomponent reactions leading to a highly efficient method for multiple-bond and stereocenter formation without intermediate purifications.[2] The simplicity of these reactions, minimising the number of manual operations, makes them a very attractive choice for organic synthesis and industry. However, designing high-yielding one-pot multistep reactions with good stereoselective control has proven to be a difficult task.

In this paper, we will present a different protocol for the introduction of an amine functionality to α,β-unsaturated al-

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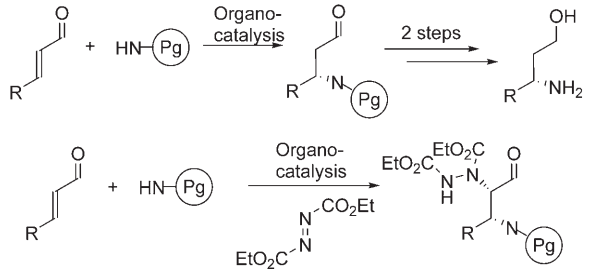
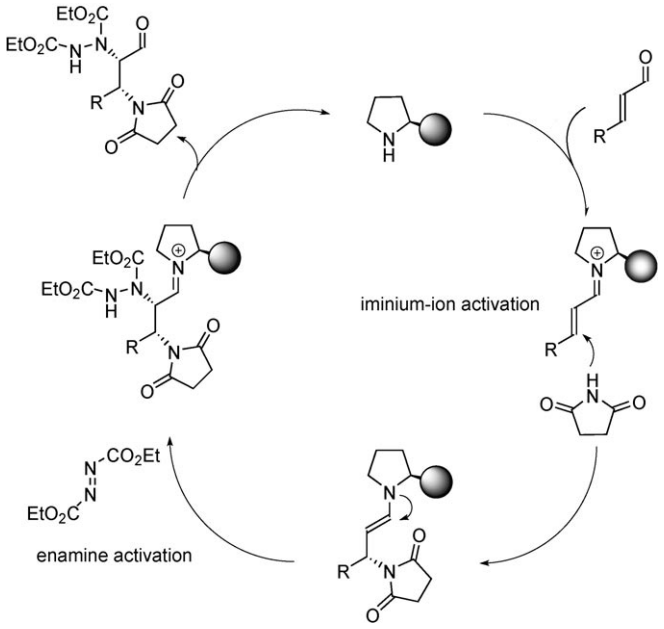
dehydes by using the commercially available and cheap succinimide as the nitrogen source (Scheme 1, top). This represents an easy and practical method to obtain protected opti-



Scheme 1. Top: Organocatalytic enantioselective β-amination of α,β-unsaturated aldehydes by using succinimide as the nitrogen source. Bottom: One-pot multi-step organocatalytic *syn* diamination of α,β-unsaturated aldehydes by using succinimide as the nucleophile and diethyl azodicarboxylates as the electrophile. HN-Pg = Succinimide.

cally active β-amino aldehydes and alcohols in good yields and enantioselectivities. These products represent a common motif in bioactive peptidomimics, for example, fibrinogen receptor antagonists,[12] which have promising potentials as leads in many pharmacological studies.

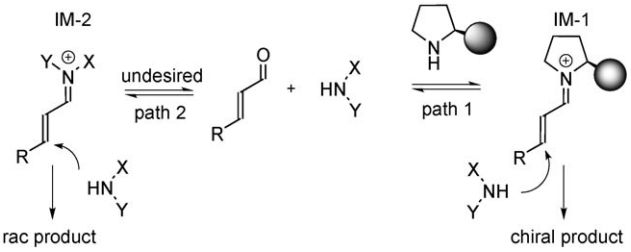
We will also report a strategy, taking advantage of both the enamine- and iminium-ion activation by secondary amine catalysts, resulting in a stereocontrolled *syn*-selective diamination of α,β-unsaturated aldehydes (Scheme 1, bottom; Scheme 2). Under simple reaction conditions, the electrophile can be added in situ to the β-aminated aldehydes thereby forming multiple C–N bonds with good stereo- and regioselectivity in one pot.



Scheme 2. Combination of enamine and iminium-ion activation leading to one-pot diaminated products.

Results and Discussion

β-Amination of α,β-unsaturated aldehydes: To accomplish the β-amination of α,β-unsaturated aldehydes by applying chiral secondary amine catalysis, the choice of nucleophile is essential. The nitrogen source of choice has to be both chemo- and regioselective, given that it must demonstrate the ability to add to the iminium-activated α,β-aldehyde in an enantioselective fashion (Scheme 3, path 1), rather than the iminium-ion formation by reaction of the nucleophile with the carbonyl group (Scheme 3, path 2).

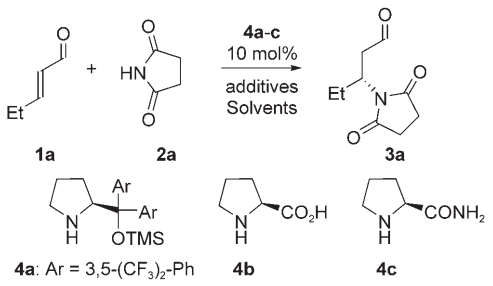


Scheme 3. Problems and considerations: Choice of nitrogen source.

To our delight, initial studies revealed that in CH_2Cl_2, succinimide[13] **2a** showed excellent reactivity as a nucleophile in the conjugated addition towards iminium-ion activated α,β-unsaturated aldehydes by using **4a** as the catalyst (Scheme 3, path 1). In the absence of the catalyst, no reaction was observed indicating that the undesired reaction course can be neglected. A further advantage is that **2a** is cheap and may serve as a stable N-protecting group, which can survive most product manipulations, while an easy deprotection protocol can be employed when desired (vide infra).

During the screening process for reaction conditions, *trans*-2-pentenal **1a** was applied as the α,β-unsaturated aldehyde and succinimide **2a** as the nitrogen source in the presence of **4a–c** (10 mol%) as the catalysts (Scheme 4). Various additives, concentrations, solvents and temperatures were tested. Table 1 shows some representative screening results for the amination reaction (Scheme 4).

The β-amination is dependent on the catalyst and additives. The application of (*S*)-2-[bis(3,5-bistrifluoromethyl-



Scheme 4. Screening various reaction conditions for addition of succinimide to *trans*-2-pentenal.

Table 1. Organocatalytic β-amination of α,β-unsaturated aldehyde **1a** with succinimide **2a** under various conditions.[a]

Entry	Cat.	Additive [mol%]	Conv. [%][b]	*ee* [%][c]
1	**4a**	–	47	nd
2	**4a**	HCl (20)	6	nd
3	**4a**	$PhCO_2H$ (20)	42	nd
4	**4a**	$KCO_3/KHCO_3$ (20)	60	nd
5	**4a**	NaOAc (20)	70	88
6	**4a**	Et_3N (20)	27	nd
7	**4a**	NaOH (20)	16	nd
8	**4a**	H_2O (200)–NaOAc (20)	72	88
9	**4b**	NaOAc (20)	90	15
10	**4c**	NaOAc (20)	7	nd

[a] Experimental conditions: *trans*-2-pentenal **1a** (1.5 equiv, 0.375 mmol) was added to a stirring solution of **2a** (1 equiv, 0.250 mmol), 10 mol% of catalyst **4a–c** and the respective additive in the given amount in CH_2Cl_2 (0.5 mL). The reaction time is 20 h. [b] The conversion is determined by NMR spectroscopy. [c] The *ee* was determined, unless otherwise noted, by reduction of the product aldehyde **3a** with $NaBH_4$ followed by esterification to the corresponding *p*-chlorobenzoyl ester.

phenyl)trimethylsilanyloxymethyl]pyrrolidine (**4a**) as the catalyst (10 mol%) in CH_2Cl_2 and by employing *trans*-2-pentenal (**1a**) and succimide (**2a**) in ratio of 1.5:1 gave, in the absence of additive, moderate conversion (Table 1, entry 1). A number of additives were evaluated in order to improve the conversion (entries 2–8) and it turned out that the presence of 20 mol% NaOAc or H_2O/NaOAc gave a significant improvement in conversion (entries 5, 8). The role of NaOAc is probably to promote deprotonation of **2a** to make it into a better nucleophile. Under these reaction conditions, the enantioselectivity of the product was formed in up to 88% *ee* (*ee* = enantiomeric excess; entry 5). The application of a strong acid, such as HCl (entry 2), probably resulted in protonation of the secondary amine and deprotection of the TMS (TMS = trimethylsilyl) group of the catalyst. In presence of weaker acids, such as $PhCO_2H$, the reaction still took place, but at a much lower rate (entry 3). Generally, under non-basic conditions, several side reactions were observed (entry 1–3). Bases, such as NaOH or Et_3N (entries 6, 7), also promoted very poor reactivity and led to decomposition of the starting materials. Only $KCO_3/KHCO_3$ (entry 4) gave results comparable to those obtained by NaOAc and H_2O/NaOAc.

A number of other catalysts were also evaluated, for example, proline **4b** and proline amide **4c** turned out to be much less effective compared to **4a**. Proline **4b** gave a good conversion, but failed to have any mentionable stereoselective control (entry 9), while **4c** did not show any considerable conversion (entry 10).

A screening of the most frequently employed solvents spanning over different polarities and hydrogen-bonding properties (MeCN, toluene, CH_2Cl_2, DMSO, Et_2O, THF, xylene, H_2O and EtOH) was also performed. It turned out that only in CH_2Cl_2 and EtOH acceptable conversions, 70 and 51%, and enantioselectivities 88 and 62% *ee*, respectively, were obtained. However, for the reaction conducted in EtOH, a number of byproducts—1,4- and 1,2-ethanol addition products—were formed.

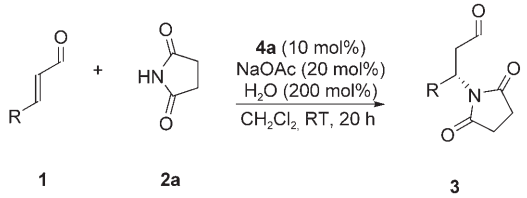
The reaction is also temperature dependent; at 4°C, the conversion was only 34% after 24 h and **3a** was formed with 78% *ee*, while at −24°C no conversion was observed. At 40°C, an improvement in conversion to 78% was found, while the enantioselectivity decreased to 75% *ee*. At this temperature, the reaction time was reduced significantly; however, full conversion was never achieved. Additionally, decomposition and side reactions are also promoted by the high temperature.

It was also observed that even after a prolonged reaction time, the succinimide **2a** was not fully consumed in the presence of excess aldehyde. To our delight, it was found that the conversion for the reaction (Scheme 4) could be further improved from 70% (of **2a**) to ≈90% (of aldehyde) by changing the *trans*-2-pentenal **1a** and **2a** ratio of 1.5:1 to 1:1.5, without changing the enantioselectivity (88% *ee*) of the reaction. Increasing the amount of **2a** relative to **1a** further led to the decomposition of product **3a**. It is also worth mentioning that by adding H_2O (2 equiv), the reaction time is considerably shortened. It has previously been suggested that water makes the catalytic cycle faster.[6r,s]

Finally, a closely related imide, phtalimide **2b**, was also tested as a possible nitrogen source. By using the developed reaction conditions, only a trace of the addition product was observed, which might be due to solubility problems of **2b** in CH_2Cl_2. Changing to the more polar solvent EtOH, moderate conversion was observed; however, the reaction gave rise to many ethanol-addition byproducts. In dioxane, full conversion was achieved by using **2b** as a nucleophile and **4a** and DBU (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) as catalyst and co-catalyst, respectively; however, only racemic products were obtained.

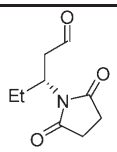
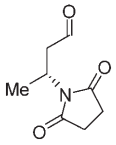
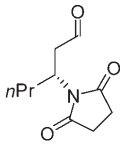
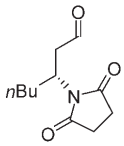
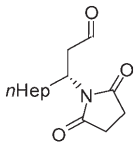
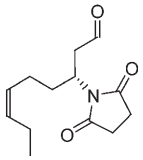
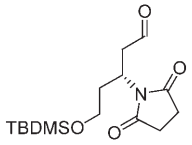
A number of different α,β-unsaturated aldehydes **1** were reacted with succinimide **2a** (Scheme 5) in order to show the scope of the presented organocatalytic enantioselective β-amination reaction. The results are presented in Table 2.

It appears from the results in Table 2 that the β-amination reaction proceeds well for different aliphatic α,β-unsaturated aldehydes giving yields from 65 to 74% and with enantioselectivities up to 90% *ee*. The β-succinimide group, being a good leaving group, makes the product prone to elimination thereby reintroducing the double bond preventing higher yields. The enantioselectivities of the isolated products ranged from 87 to 90% *ee*, except in the case of crotonaldehyde (78% *ee*) for which the aliphatic chain only consists of a small methyl group. For the remaining alde-



Scheme 5. Scope of the organocatalytic enantioselective 1,4-addition of succinimide to α,β-unsaturated aldehydes.

Table 2. Organocatalytic enantioselective β-amination of α,β-unsaturated aldehydes **1** with **2a** as a nucleophile catalysed by **4a** (10 mol%) in CH_2Cl_2 at RT to give products **3**.[a]

Entry	Product	Yield [%][b]	*ee* [%][c]
1		**3a**: 72	88
2		**3b**: 65	78[d]
3		**3c**: 66	87
4		**3d**: 65	87
5		**3e**: 73	90
6		**3f**: 72	89
7		**3g**: 74	89

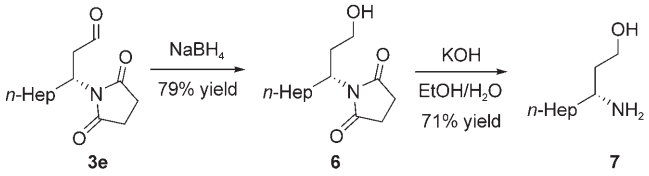
[a] Experimental conditions: α,β-unsaturated aldehyde **1** (1 equiv, 0.250 mmol) was added to a stirring solution of **2a** (1.5 equiv, 0.375 mmol), 10 mol% of catalyst **4a**, 200 mol% H_2O and 20 mol% NaOAc in CH_2Cl_2 (0.5 mL). [b] Isolated yield. [c] The *ee* was determined, unless otherwise noted, by reduction of the product aldehyde **3** with $NaBH_4$ followed by esterification to the corresponding *p*-chlorobenzoyl ester **5**. [d] The *ee* was determined by GC analysis by using a chiral Chrompack CP Chiralsil-Dex Cβ column.

hydes, variations in the chain length, as well as other functional groups, for example, a non-conjugated double bond (entry 6) or −OTBDMS group (entry 7), are well tolerated.

α,β-Unsaturated aldehydes with an aromatic or heteroaromatic ring in direct conjugation to the double bond do not undergo the described reaction. This might be due to the stability of the prolonged conjugated system.

An scale-up of the investigated reaction is also possible. This was done by using crotonaldehyde (5 mmol) which gave a good yield of 83% without loss of enantioselectivity. Furthermore, it was shown that the obtained products were stable at 4°C for five days without decomposition or racemization.

The cleavage of the succinimide group thereby liberating the amine functionality is a well-described reaction in literature.[14] We performed a base-mediated deprotection of the corresponding β-succinimide alcohol **6** obtaining a yield of 71% of the amino alcohol **7** (Scheme 6).

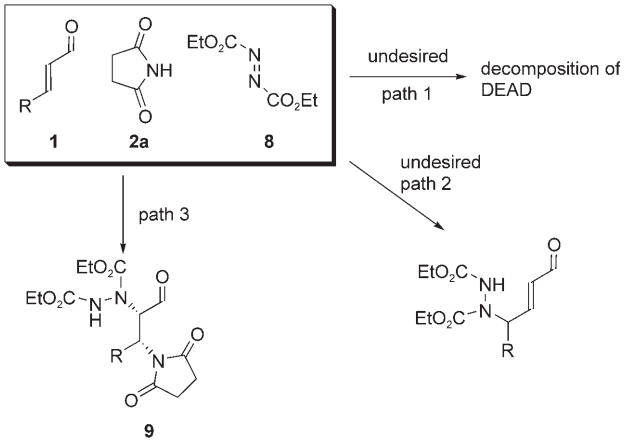


Scheme 6. Reduction and deprotection of the products.

The absolute configuration was determined for 3-(2,5-dioxopyrrolidin-1-yl)butanal **3b** by chemical correlation after oxidation and ethyl esterification.[15] The measured optical rotation corresponds well to the literature confirming the *R* configuration of the β-stereocenter, as expected by comparison to earlier results.[4o] The remaining configurations are assumed by analogy.

Diamination of α,β-unsaturated aldehydes: The first challenge we faced during the design process was a proper choice of eletrophilic nitrogen-source. Several organocatalytic α-amination protocols have been presented in the past.[8] Among the applied electrophiles, azodicarboxylates have proved to be efficient, giving both good yields and stereoselectivity. We therefore decided to explore the possibility of a multicomponent one-pot *syn* diamination by using succinimide **2a** as the nucleophile and diethyl azodicarboxylates (DEAD) **8** as the electrophile.

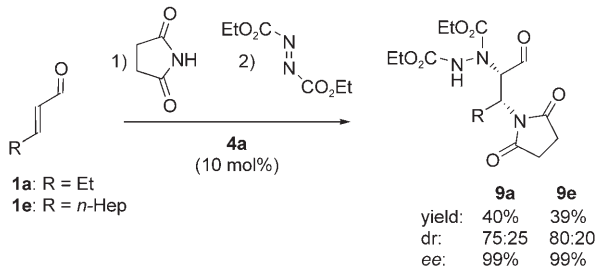
As outlined in Scheme 7, several undesired competitive reactions, for example, the decomposition of the eletrophilic nitrogen-source caused by succinimide (path 1), have to be



Scheme 7. Competitive reaction paths.

avoided. Furthermore, earlier studies have shown that azodicarboxylates can react as a dienophile towards α,β-unsaturated aldehydes under similar conditions, also catalysed by **4a**[5a] (path 2).

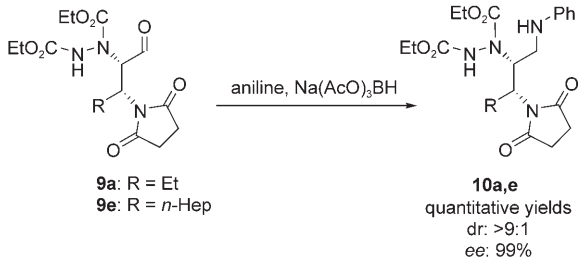
Realizing these difficulties, we employed a sequential addition of succinimide **2a** and **8**. After the completion of the 1,4-addition of **2a** to the α,β-unsaturated aldehyde by employing the previously optimised reaction conditions, **8** was added at −24 °C. However, the diaminated product **9** was formed in low yield due to a low conversion of the second reaction step, presumably caused by decomposition of **8** in the presence of **2a**. Limiting the amount of **2a** during the second reaction step was therefore crucial for the yield of **9**. A complete exclusion of **2a** is impossible as the rate of the 1,4-addition of **2a** becomes slow after reaching a plateau of 85–90 % conversion of the aldehyde. However, a careful examination showed that a small amount of **2a** is in fact tolerated under non-basic conditions. Therefore, it was decided to change the acidity of the reaction after the β-amination step by in situ addition of $PhCO_2H$ (0.4 equiv) before adding the electrophile **8**. The ratio of the aldehyde **1** and **2a** was changed to 1.5:1 in favour of the aldehyde, in order to limit the amount of remaining **2a** during the addition of **8**. Scheme 8 shows the scope of the organocatalytic asymmetric *syn* diamination reaction.



Scheme 8. Organocatalytic asymmetric *syn* diamination reaction.

The in situ addition of **8** to the preformed β-aminated aldehydes in slightly acidic media resulted in near full conversion to the *syn* diaminated products **9** within 2.5 h at −24 °C. The enantioselectivity, overall yield and dr (diastereomeric ratio) were up to 99 % *ee*, 40 % and 8:2 dr, respectively. We have observed that the dr in the reaction mixture was slightly higher (≈9:1); however, the diaminated product is prone to epimerisation, as well as retro-reaction on silica gel resulting in a decrease of dr to 75:25–80:20 of the isolated product.

The cleavage of the N−N bond liberating the free α-amino group has been described in the literature.[16] Further functionalisation of the *syn*-diaminated aldehydes was achieved by reductive amination[17] with, for example, aniline giving 1,2,3-triaminated products (Scheme 9). The reductive amination with aniline is a quantitative reaction giving products **10a**,**e** as enantiopure compounds as outlined in Scheme 9.



Scheme 9. Derivatisation of the *syn* diaminated products

Conclusion

We have presented an easy and organocatalytic approach to form β-aminated aldehydes with high enantioselectivity and yields by using a cheap and commercially available nucleophile, succinimide. The obtained β-aminated aldehydes are easily transformed to 1,3-aminoalcohols, which are important building blocks in, for example, life science. We have also shown that an one-pot *syn* diamination of α,β-unsaturated aldehydes by using succinimide as a nucleophile and diethyl azodicarboxylate as the electrophile is possible, giving good yields and excellent diastereo- and enantioselectivity of the *syn*-aminated products.

Experimental Section

General: NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 and 100 MHz for ^1H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^1H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). ^{13}C NMR spectra were acquired on a broad-band decoupled mode. Mass spectra were recorded on a Micromass LCT spectrometer by using electrospray (ES^+) ionisation techniques. Analytical TLC was performed by using precoated aluminium-backed plates (Merck Kieselgel 60 F254) and visualised by ultraviolet irradiation or $KMnO_4$ dip. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AS/AD or Daicel Chiralcel OD/OJ columns).

Materials: Analytical grade solvents, α,β-unsaturated aldehydes **1a–f**, DEAD (**8**) and succinimide **2a** are commercially available reagents and were used as received. Substrates **1g** were prepared according to the literature.[18] Flash chromatography was carried out by using Iatrobeads 6RS-8060 (spherical silica gel) or silica gel purchased from Fluka (silica gel 60, 230–400 mesh). Racemic samples were prepared by using a racemic mixture of the catalyst.

General procedure for the conjugate addition of succinimide to α,β-unsaturated aldehydes: Catalyst **4a** (10 mol %, 0.025 mmol), **2a** (0.375 mmol, 1.5 equiv), CH_2Cl_2 (0.5 mL), H_2O (9 μL, 2 equiv) and NaOAc (20 mol %, 0.050 mmol) were added to a sample vial equipped with a magnetic stirring bar. The mixture was stirred for a short time at ambient temperature and then one of the aldehydes **1a–g** (0.250 mmol, 1 equiv) was added. After about 20–24 h (monitored by TLC or NMR spectroscopy), the reaction was completed and the reaction mixture was loaded onto Iatro-

beads 6RS-8060 and the product (**3a**–**g**) was obtained by flash chromatography eluting with CH_2Cl_2/Et_2O (80:20).

General procedure for the reduction and esterification of β-aminated aldehydes: The chosen aldehyde (**3a**–**g**; 0.25 mmol), dissolved in CH_2Cl_2 (0.5 mL), was diluted with MeOH (2 mL) and $NaBH_4$ (0.40 mmol, 15 mg) was added. After 30 min, NH_4Cl (sat.) solution was added and the aq. phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried over Na_2SO_4. The solvent was evaporated after filtration to yield the crude alcohol. The alcohol was dissolved in CH_2Cl_2 (2 mL) and Et_3N (0.50 mmol, 69 μL) and 4-chlorobenzoylchloride (0.50 mmol, 63 μL) were added. After 1–3 h, the reaction mixture was purified directly by flash chromatography, eluting with CH_2Cl_2/Et_2O 95:5→90:10 to give **5**.

General procedure for the reduction of the β-aminated aldehydes to give the corresponding alcohol: Aldehyde **3**, dissolved in CH_2Cl_2 (0.5 mL), was diluted with MeOH (2 mL) and $NaBH_4$ (15 mg) was added. After 30 min, NH_4Cl (sat.) solution was added and the aq. phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated after filtration and the crude product was purified by flash chromatography, eluting with CH_2Cl_2/*i*PrOH 98:2.

General procedure for the succinimide deprotection of the β-aminated alcohol to give the corresponding 1,3-aminoalcohol: A mixture of **6** (0.25 mmol) in EtOH (0.5 mL) and KOH (2.2 mmol, 123 mg) dissolved in H_2O (0.4 mL) was refluxed for 5 h. After cooling, the EtOH was removed under reduced pressure and the residue obtained was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (10×15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo to give the aminoalcohol **7**.

General procedure for the one-pot diamination of α,β-unsaturated aldehydes: To a sample vial equipped with a magnetic stirring bar was added the catalyst **4a** (10 mol%, 0.025 mmol, 15 mg), **2a** (0.25 mmol, 1 equiv, 24.8 mg), CH_2Cl_2 (0.125 mL) and NaOAc (20 mol%, 0.050 mmol, 4 mg). The mixture was stirred for a short time at ambient temperature and then **1a** or **1e** (0.375 mmol, 1.5 equiv) was added. After about 20 h, the reaction mixture was diluted with additional CH_2Cl_2 (0.375 mL) and benzoic acid was added (40 mol%, 0.10 mmol). The temperature was then lowered to −24 °C and **8** (0.375 mmol, 1.5 equiv, 59 μL) was added. After 2.5 h, the solvent was removed and the crude mixture was purified by flash chromatography, eluting with CH_2Cl_2/Et_2O 95:5→90:10. The columned product was diluted by hexane/CH_2Cl_2 1:1 (10 mL) and the organic layer was washed twice with water and then concentrated in vacuo to give the final product **9a** or **9e**.

Representative procedure for reductive amination of the diaminated aldehydes: The diaminated aldehyde **9a** or **9e** (0.25 mmol) was dissolved in dry DCE (1.0 mL). Aniline (0.25 mmol, 22.8 μL) and $NaBH(OAc)_3$ (0.35 mmol, 74 mg) were added, and the heterogeneous mixture was stirred under N_2 at RT for 20 h. Saturated $NaHCO_3$ (1 mL) was added, and the mixture was extracted with EtOAc (3×5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil. The crude amine was purified by flash chromatography, eluting with CH_2Cl_2/Et_2O 90:10 to give **10a** or **10e**.

3-(2,5-Dioxopyrrolidin-1-yl)pentanal (3a): The title compound was obtained according to the general procedure (72% yield). $[\alpha]_D^{20}=+10.6$ ($c=0.55$ in CH_2Cl_2); ^{1}H NMR: $\delta=9.70$ (s, 1H), 4.47–4.55 (m, 1H), 3.25 (ddd, $J=1.5$, 9.2, 18.0 Hz, 1H), 2.86 (ddd, $J=1.0$, 5,2, 18.0 Hz, 1H), 2.66 (s, 4H), 1.87–1.98 (m, 1H), 1.65–1.75 (m, 1H), 0.84 ppm (t, $J=7.4$ Hz, 3H); ^{13}C NMR: $\delta=199.4$, 177.3, 47.9, 45.0, 27.9, 24.7, 10.7 ppm; HRMS: *m*/*z*: calcd for $C_9H_{13}NNaO_3$: 206.0788 $[M+Na]^+$; found: 206.0789; the *ee* was determined by HPLC analysis of the corresponding *p*-chlorobenzoyl ester by using a Chiralpak AD column hexane/*i*PrOH 90:10; flow rate = 1.0 mL min^{-1}; $\tau_{major}=17.2$ min, $\tau_{minor}=15.2$ min (88% *ee*).

3-(2,5-Dioxopyrrolidin-1-yl)butanal (3b): The title compound was obtained according to the general procedure (65% yield). $[\alpha]_D^{20}=-2.8$ ($c=0.5$ in CH_2Cl_2); ^{1}H NMR: $\delta=9.64$ (s, 1H), 4.62–4.71 (m, 1H), 3.20 (ddd, $J=1.4$, 8.5, 18.2 Hz, 1H), 2.86 (ddd, $J=1.0$, 6,0, 18.2 Hz, 1H), 2.60 (s, 4H), 1.32 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta=199.2$, 177.0, 46.2, 41.8, 27.8, 17.8 ppm; MS: *m*/*z*: calcd for $C_8H_{11}NNaO_3$: 92.06 $[M+Na]^+$; found: 192.02; this compound was too unstable for determination of exact mass. The excact mass was instead determined by derivatisation to ethyl 3-(2,5-dioxopyrrolidin-1-yl)butanoate. The *ee* was determined by GC by using a chiral Chrompack CP Chiralsil-Dex Cβ column; temperature program: from 70 to 130 °C at a rate of 10 °C min^{-1}, maintaining the temperature for 30 min, then to 180 °C at a rate of 10 °C min^{-1}; $\tau_{major}=20.4$ min, $\tau_{minor}=22.6$ min (78% *ee*).

3-(2,5-Dioxopyrrolidin-1-yl)hexanal (3c): The title compound was obtained according to the general procedure (66% yield). $[\alpha]_D^{20}=+9.1$ ($c=0.60$ in CH_2Cl_2); ^{1}H NMR: $\delta=9.68$ (s, 1H), 4.56–4.63 (m, 1H), 3.23 (dd, $J=9.1$, 18.0 Hz, 1H), 2.84 (dd, $J=5.3$, 18.0 Hz, 1H), 2.65 (s, 4H), 1.84–1.96 (m, 1H), 1.54–1.62 (m, 1H), 1.16–1.28 (m, 2H), 0.88 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR: $\delta=199.5$, 177.2, 46.1, 45.2, 33.5, 27.8, 19.4, 13.5 ppm; HRMS: *m*/*z*: calcd for $C_{10}H_{15}NNaO_3$: 220.0944 $[M+Na]^+$; found: 220.0938; the *ee* was determined by HPLC analysis of the corresponding *p*-chlorobenzoyl ester by using a Chiralpak AD column (hexane/*i*PrOH 90:10); flow rate = 1.0 mL min^{-1}; $\tau_{major}=14.4$ min, $\tau_{minor}=13.3$ min (87% *ee*).

3-(2,5-Dioxopyrrolidin-1-yl)heptanal (3d): The title compound was obtained according to the general procedure (65% yield). $[\alpha]_D^{20}=+15.3$ ($c=0.58$ in CH_2Cl_2); ^{1}H NMR: $\delta=9.69$ (s, 1H), 4.55–4.62 (m, 1H), 3.24 (dd, $J=9.2$, 18.0 Hz, 1H), 2.85 (dd, $J=5.3$, 18.0 Hz, 1H), 2.66 (s, 4H), 1.87–1.97 (m, 1H), 1.57–1.67 (m, 1H), 1.07–1.38 (m, 4H), 0.86 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR: $\delta=199.5$, 177.2, 46.4, 45.2, 31.2, 28.3, 27.9, 22.1, 13.9 ppm; HRMS: *m*/*z*: calcd for $C_{11}H_{17}NNaO_3$: 234.1101 $[M+Na]^+$; found: 234.1112; the *ee* was determined by HPLC analysis of the corresponding *p*-chlorobenzoyl ester by using a Chiralpak AD column (hexane/*i*PrOH 90:10); flow rate = 1.0 mL min^{-1}; $\tau_{major}=13.7$ min, $\tau_{minor}=12.6$ min (87% *ee*).

3-(2,5-Dioxopyrrolidin-1-yl)decanal (3e): The title compound was obtained according to the general procedure (73% yield). $[\alpha]_D^{20}=+15.9$ ($c=0.78$ in CH_2Cl_2); ^{1}H NMR: $\delta=9.69$ (s, 1H), 4.55–4.62 (m, 1H), 3.24 (ddd, $J=1.3$, 9.2, 18.0 Hz, 1H), 2.85 (dd, $J=5.2$, 18.0 Hz, 1H), 2.66 (s, 4H), 1.87–1.96 (m, 1H), 1.58–1.67 (m, 1H), 1.16–1.30 (m, 10H), 0.86 ppm (t, $J=7.0$ Hz, 3H); ^{13}C NMR: $\delta=199.5$, 177.3, 46.4, 45.2, 31.7, 31.5, 29.1, 29.0, 27.9, 26.2, 22.6, 14.0 ppm. HRMS: *m*/*z*: calcd for $C_{14}H_{23}NNaO_3$: 276.1570 $[M+Na]^+$; found: 276.1567; the *ee* was determined by HPLC analysis of the corresponding *p*-chlorobenzoyl ester by using a Chiralpak AD column (hexane/*i*PrOH 98:2); flow rate = 1.0 mL min^{-1}; $\tau_{major}=26.8$ min, $\tau_{minor}=25.3$ min (90% *ee*).

(*Z*)-3-(2,5-Dioxopyrrolidin-1-yl)non-6-enal (3f): The title compound was obtained according to the general procedure (72% yield). $[\alpha]_D^{20}=+22.8$ ($c=0.74$ in CH_2Cl_2); ^{1}H NMR: $\delta=9.69$ (s, 1H), 5.32–5.39 (m, 1H), 5.20–5.26 (m, 1H), 4.57–4.64 (m, 1H), 3.22 (ddd, $J=1.6$, 9.1, 18.0 Hz, 1H), 2.84 (dd, $J=5.2$, 18.0 Hz, 1H), 2.64 (s, 4H), 1.93–2.07 (m, 5H), 1.64–1.72 (m, 1H), 0.92 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR: $\delta=199.3$, 177.2, 132.8, 127.0, 46.2, 45.2, 31.3, 27.8, 23.9, 20.5, 14.2 ppm; HRMS: *m*/*z*: calcd for $C_{13}H_{19}NNaO_3$: 260.1257 $[M+Na]^+$; found: 260.1257; the *ee* was determined by HPLC analysis of the corresponded *p*-chlorobenzoyl ester by using a two Chiralpak AS column (hexane/*i*PrOH 99:1); flow rate = 1.0 mL min^{-1}; $\tau_{major}=44.0$ min, $\tau_{minor}=60.7$ min (89% *ee*).

5-(*tert*-Butyldimethylsilyloxy)-3-(2,5-dioxopyrrolidin-1-yl)pentanal (3g): The title compound was obtained according to the general procedure (74% yield). ^{1}H NMR $\delta=9.68$ (s, 1H), 4.75–4.82 (m, 1H), 3.54–3.65 (m, 2H), 3.19 (ddd, $J=1.7$, 9.1, 17.7 Hz, 1H), 2.90 (ddd, $J=1.0$, 5.3, 17.7 Hz, 1H), 2.63 (s, 4H), 2.09–2.18 (m, 1H), 1.84–1.92 (m, 1H), 0.86 (s, 9H), 0.00 ppm (s, 3H); ^{13}C NMR: $\delta=199.5$, 177.1, 60.2, 45.3, 44.2, 34.2, 27.9, 25.8, 18.2, −5.5 ppm; HRMS: calcd for $C_{15}H_{27}NNaO_4Si$: 336.1602 $[M+Na]^+$; found: 336.1596; the *ee* was determined by HPLC analysis of the corresponding *p*-chlorobenzoyl ester by using a Chiralcel OD column (hexane/*i*PrOH 90:10); flow rate = 1.0 mL min^{-1}; $\tau_{major}=28.5$ min, $\tau_{minor}=18.7$ min (89% *ee*); $[\alpha]_D^{20}=+9.2$ ($c=1.15$ in CH_2Cl_2).

1-(1-Hydroxydecan-3-yl)pyrrolidine-2,5-dione (6): The title compound was obtained according to the general procedure (79% yield). ^{1}H NMR: $\delta=4.23$–4.27 (m, 1H), 3.58–3.64 (m, 1H), 3.44–3.50 (m, 1H), 2.68 (s, 4H), 2.09–2.17 (m, 1H), 2.05–2.08 (m, 1H), 1.79–1.89 (m, 1H), 1.61–1.70 (m, 1H), 1.23 (m, 10H), 0.86 ppm (t, $J=6.5$ Hz, 3H); ^{13}C NMR: $\delta=$

178.1, 59.6, 49.8, 34.0, 31.1, 29.0, 27.9, 26.5, 22.5, 14.0 ppm; HRMS: *m/z*: calcd for $C_{14}H_{25}NNaO_3$: 278.1727 $[M+Na]^+$; found: 278.1733.

3-Aminodecan-1-ol (7): The title compound was obtained according to the general procedure (71% yield). $[\alpha]_D^{20}=+3.3$ ($c=0.54$ in CH_2Cl_2); ^{1}H NMR (50°C): $\delta=3.73$–3.89 (m, 2H), 2.88 (brs, 1H), 2.41 (brs, 2H), 1.61–1.68 (m, 1H), 1.39–1.51 (m, 2H), 1.28 (m, 12H), 0.88 ppm (t, J 6.9 Hz, 3H); ^{13}C NMR: $\delta=62.8$, 53.0, 39.8, 37.4, 31.8, 29.5, 29.2, 25.8, 22.6, 14.1 ppm; HRMS: *m/z*: calcd for $C_{10}H_{24}NO$: 174.1852 $[M+H]^+$; found: 174.1843.

Ethyl 3-(2,5-dioxopyrrolidin-1-yl)butanoate: Aldehyde **3b** (100 mg) was dissolved in *t*BuOH (3 mL), NaH_2PO_4 (1M, 3 mL) and $KMnO_4$ (1M, 3 mL). After 3 min, sat. $NaHSO_3$ (5 mL) was added. The pH was adjusted to 3 with 4M HCl. The mixture was then extracted three times with EtOAc (10 mL), the combined organic layers were washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo to give the corresponding carboxylic acid. Etheral diazomethane was prepared by slow addition behind safety glass at 0°C of *N*-nitroso-*N*-ethylurea to a two-phase system consisting of 50% aq. KOH (2.1 mL) and Et_2O (7 mL). The solution was stirred as the addition proceeded and after 15 min the ethereal layer was decanted onto KOH pellets for drying at 0°C. After 0.5 h, the ethereal layer was again decanted into a precooled flask and added dropwise to the oxidised aldehydes in Et_2O (2 mL) at 0°C until the yellow colour persisted. The solution was left to warm up to RT and then stand for 0.5 h. AcOH (concn, 1–3 drops) was added and the solvent evaporated to give a pure brown oil. $[\alpha]_D^{20}=-2.0$ ($c=1.55$ in $CHCl_3$); ^{1}H NMR: $\delta=4.56$–4.65 (m, 1H), 4.07 (q, $J=7.1$ Hz, 1H), 4.06 (q, $J=7.1$ Hz, 1H), 3.07 (dd, $J=9.4$, 16.0 Hz, 1H), 2.64 (dd, $J=5.7$, 16.0 Hz, 1H), 2.65 (s, 4H), 1.37 (d, $J=7.0$ Hz, 3H), 1.20 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR: $\delta=177.1$, 170.8, 60.6, 44.1, 36.8, 28.0, 17.9, 14.1 ppm; HRMS: *m/z*: calcd for $C_{10}H_{15}NNaO_4$: 236.0893 $[M+Na]^+$; found: 236.0889.

Diethyl 1-(3-(2,5-dioxopyrrolidin-1-yl)-1-oxopentan-2-yl)hydrazine-1,2-dicarboxylate (9a): The title compound was obtained according to the general procedure (40% yield) and a mixture of two diatereoisomers (major and minor). ^{1}H NMR (50°C): $\delta=9.81$ (s, 1H; major), 9.71* (s, 1H; minor), 6.60–6.68 (m, 2H; both diastereomers), 5.31 (brs, 1H; major), 5.10* (d, $J=8.4$ Hz, 1H; minor), 4.58* (brs, 1H; minor), 4.52 (dt, $J=3.6$, 10.6 Hz, 1H; major), 4.10–4.28 (m, 8H; both diastereomers), 2.65–2.69 (m, 8H; both diastereomers), 2.10–2.31 (m, 2H; both diastereomers), 1.77–1.95 (m, 2H; both diastereomers), 1.20–1.30 (m, 12H; both diastereomers), 0.89 (t, $J=7.3$ Hz, 3H; major), 0.84* (t, $J=7.2$ Hz, 3H; minor), * corresponds to signals of the minor diastereomer; ^{13}C NMR: $\delta=197.7$, 197.0, 177.9, 177.6, 156.5, 155.9, 68.0, 66.7, 66.2, 63.6, 63.5, 63.3, 63.1, 62.5, 62.1, 51.4, 50.8, 50.3, 27.9, 27.4, 22.2, 21.0, 20.7, 14.2, 10.5, 10.3, 10.0 ppm (additional peaks and line broadenings are observed due to rotameric species); HRMS: $[M+Na]^+$ calcd for $C_{15}H_{23}N_3NaO_7$: 380.1428; found: 380.1432; the *ee* was determined by chiral HPLC after derivatisation to **10a**.

Diethyl 1-(3-(2,5-dioxopyrrolidin-1-yl)-1-oxodecan-2-yl)hydrazine-1,2-dicarboxylate (9e): The title compound was obtained according to the general procedure (39% yield). ^{1}H NMR (50°C): $\delta=9.77$ (s, 1H; major), 9.67* (s, 1H; minor), 6.81* (brs, 1H; minor), 6.71 (s, 1H; major), 5.23 (brs, 1H; major), 5.02* (d, $J=8.3$ Hz, 1H; minor), 4.62* (brs, 1H; minor), 4.55 (dt, $J=3.0$, 10.7 Hz, 1H; minor), 4.10–4.21 (m, 8H; both diastereomers), 2.65* (s, 4H; minor), 2.63 (s, 4H; major), 2.11–2.29 (m, 2H; both diastereomers), 1.66–1.81 (m, 2H; both diastereomers), 1.11–1.28 (m, 32H; both diastereomers), 0.84 ppm (t, $J=7.0$ Hz, 6H; both diastereomers), * corresponds to signals of the minor diastereomer; ^{13}C NMR: $\delta=197.8$, 197.1, 177.9, 156.6, 156.0, 68.0, 66.7, 63.6, 63.2, 62.6, 62.2, 50.2, 49.5, 48.9, 31.6, 29.0, 28.9, 28.0, 27.8, 26.2, 26.0, 22.5, 14.3, 14.0 ppm (additional peaks and line broadenings are observed due to rotameric species); HRMS: *m/z*: calcd for $C_{20}H_{33}N_3NaO_7$: 450.2211 $[M+Na]^+$; found: 450.2201; the *ee* was determined by chiral HPLC after derivatisation to **10e**.

Diethyl 1-(3-(2,5-dioxopyrrolidin-1-yl)-1-(phenylamino)pentan-2-yl)hydrazine-1,2-dicarboxylate (10a): The title compound was obtained according to the general procedure (quant. yield). $[\alpha]_D^{20}=+84.8$ ($c=0.57$ in $CHCl_3$); ^{1}H NMR (50°C): $\delta=7.16$ (t, $J=7.6$ Hz, 2H), 6.60–6.70 (m, 4H), 5.17 (brs, 1H), 4.90 (t, $J=10.2$ Hz, 1H), 3.90–4.28 (m, 5H), 3.54 (d, $J=13.2$ Hz, 1H), 3.04 (t, $J=11.4$ Hz, 1H), 2.62 (brs, 4H), 2.34–2.46 (m, 1H), 1.64–1.75 (m, 1H), 1.29 (t, $J=6.7$ Hz, 3H), 0.95–1.20 (m, 3H), 0.86 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR: $\delta=178.8$, 176.6, 157.7, 156.2, 147.7, 129.2, 117.6, 113.6, 62.9, 62.5, 57.1, 53.6, 41.4, 37.4, 29.7, 27.9, 19.9, 14.4, 13.8, 10.8 ppm (additional peaks and line broadenings are observed due to rotameric species); HRMS: $[M+Na]^+$ calcd for $C_{21}H_{30}N_4NaO_6$: 457.2058; found: 457.2072; the *ee* was determined by HPLC using a Chiralcel OD column (hexane/*i*PrOH 90:10); flow rate = 1.0 mL min^{-1}; major diastereomer: $\tau_{major}=28.9$ min, $\tau_{minor}=20.1$ min (99% *ee*); minor diastereomer: $\tau_{major}=82.6$ min, $\tau_{minor}=50.9$ min (99% *ee*); dr = 9:1.

Diethyl 1-(3-(2,5-dioxopyrrolidin-1-yl)-1-(phenylamino)decan-2-yl)hydrazine-1,2-dicarboxylate (10e): The title compound was obtained according to the general procedure (quant. yield). $[\alpha]_D^{20}=+73.6$ ($c=0.57$ in $CHCl_3$); ^{1}H NMR (50°C): $\delta=7.16$ (t, $J=7.5$ Hz, 2H), 6.57–6.70 (m, 4H), 5.19 (brs, 1H), 4.89 (dt, $J=2.7$, 10.3 Hz, 1H), 3.89–4.30 (m, 5H), 3.54 (d, $J=13.6$ Hz, 1H), 3.03 (t, $J=12.3$ Hz, 1H), 2.60 (brs, 4H), 2.34–3.47 (m, 1H), 1.53–1.61 (m, 1H), 0.95–1.36 (m, 16H), 0.89 ppm (t, $J=6.9$ Hz, 3H); ^{13}C NMR: $\delta=178.7$, 176.9, 157.7, 156.3, 147.7, 129.2, 117.5, 113.6, 62.9, 62.5, 57.2, 52.0, 41.3, 31.6, 29.1, 29.0, 27.8, 26.4, 22.5, 14.3, 14.0, 13.8 ppm, additional peaks and line broadenings are observed due to rotameric species; HRMS: calcd for $C_{26}H_{40}N_4NaO_6$: 527.2840 $[M+Na]^+$; found: 527.2839; the *ee* was determined by HPLC using a Chiralcel OD column (hexane/*i*PrOH 95:5); flow rate = 1.0 mL min^{-1}; major diastereomer: $\tau_{major}=40.1$ min, $\tau_{minor}=17.4$ min (99% *ee*); minor diastereomer: $\tau_{major}=123.4$ min, $\tau_{minor}=61.8$ min (99% *ee*); dr = 94:6.

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