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Generation of Quaternary Stereocenters by Asymmetric Michael Reactions: Enamine Regiochemistry as Configuration Switch

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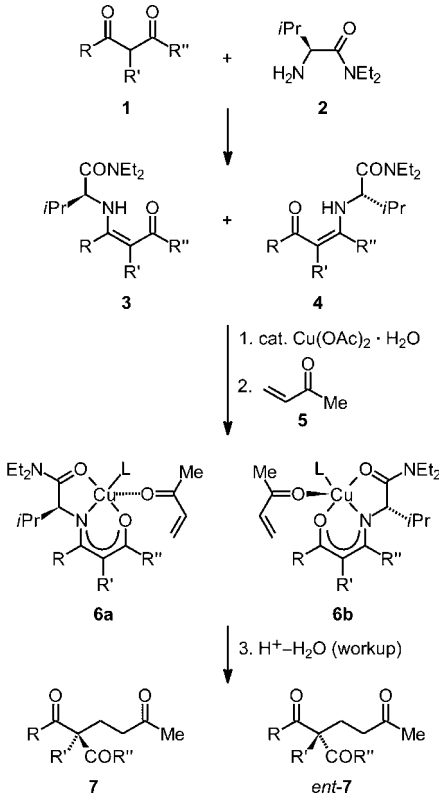
Abstract: Regioselective enamine formation from cyclic β-diketones **1** is obtained by the appropriate choice of activating agent: Brønsted acid catalyzed condensation gives endocyclic enamines **3** as the thermodynamically favored products. Activation with Lewis acid $BF_3{\cdot}OEt_2$ affords betaines **8** as intermediate products, which can be reacted with L-valine diethylamide (**2**) to preferentially furnish exocyclic enamines **4** as kinetic products. Derivatives with quaternary stereocenters were accessible from both isomeric enamines by using asymmetric, copper(II)-catalyzed Michael reactions at ambient temperature. Both regioisomers afford the triketones **7** with the same constitution but bearing the opposite absolute configuration at the quaternary stereocenter. Thus, both enantiomers of the product are prepared by using the same chiral auxiliary derived from L-valine.

Keywords: boron · chiral auxiliaries · enamines · Michael addition · regioselectivity

Introduction

The stereoselective generation of quaternary stereocenters is still one of the most challenging tasks in organic synthesis and the definitive landmark for any asymmetric C–C bond-forming reaction.[1] Conjugate additions or 1,4-additions of enolates or other carbon nucleophiles to acceptor-substituted olefins (Michael reaction) belong to the most important and versatile group of reactions for the synthesis of quaternary as well as tertiary stereocenters.[2,3] Enantioselective Michael reactions applying chiral Brønsted base catalysts[4] or using metal catalysts together with chiral ligands[5] have been established. In some cases, the application of chiral auxiliaries, however, turned out to be more promising.[6] Thus, the copper(II)-catalyzed Michael reaction with L-valine diethylamide as the chiral auxiliary is an established method for the highly enantioselective construction of quaternary stereocenters at ambient temperature.[7] The auxiliary initially reacts with the substrate, typically β-oxo esters and β-diketones, to form chiral enamines. As shown in Scheme 1, the reaction of β-diketones **1** might result in mixtures of isomeric enamines **3** and **4**.[8] This fact may be used synthetically in the subsequent Michael reaction if both enamines **3**



Scheme 1. Regioisomeric enamines **3** and **4**, derived from 1,3-diketones **1** and the chiral auxiliary L-valine diethylamide (**2**), gave Michael addition products **7** with the opposite configuration.

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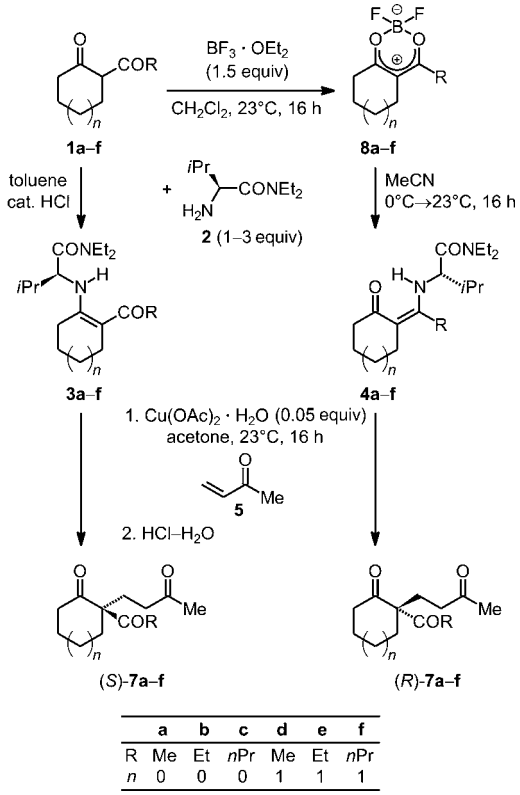
and **4** are obtained regioselectively. According to the proposed mechanism, the Cu^{II}-catalyzed addition reaction[9] proceeds via a six-membered copper azadiketonato complex **6**. Depending on the starting enamine, the acceptor methyl vinyl ketone (**5**) either coordinates to the Cu center and attacks from the back face (complex **6a**) or through acceptor coordination and attack occurs from the front face (complex **6b**). Reaction intermediates **6a** and **b** in the catalytic cycle are constitutional isomers, yielding, after aqueous, acidic workup, optically active triketones **7** and *ent*-**7** with opposite absolute configuration by use of the (*S*)-isomer of the valine derivative (Scheme 1). However, in the case of cyclic 1,3-diketone **1d** (R, R′=-$(CH_2)_4$-) with an acetyl moiety (R″=Me), instead of an open-chain product, subsequent spirocyclization of the exocyclic enamine (like **4**) has been observed.[10] The question arises as to whether the methyl group (R″=Me) is responsible for this spirocyclization and it will be addressed in this work.

In the present paper we wish to report on the regioselective generation of enamines from cyclic β-diketones **1** and L-valine diethylamide **2** by means of either Lewis or Brønsted acid activation. The resulting regioisomers are then used in asymmetric Michael reactions. Furthermore, we have prepared homologous cyclic β-alkanoyl ketones in order to investigate whether the alkyl substituent influences the course of the Michael reaction to give spirocyclic or open-chain addition products.



	a	b	c	d	e	f
R	Me	Et	*n*Pr	Me	Et	*n*Pr
n	0	0	0	1	1	1

Scheme 2. Preparation of endo- and exocyclic enamines **3** and **4** and their use as a configuration switch in asymmetric copper(II)-catalyzed Michael reactions.

Results and Discussion

Regioselective formation of endo- and exocyclic enamines from β-diketones 1: Our synthetic strategy for selectively preparing endo- and exocyclic enamines **3** and **4** is depicted in Scheme 2.

In order to prepare exocyclic enamines **4a–f**, which can be considered as the kinetically favored regioisomers, β-diketones **1a–f** and the effective Lewis acid activating agent BF_3•OEt_2[11] were first reacted in CH_2Cl_2 at ambient temperature to give oxonia–boranuida betaines **8a–f** in good yields (Table 1). Betaines **8** are oils or crystalline solids stable towards air and moisture.

Table 1. Prepared oxonia–boranuida compounds **8**.

Betaine	*n*	R	Yield [%]
8a	0	Me	81
8b	0	Et	62
8c	0	*n*Pr	91
8d	1	Me	85
8e	1	Et	90
8f	1	*n*Pr	84

From several betaines, single crystals suitable for X-ray diffraction analysis were obtained by recrystallization from diethyl ether. As exemplified for **8f** (Figure 1a),[12] all structures show planarity at the former β-diketone moiety and have C–C distances of 1.38 Å representing a bond order of about 1.5. Therefore, compound **8f** is best represented by the two mesomeric structures depicted in Figure 1b.

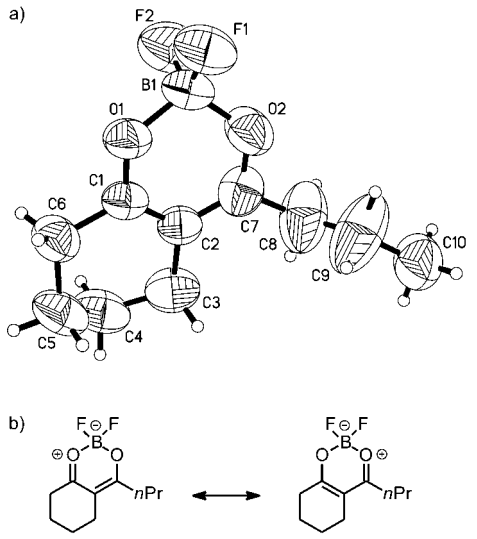


Figure 1. a) Molecular structure of borate–betaine complex **8f** in the solid state (ORTEP representation) and b) mesomeric structures. Selected bond lengths (Å): 1.31 (C1–O1), 1.37 (C1–C2), 1.38 (C2–C7), 1.30 (C7–O2).

The effect of ring size on the Brønsted acid catalyzed formation of exo- or endocyclic enamines from α-acetylcycloalkanones was investigated by Enriquez and Reynolds.[8] In all cases, they observed mixtures of both isomers. In their study, 2-acetylcyclohexanone (**1d**) showed a strong preference for the endocyclic enamine, whereas its five-membered homologue (**1a**) slightly preferred the exocyclic double bond. These results are in accordance with the Dieckmann–Kon rule[13] of the regioselective enolization of cyclic β-oxo esters. In our studies we found that α-alkanoylcyclopentanones **1a–c** initially gave mixtures of both regioisomers in the acid-catalyzed conversion with L-valine diethylamide, with slight preference for the kinetically favored exocyclic double bond (Table 2). However, prolonged heating of the reaction mixture leads to isomerization of this double bond to give the endocyclic enamines as thermodynamically favored products in good yields. For **1c**, this isomerization step proceeded quantitatively (Table 2). No water-scavenging agent was used in order not to remove a needed equilibrium component. In contrast to the cyclopentanone series, the conversion of all six-membered β-diketones **1d–f** gave the endocyclic enamines **3d–f** exclusively.

Table 2. Synthesis of endo- and exocyclic enamines **3** and **4** starting from β-diketones **1** and betaines **8**, respectively.

SM[a]	*n*	R	Enamine	*T* [°C]	*t*	Yield [%]	*exo*:*endo*
1a	0	Me	**3a**	100	5 d	65	13:87
1b	0	Et	**3b**	65	14 d	62	3:97
1c	0	*n*Pr	**3c**	100	48 h	77	0:100
1d	1	Me	**3d**	50	18 h	63	0:100
1e	1	Et	**3e**	23	72 h	87	0:100
1f	1	*n*Pr	**3f**	55	16 h	88	0:100
8a	0	Me	**4a**	0→23	16 h	93	100:0
8b	0	Et	**4b**	0→23	16 h	91	100:0
8c	0	*n*Pr	**4c**	0→23	16 h	82	100:0
8d	1	Me	**4d**	0→23	16 h	87	97.5:2.5
8e	1	Et	**4e**	0→23	16 h	52[b]	63:37
8f	1	*n*Pr	**4f**	0→23	16 h	34[c]	68:32

[a] SM = Starting material. [b] 30% of isolated endocyclic enamine **3e**. [c] 16% of isolated endocyclic enamine **3f**.

Betaines **8** were reacted with L-valine diethylamide in MeCN or CH_2Cl_2 to give the exocyclic enamines **4** as major isomers in all cases (Table 2). The five-membered betaines **8a–c** formed the exocyclic enamines **4a–c** exclusively and in high yields. However, the six-membered ring betaines **8d–f** gave mixtures of both regioisomers. Compound **4d** was first obtained as an *exo*:*endo* = 80:20 mixture at ambient temperature. This selectivity could be enhanced to 97.5:2.5 in favor of the exocyclic product **4d** by lowering the temperature to 0°C. Further temperature reduction did not affect the selectivity any more. Lower selectivities were obtained for the propionyl and butyryl derivatives **4e** and **4f** (Table 2), however, the undesired endocyclic enamines **3e** and **3f** could be separated by column chromatography on alumina.

All kinetic enamines **4** were obtained as the (*Z*)-configured isomers stabilized by hydrogen bonds between the nitrogen and oxygen atoms indicated by ^1H chemical shifts of around 12 ppm. These studies show that an appropriate choice of activating agent (Brønsted vs Lewis acid) and temperature allows the determination of the enamine-formation position from β-diketones, in moderate to excellent selectivities.

Copper-catalyzed asymmetric Michael reactions: The behavior of endocyclic enamines **3** and their exocyclic congeners **4** in asymmetric Michael reactions has been investigated. They were stirred with a catalytic amount (5 mol%) of $Cu(OAc)_2 \cdot H_2O$ in acetone to furnish a dark-green copper(II) azadionato complex. Methyl vinyl ketone (**5**) was added, and the reaction progress is visible by the disappearance of the green color. Whereas endocyclic enamines **3** generally reacted completely within 16 h, exocyclic enamines **4** required five days until the reaction was finished. Hydrolysis with aqueous hydrochloric acid finally afforded the respective addition products (*S*)- and (*R*)-**7** (Scheme 2, Table 3).

As expected, in all cases the opposite stereoisomer was obtained: endocyclic enamines afforded (*S*)-configured Michael products **7** showing positive optical rotation, whereas all exocyclic enamines furnished the complementary (*R*)-enantiomers **7** with negative optical-rotation values. All *ee* values were determined by GLC on a chiral phase. Baseline separation was optimized with racemic reference materials prepared by conversion of β-diketones **1** with methyl vinyl ketone (**5**) in the presence of catalytic quantities of $FeCl_3 \cdot 6H_2O$.[14]

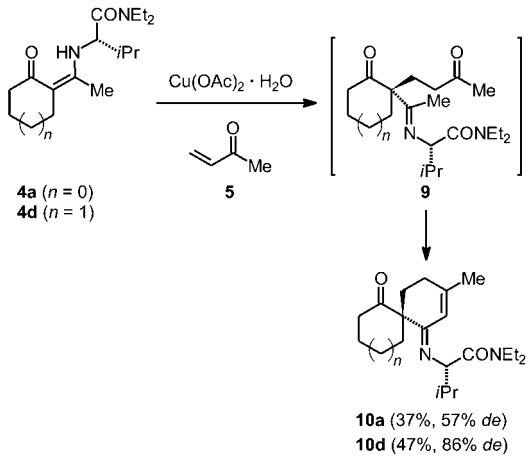
Table 3. Formation of Michael addition products (*S*)-**7** and (*R*)-**7** from chiral endo- and exocyclic enamines, respectively, and methyl vinyl ketone (**5**).

		Starting with endocyclic enamines **3**			Starting with exocyclic enamines **4**		
n	R	product	yield [%]	*ee* [%]	product	yield [%]	*ee* [%]
0	Me	(*S*)-**7a**	46	87	(*R*)-**7a**	5[a]	61
0	Et	(*S*)-**7b**	85	88	(*R*)-**7b**	30	13
0	*n*Pr	(*S*)-**7c**	69	82	(*R*)-**7c**	73	39
1	Me	(*S*)-**7d**	67	96	(*R*)-**7d**	–[b]	–[b]
1	Et	(*S*)-**7e**	76	97	(*R*)-**7e**	72	67
1	*n*Pr	(*S*)-**7f**	73	98	(*R*)-**7f**	23	83

[a] The respective spirocyclic imine **10a** was obtained as the major product. [b] Exclusive formation of imine **10d** (see Scheme 3).

As can be seen from Table 3, for products (*S*)-**7** derived from endocyclic enamines **3**, good yields of about 75% and enantiomeric excesses from 82 to 98% were realized. In the case of triketones (*R*)-**7** from exocyclic enamines **4**, yields and selectivities were lower.

Table 3 reveals that acetylcyclopentanone (*R*)-**7a** was obtained from the corresponding exocyclic enamine **4a** in trace amounts only. Instead, the spirocyclic imine **10a** was isolated as the major product (Scheme 3). In the case of the



Scheme 3. Formation of spirocyclic imines **10a**,**d** from exocyclic enamines **4a**,**d**.

six-membered exocyclic enamine **4d**, the spirocyclic imine **10d** was even formed exclusively. This result is in accordance with a previous report.[10] Under the reaction conditions used, the initial resultant imine intermediate **9** was evidently deprotonated to give an aza enolate. The latter subsequently spirocyclizes in a Robinson-type annulation to yield imines **10**. A comparable spirocyclization was observed by Pfau and co-workers when using phenethylamine as a chiral auxiliary.[15]

The substitution of the methyl substituent by the longer alkyl groups ethyl and propyl, indeed suppressed the spirocyclization, and the respective exocyclic enamines **4b**,**c**,**e**,**f** furnished the desired open-chain Michael adducts **7b**,**c**,**e**,**f**. In these cases, the additional inductive effect of the substituent seems to destabilize a conceivable aza enolate, therefore preventing it from deprotonation and annulation.

Conclusion

We were able to point out that control of the regioselectivity of endo- and exocyclic enamine formation allows the complementary preparation of either stereoisomer of triketones **7** by using the same chiral auxiliary, that is, the (*S*)-enantiomer of valine diethylamide available from the natural source. The regioselectively formed enamines thus act as a configuration switch. Replacement of the acetyl moiety in the cyclic β-diketones by propionyl or butyryl prevents deprotonation, and thus, Robinson annulation to give an undesired spirocyclic product from the exocyclic precursors is inhibited.

Experimental Section

General: Melting points were measured on a Büchi 510 apparatus and are uncorrected. Starting materials **1a** and **d** are commercially available. BF_3·OEt_2 was purchased from Aldrich Chemical Co. The following compounds were prepared according to literature procedures: **1b**,**c**,**e**,**f**,[16] **3a**,[17] **d**,[7b] **8a**,[11] **d**,[17] **4a**,**e**, and **10a**,**d**.[17] Column chromatography was carried out using Merck silica gel 60 or Merck basic alumina (act. I) with petroleum ether (PE, b.p. 40–60°C) and ethyl acetate (EA) as eluents. ^{1}H NMR spectra were recorded on a Bruker ARX 500 (500 MHz) or a Bruker ARX 300 (300 MHz) apparatus. ^{13}C NMR spectra were recorded on a Bruker ARX 500 (126 MHz), a Bruker ARX 300 (75 MHz), or a Bruker AC 250 (63 MHz) apparatus. Multiplicities were determined with distortionless enhancement by polarization transfer (DEPT) experiments. ^{19}F NMR spectra were recorded on a Bruker AC 250 (250 MHz) apparatus with trifluoroacetic acid ($\delta^{19}F = -77.00$ ppm) as internal standard. IR sprectra were recorded on a Bruker Vector 22 (ATR = attenuated total reflectance). GC analyses were performed with a HRGC 5300 (Carlo Erba Strumentazione) with flame ionization detector (FID), and a Bondex unα/β (20 m × 0.3 mm) or Lipodex E (25 m × 0.3 mm) column with hydrogen carrier gas (0.4 bar).

General procedure for the preparation of endocyclic enamines 3: To a solution of the respective β-diketone **1** and L-valine diethylamide (**2**) in toluene (for **3b**: $CDCl_3$), a drop of concentrated hydrochloric acid was added. The mixture was stirred at the respective temperature for the time given in Table 2. After evaporation of all volatile materials, the residue was purified by column chromatography (alumina, PE/EA).

***N*-(2-Propionyl-1-cyclopentenyl)-L-valine diethylamide (3b)**: According to the general procedure, 2-propionylcyclopentanone (**1b**; 500 mg, 3.57 mmol), L-valine diethylamide (**2**; 500 mg, 2.90 mmol), and a drop of concentrated hydrochloric acid were reacted in $CDCl_3$ (3 mL). Chromatography (alumina, PE/EA 1:2, R_f(silica gel) = 0.28) yielded a mixture of **3b** and **4b** in a ratio of 93:7 (determined from integrals of the NH protons in the ^{1}H NMR) as a pale-yellow solid (530 mg, 1.80 mmol, 62%). M.p. 67–69°C; $[\alpha]_D^{20} = +150$ ($c = 9.1$ in $CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.98$ (d, $^3J = 6.6$ Hz, 3H; $CHCH_3$), 1.01 (d, $^3J = 6.6$ Hz, 3H; $CHCH_3$), 1.10 (t, $^3J = 7.4$ Hz, 3H; CH_3), 1.12 (t, $^3J = 7.1$ Hz, 3H; NCH_2CH_3), 1.19 (t, $^3J = 7.1$ Hz, 3H; NCH_2CH_3), 1.85 (quint, $^3J = 7.5$ Hz, 2H; 4′-H), 2.08 (oct, $^3J = 6.7$ Hz, 1H; $CHCH_3$), 2.35 (q, $^3J = 7.4$ Hz, 2H; CH_2Me), 2.56 (t, $^3J = 5.9$ Hz, 2H), 2.59 (t, $^3J = 6.8$ Hz, 2H), 3.17 (dt, $^2J = (-)13.7$, $^3J = 6.9$ Hz, 1H; NCH_2), 3.30 (dt, $^2J = (-)14.5$, $^3J = 7.2$ Hz, 1H; NCH_2), 3.38 (dt, $^2J = (-)14.5$, $^3J = 7.2$ Hz, 1H; NCH_2), 3.58 (dt, $^2J = (-)13.7$, $^3J = 6.9$ Hz, 1H; NCH_2), 3.96 (dd, $^3J = 9.5$, $^3J = 6.5$ Hz, 1H; $CHNH$), 9.75 ppm (br d, $^3J = 9.5$ Hz, 1H; NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): $\delta = 8.14$ (CH_3), 12.72 (CH_3; CH_2CH_3), 14.46 (CH_3; CH_2CH_3), 17.72 (CH_3; $CHCH_3$), 19.68 (CH_3; $CHCH_3$), 21.25 (C-4′), 29.52 (CH_2; C-5′), 31.97 (CH_2; CH_2Me), 32.23 (CH; $CHCH_3$), 33.22 (CH_2; C-3′), 40.14 (CH_2; NCH_2), 41.44 (CH_2; NCH_2), 60.78 (CH; CHNH), 104.67 (C; C-2′), 168.86 (C; C-1′), 169.97 (C; CON), 196.65 ppm (C; COEt); IR (ATR): $\tilde{\nu} = 3248$ (m), 2965 (m), 2934 (m), 1714 (m), 1622 (vs), 1553 (s), 1460 (m), 2357 (m), 1278 (w), 1244 (m), 1216 (m), 1184 (m), 1153 (m), 1097 (w), 1035 (m), 893 (m), 867 (w), 851 (w), 786 (m), 723 (w), 631 cm^{-1} (vs); MS (70 eV, EI): m/z (%): 294 (7) [M^+], 251 (1), 228 (1), 194 (100) [$M^+ - CONEt_2$], 150 (4), 128 (3), 100 (3) [$CONEt_2^+$], 72 (12) [NEt_2^+], 57 (4) [$C_3H_5O^+$]; elemental analysis calcd (%) for $C_{17}H_{30}N_2O_2$ (294.43): C 69.35, H 10.27, N 9.52; found: C 68.79, H 10.26, N 9.43; HRMS (70 eV, EI): m/z calcd for $C_{17}H_{30}N_2O_2$: 294.2307; found: 294.2308.

***N*-(2-Butyryl-1-cyclopentenyl)-L-valine diethylamide (3c)**: According to the general procedure, 2-butyrylcyclopentanone (**1c**; 1.00 g, 6.48 mmol), L-valine diethylamide (**2**; 1.11 g, 6.48 mmol), and four drops of concentrated hydrochloric acid were reacted in toluene (2 mL) for 2 d at 100°C. Chromatography (alumina, PE/EA 1:1, R_f(silica gel) = 0.24) yielded **3c** as

a colorless solid (1.53 g, 4.96 mmol, 77%). M.p. 67–68°C; $[\alpha]_D^{20}=+131$ ($c=25.0$ in $CDCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): $\delta=0.94$ (t, $^3J=7.4$ Hz, 3H; CH_3), 0.98 (d, $^3J=6.8$ Hz, 3H; $CHCH_3$), 1.00 (d, $^3J=6.9$ Hz, 3H; $CHCH_3$), 1.11 (t, $^3J=7.2$ Hz, 3H; NCH_2CH_3), 1.19 (t, $^3J=7.2$ Hz, 3H; NCH_2CH_3), 1.64 (sex, $^3J=7.4$ Hz, 2H; CH_2Me), 1.84 (quint, $^3J=7.6$ Hz, 2H; 4′-H), 2.07 (oct, $^3J=6.9$ Hz, 1H; $CHCH_3$), 2.28 (t, $^3J=7.4$ Hz, 2H), 2.44–2.54 (m, 2H), 2.59 (t, $^3J=7.2$ Hz, 2H; CH_2Et), 3.18 (dq, $^2J=(-)13.7$, $^3J=6.9$ Hz, 1H; NCH_2), 3.25–3.47 (m, 2H; NCH_2), 3.58 (dq, $^2J=(-)13.7$, $^3J=6.9$ Hz, 1H; NCH_2), 3.95 (dd, $^3J=9.5$, $^3J=6.5$ Hz, 1H; CHNH), 9.79 ppm (br d, $^3J=9.2$ Hz, 1H; NH); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): $\delta=12.90$ (NCH_2CH_3), 14.24 (CH_3), 14.64 (NCH_2CH_3), 17.81 ($CHCH_3$), 17.91 (CH_2), 19.85 ($CHCH_3$), 21.41 (CH_2), 29.78 (CH_2), 32.15 (CH_2), 32.37 (CH; $CHCH_3$), 40.29 (CH_2; NCH_2), 41.59 (CH_2; NCH_2), 42.53 (CH_2; CH_2Et), 61.00 (CH; CHNH), 105.12 (C; C-2′), 164.22 (C; C-1′), 170.09 (C; CON), 196.34 ppm (C; COPr); IR (ATR): $\tilde{\nu}=3262$ (br w), 2959 (m), 2324 (w), 2872 (w), 2839 (w), 1714 (w), 1614 (vs), 1545 (s), 1449 (s), 1430 (s), 1360 (m), 1328 (m), 1314 (m), 1276 (s), 1237 (s), 1216 (s), 1176 (w), 1132 (m), 1119 (m), 1087 (m), 1034 (m), 949 (w), 824 (w), 702 cm^{-1} (m); MS (70 eV, EI): m/z (%): 308 (3) [M^+], 242 (4), 208 (39) [$M^+-CONEt_2$], 164 (2), 142 (20), 129 (4), 100 (17) [$CONEt_2^+$], 72 (100) [NEt_2^+], 55 (5), 43 (11) [$C_3H_7^+$]; HRMS (70 eV, EI): m/z calcd for $C_{18}H_{32}N_2O_2$: 308.2464; found: 308.2464.

***N*-(2-Propionyl-1-cyclohexenyl)-L-valine diethylamide (3e)**: According to the general procedure, 2-propionylcyclohexanone (**1e**; 800 mg, 5.19 mmol), L-valine diethyl amide (**2**; 1.00 g, 5.80 mmol), one drop of concentrated hydrochloric acid, and molecular sieves (4 g, 4 Å) were reacted in toluene (5 mL) for 3 d at 23°C. Chromatography (alumina, PE/EA 1:2, R_f(silica gel)=0.42) yielded **3e** as a pale-yellow solid (1.40 g, 1.80 mmol, 87%). M.p. 53°C; $[\alpha]_D^{20}=+255$ ($c=10.1$ in $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): $\delta=1.05$ (d, $^3J=6.8$ Hz, 3H; $CHCH_3$), 1.10 (d, $^3J=6.7$ Hz, 3H; $CHCH_3$), 1.12 (t, $^3J=7.3$ Hz, 3H; CH_3), 1.14 (t, $^3J=7.1$ Hz, 3H; NCH_2CH_3), 1.19 (t, $^3J=7.1$ Hz, 3H; NCH_2CH_3), 1.59–1.69 (m, 4H; 4′-H and 5′-H), 2.12 (oct, $^3J=6.8$ Hz, 1H; $CHCH_3$), 2.20 (dt, $^2J=(-)17.7$, $^3J=5.8$ Hz, 1H; NCH_2), 2.35–2.39 (m, 3H), 2.43 (q, $^3J=7.3$ Hz, 1H; CH_2Me), 2.44 (q, $^3J=7.3$ Hz, 1H; CH_2Me), 3.27 (dq, $^2J=(-)14.1$, $^3J=7.0$ Hz, 1H; NCH_2), 3.41 (q, $^3J=7.1$ Hz, 1H; NCH_2), 3.41 (q, $^3J=7.2$ Hz, 1H; NCH_2), 3.53 (dq, $^2J=(-)14.1$, $^3J=7.0$ Hz, 1H; NCH_2), 4.14 (dd, $^3J=8.4$, $^3J=6.8$ Hz, 1H; CHNH), 11.80 ppm (d, $^3J=8.2$ Hz, 1H; NH); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): $\delta=8.81$ (CH_3), 12.81 (CH_3; NCH_2CH_3), 14.43 (CH_3; NCH_2CH_3), 18.60 (CH_3; $CHCH_3$), 19.99 (CH_3; $CHCH_3$), 22.01 (CH_2), 23.04 (CH_2), 25.38 (CH_2), 26.84 (CH_2; C-6′), 32.06 (CH; $CHCH_3$), 32.07 (CH_2; CH_2Me), 40.33 (CH_2; NCH_2), 41.56 (CH_2; NCH_2), 60.01 (CH; CHNH), 100.76 (C; C-2′), 159.42 (C; C-1′), 170.48 (C; CON), 199.55 ppm (COEt); IR (ATR): $\tilde{\nu}=2967$ (m), 2931 (m), 2871 (w), 2831 (m), 1714 (w), 1628 (s), 1595 (s), 1557 (s), 1455 (s), 1425 (s), 1367 (m), 1328 (m), 1276 (m), 1215 (vs), 1160 (m), 1138 (m), 1119 (s), 1097 (m), 1064 (m), 1040 (m), 1013 (w), 960 (m), 829 (m), 813 (m), 776 (w), 718 (w), 701 cm^{-1} (w); MS (70 eV, EI): m/z (%): 308 (5) [M^+], 208 (100) [$M^+-CONEt_2$], 190 (4), 164 (4), 152 (11) [$C_9H_{14}NO^+$], 125 (11), 110 (11), 82 (27), 72 (52) [NEt_2^+], 57 (15) [$COEt^+$]; HRMS (70 eV, EI): m/z calcd for $C_{18}H_{32}N_2O_2$: 308.2464; found: 308.2463.

***N*-(2-Butyryl-1-cyclohexenyl)-L-valine diethylamide (3f)**: According to the general procedure, 2-butyrylcyclohexanone (**1f**; 1.00 g, 6.16 mmol), L-valine diethylamide (**2**; 1.27 g, 7.40 mmol), and one drop of concentrated hydrochloric acid were reacted in toluene (5 mL) at 55°C for 16 h. Chromatography (alumina, PE/EA 1:2, R_f(silica gel)=0.47) yielded **3f** as a yellow oil (1.75 g, 5.43 mmol, 88%). $[\alpha]_D^{20}=+238$ ($c=19.2$ in $CDCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): $\delta=0.94$ (t, $^3J=7.5$ Hz, 3H; CH_3), 1.01 (d, $^3J=6.8$ Hz, 3H; $CHCH_3$), 1.06 (d, $^3J=6.6$ Hz, 3H; $CHCH_3$), 1.11 (t, $^3J=7.0$ Hz, 3H; NCH_2CH_3), 1.16 (t, $^3J=7.0$ Hz, 3H; NCH_2CH_3), 1.61–1.67 (m, 6H; 4′-H, 5′-H, and CH_2Me), 2.08 (oct, $^3J=6.7$ Hz, 1H; $CHCH_3$), 2.17 (dt, $^2J=(-)17.4$, $^3J=6.3$ Hz, 1H), 2.32–2.38 (m, 5H), 3.24 (dq, $^2J=(-)13.6$, $^3J=6.7$ Hz, 1H; NCH_2), 3.38 (q, $^3J=7.1$ Hz, 2H; NCH_2), 3.49 (dq, $^2J=(-)13.9$, $^3J=6.7$ Hz, 1H; NCH_2), 4.10 (dd, $^3J=7.9$, $^3J=7.1$ Hz, 1H; CHNH), 11.84 ppm (br d, $^3J=8.0$ Hz, 1H; NH); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): $\delta=12.74$ (CH_3; NCH_2CH_3), 14.19 (CH_3), 14.35 (CH_3; NCH_2CH_3), 18.16 (CH_2; CH_2Me), 18.58 (CH_3; $CHCH_3$), 19.92 (CH_3; $CHCH_3$), 21.96 (CH_2), 23.03 (CH_2), 25.49 (CH_2), 26.79 (CH_2; C-6′), 31.97 (CH; $CHCH_3$), 40.28 (CH_2; NCH_2), 41.09 (CH_2; CH_2Et), 41.40 (CH_2; NCH_2), 60.18 (CH; CHNH), 100.88 (C; C-2′), 159.60 (C; CON), 170.41 (C; C-1′), 198.93 ppm (C; COPr); IR (ATR): $\tilde{\nu}=2970$ (w), 2926 (m), 2866 (w), 2834 (w), 1714 (w), 1630 (s), 1598 (s), 1558 (vs), 1486 (s), 1367 (m), 1338 (m), 1297 (m), 1276 (s), 1237 (m), 1207 (vs), 1168 (s), 1158 (s), 1134 (s), 1107 (m), 1096 (m), 1063 (s), 973 (w), 823 (m), 779 (m), 740 cm^{-1} (w); MS (70 eV, EI): m/z (%): 322 (6) [M^+], 279 (1) [$M^+-C_3H_7$], 222 (100) [$M^+-CONEt_2$], 178 (5), 152 (8), 100 (5) [$CONEt_2^+$], 82 (15), 72 (14) [NEt_2^+], 67 (7), 55 (6), 43 (8) [$C_3H_7^+$]; HRMS (70 eV, EI): m/z calcd for $C_{19}H_{34}N_2O_2$: 322.2620; found: 322.2619.

5-Ethyl-3,3-difluoro-4-oxa-2-oxonia-3-boratabicyclo[4.3.0]nona-1,5-diene (8b): 2-Propionylcyclopentanone (**1b**; 6.00 g, 4.19 mmol) and $BF_3{\cdot}OEt_2$ (7.10 g, 50.3 mmol) in CH_2Cl_2 (8 mL) were stirred for 90 h at 23°C. The mixture was poured into water (20 mL) and then extracted with CH_2Cl_2 (3×20 mL). After drying ($MgSO_4$) and evaporation of all volatile materials, the residue was purified by column chromatography (silica gel, PE/EA 3:1 $R_f=0.24$) to yield **8b** as a brown oil (4.68 g, 25.9 mmol, 62%). ^1H NMR ($CDCl_3$, 300 MHz): $\delta=1.25$ (t, $^3J=7.5$ Hz, 3H; CH_3), 2.10 (tt, $^3J=5.7$, $^3J=5.1$ Hz, 2H; 8-H), 2.54 (q, $^3J=7.2$ Hz, 2H; CH_2Me), 2.67 (dd, $^3J=7.8$, $^3J=6.9$ Hz, 2H), 2.75 ppm (t, $^3J=7.8$ Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): $\delta=8.92$ (CH_3), 20.45 (CH_2), 25.25 (CH_2), 29.25 (CH_2), 34.78 (CH_2), 112.42 (C; C-6), 191.11 (C; CO), 199.29 ppm (C; CO); $^{19}F\{^1H\}$ NMR ($CDCl_3$, 235 MHz): $\delta=-139.76$ ppm (s); IR (ATR): $\tilde{\nu}=2987$ (w), 2946 (w), 1607 (s), 1538 (vs), 1462 (w), 1404 (w), 1383 (w), 1361 (w), 1311 (w), 1187 (m), 1088 (w), 1037 cm^{-1} (m); MS (70 eV, EI): m/z (%): 188 (18) [M^+], 169 (4) [M^+-F], 159 (100) [$M^+-C_2H_5$], 131 (4), 103 (3), 79 (3), 65 (6) [BF_2O^+]; elemental analysis calcd (%) for $C_8H_{11}BF_2O_2$ (187.98): C 51.11, H 5.90; found: C 51.21, H 5.95.

3,3-Difluoro-5-propyl-4-oxa-2-oxonia-3-boratabicyclo[4.3.0]nona-1,5-diene (8c): As reported above for **8b**, 2-butyrylcyclopentanone (**1c**, 3.00 g, 19.5 mmol) and $BF_3{\cdot}OEt_2$ (4.14 g, 29.2 mmol) were reacted for 16 h in CH_2Cl_2 (5 mL). Column chromatography (silica gel, PE/EA 3:1, $R_f=0.32$) yielded **8c** as a brown oil (3.57 g, 17.7 mmol, 91%). ^1H NMR ($CDCl_3$, 300 MHz): $\delta=1.00$ (t, $^3J=7.5$ Hz, 3H; CH_3), 1.76 (sex, $^3J=7.5$ Hz, 2H; CH_2Me), 2.09 (tt, $^3J=7.8$, $^3J=6.6$ Hz, 2H; 8-H), 2.48 (t, $^3J=7.2$ Hz, 2H; CH_2Et), 2.67 (dd, $^3J=7.5$, $^3J=7.2$ Hz, 2H), 2.75 ppm (t, $^3J=7.8$ Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): $\delta=13.74$ (CH_3), 18.19 (CH_2), 18.59 (CH_2), 20.12 (CH_2), 25.10 (CH_2), 34.48 (CH_2), 37.33 (CH_2), 112.36 (C; C-6), 190.00 (C; CO), 199.00 ppm (C; CO); $^{19}F\{^1H\}$ NMR ($CDCl_3$, 235 MHz): $\delta=-137.99$ ppm (s); IR (ATR): $\tilde{\nu}=2966$ (w), 2877 (w), 1970 (w), 1708 (m), 1601 (s), 1529 (vs), 1464 (w), 1405 (m), 1366 (m), 1311 (m), 1184 (s), 1100 (w), 1073 (m), 1033 cm^{-1} (s); MS (70 eV, EI): m/z (%): 202 (16) [M^+], 183 (5) [M^+-F], 174 (9), 159 (100) [$M^+-C_3H_7$], 131 (4), 121 (4), 103 (3), 91 (2) [$HBF_2O_2^+$], 79 (4), 65 (9) [BF_2O^+], 55 (3), 39 (5); HRMS (70 eV, EI): m/z calcd for $C_9H_{13}BF_2O_2$: 202.0977; found: 202.0977; elemental analysis calcd (%) for $C_9H_{13}BF_2O_2$ (202.01): C 53.51, H 6.49; found: C 53.97, H 6.60.

5-Ethyl-3,3-difluoro-4-oxa-2-oxonia-3-boratabicyclo[4.4.0]deca-1,5-diene (8e): 2-Propionylcyclohexanone (**1e**; 10.0 g, 64.8 mmol) and $BF_3{\cdot}OEt_2$ (11.0 g, 77.8 mmol) were stirred in CH_2Cl_2 (10 mL) for 16 h. Evaporation of all volatile materials and twofold recrystallization of the residue from Et_2O furnished **8e** as colorless crystals (11.8 g, 58.40 mmol, 90%). M.p. 32°C; ^1H NMR ($CDCl_3$, 500 MHz): $\delta=1.24$ (t, $^3J=7.5$ Hz, 3H; CH_3), 1.74–1.81 (m, 4H; 8-H and 9-H), 2.39 (t, $^3J=6.0$ Hz, 2H; 7-H), 2.57 (t, $^3J=6.2$ Hz, 2H; 10-H), 2.60 ppm (q, $^3J=7.4$ Hz, 2H; CH_2Me); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): $\delta=8.45$ (CH_3), 20.95 (CH_2), 21.96 (CH_2), 22.65 (CH_2), 28.24 (CH_2; $COCH_2$), 32.45 (CH_2; $COCH_2$), 108.24 (C; C-6), 189.53 (C; CO), 195.21 ppm (C; CO); $^{19}F\{^1H\}$ NMR ($CDCl_3$, 235 MHz): $\delta=-140.76$ ppm (s); IR (ATR): $\tilde{\nu}=2945$ (w), 1583 (s), 1516 (vs), 1385 (w), 1202 (m), 1050 cm^{-1} (m); MS (70 eV, EI): m/z (%): 202 (21) [M^+], 183 (5) [M^+-F], 173 (100) [$M^+-C_2H_5$], 125 (3), 79 (8), 57 (5) [$C_3H_5O^+$]; HRMS (70 eV, EI): m/z calcd for $C_9H_{13}{}^{10}BF_2O_2$: 201.1012; found: 201.1012; elemental analysis calcd (%) for $C_9H_{13}BF_2O_2$ (202.01): C 53.51, H 6.49; found: C 53.97, H 6.65.

3,3-Difluoro-5-propyl-4-oxa-2-oxonia-3-boratabicyclo[4.4.0]deca-1,5-diene (8f): As reported above for **8e**, 2-butyrylcyclohexanone (**1f**; 1.50 g, 8.92 mmol) and $BF_3{\cdot}OEt_2$ (2.53 g, 17.8 mmol) were reacted in CH_2Cl_2 (2 mL). Chromatography (silica gel, PE/EA 3:1, $R_f=0.32$) and subsequent twofold recrystallization from Et_2O yielded **8f** as a colorless oil

(1.62 g, 7.50 mmol, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.01 (t, ^3J = 7.4 Hz, 3H; CH_3), 1.71–1.81 (m, 6H; 8-H, 9-H, and CH_2Me), 2.40 (br t, ^3J = 6.1 Hz, 2H; 7-H), 2.53 (t, ^3J = 7.6 Hz, 2H; CH_2Et), 2.57 ppm (br t, ^3J = 5.7 Hz, 2H; 10-H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 13.75 (CH_3), 18.34 (CH_2), 20.89 (CH_2), 21.97 (CH_2), 22.79 (CH_2), 32.50 (CH_2; COCH_2), 36.46 (CH_2; COCH_2), 108.65 (C; C-6), 189.83 (C; CO), 194.53 ppm (C; CO); ^{19}F{^{1}H} NMR ($CDCl_3$, 235 MHz): δ = −140.95 ppm (s); IR (ATR): $\tilde{\nu}$ = 2967 (m), 2938 (m), 2878 (w), 1739 (w), 1572 (s), 1511 (vs), 1457 (m), 1385 (s), 1368 (s), 1340 (s), 1306 (m), 1200 (s), 1181 (m), 1154 (s), 1141 (s), 1101 (w), 1076 (m), 1045 (vs), 1029 (vs), 1010 cm^{-1} (s); MS (70 eV, EI): *m*/*z* (%): 216 (16) [M^+], 197 (5) [M^+−F], 173 (100) [M^+−C_3H_7], 79 (8); elemental analysis calcd (%) for $C_{10}H_{15}BF_2O_2$ (216.03): C 55.60, H 7.00; found: C 55.47, H 6.89.

General procedure for the preparation of exocyclic enamines 4: L-Valine diethylamide (**2**) was added dropwise to a solution of the respective betaine **8** in MeCN or CH_2Cl_2 at 0°C. The mixture was warmed up to 23°C and stirred for a further 16 h. All volatile materials were evaporated and the residue purified by column chromatography (alumina, PE/EA).

***N*-[1-(2-Oxocyclopentylidene)propyl]-L-valine diethylamide (4b)**: According to the general procedure, betaine **8b** (500 mg, 2.66 mmol) and L-valine diethylamide (**2**; 600 mg, 3.48 mmol) were reacted in CH_2Cl_2 (2 mL). Chromatography (PE/EA 1:1, R_f(silica gel) = 0.14) afforded **4b** as a pale-yellow oil (710 mg, 2.41 mmol, 91%). $[\alpha]_D^{20}$ = +230 (*c* = 8.7 in $CDCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.03 (d, ^3J = 6.8 Hz, 3H; CHCH_3), 1.06 (d, ^3J = 6.8 Hz, 3H; CHCH_3), 1.09 (t, ^3J = 7.7 Hz, 3H; CH_3), 1.12 (t, ^3J = 7.1 Hz, 3H; NCH_2CH_3), 1.20 (t, ^3J = 7.1 Hz, 3H; NCH_2CH_3), 1.84 (quint, ^3J = 7.8 Hz, 2H; 4′-H), 2.04–2.13 (m, 1H; CHCH$_3$), 2.16–2.23 (m, 2H; CH_2CH_3), 2.33 (t, ^3J = 7.9 Hz, 2H; 5′-H), 2.53 (t, ^3J = 7.1 Hz, 2H; 3′-H), 3.20–3.56 (m, 4H; NCH_2), 4.14 (dd, ^3J = 8.8, ^3J = 5.7 Hz, 1H; NHCH), 10.69 ppm (br d, ^3J = 9.2 Hz, 1H; NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 11.49 (CH_3; CH_2CH_3), 12.78 (CH_3; NCH_2CH_3), 14.37 (CH_3; NCH_2CH_3), 17.84 (CH_3; CHCH_3), 19.95 (CH_2; CHCH_3), 20.47 (CH_2; C-5′), 22.98 (CH_2; CH_2Me), 27.27 (CH_2; C-4′), 31.96 (CH; CHCH$_3$), 39.05 (CH_2; C-3′), 40.19 (CH_2; NCH_2), 41.39 (CH_2; NCH_2), 59.42 (CH; CHNH), 102.36 (C; C-1′), 161.59 (C; CNH), 170.19 (C; CON), 202.95 ppm (C; C-2′); IR (ATR): $\tilde{\nu}$ = 2969 (s), 2936 (m), 2876 (m), 1713 (m), 1620 (vs), 1548 (m), 1464 (s), 1382 (m), 1250 (w), 1216 cm^{-1} (w); HRMS (70 eV, EI): *m*/*z* calcd for $C_{17}H_{30}N_2O_2$: 294.2307; found: 294.2306.

***N*-[1-(2-Oxocyclopentylidene)butyl]-L-valine diethylamide (4c)**: According to the general procedure, betaine **8c** (210 mg, 1.03 mmol) and L-valine diethylamide (**2**; 580 mg, 3.38 mmol) were reacted in CH_2Cl_2 (1 mL). Chromatography (alumina, PE/EA 1:1, R_f = 0.41) yielded **4c** as a pale-yellow solid (263 mg, 0.85 mmol, 82%). $[\alpha]_D^{20}$ = +257 (*c* = 10.0 in $CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.99 (t, ^3J = 7.4 Hz, 3H; CH_3), 1.03 (d, ^3J = 6.9 Hz, 3H; CHCH_3), 1.05 (d, ^3J = 6.8 Hz, 3H; CHCH_3), 1.12 (t, ^3J = 7.1 Hz, 3H; NCH_2CH_3), 1.21 (t, ^3J = 7.1 Hz, 3H; NCH_2CH_3), 1.42–1.57 (m, 2H), 1.77–1.91 (m, 2H), 2.03–2.22 (m, 3H), 2.32 (t, ^3J = 7.8 Hz, 2H; 5′-H), 2.52 (dd, ^3J = 7.3, ^3J = 6.9 Hz, 2H; 3′-H), 3.18–3.58 (m, 4H; NCH_2), 4.12 (m, 1H; NHCH), 10.71 ppm (br d, ^3J = 9.2 Hz, 1H; NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 13.11 (CH_3), 14.72 (CH_3; NCH_2CH_3), 14.73 (CH_3; NCH_2CH_3), 18.14 (CH_3; CHCH_3), 20.32 (CH_3; CHCH_3), 20.87 (CH_2), 21.18 (CH_2), 27.98 (CH_2; C-4′), 32.25 (CH_2; CH_2Et), 32.29 (CH; CHCH$_3$), 39.45 (CH_2; C-3′), 40.51 (CH_2; NCH_2), 41.71 (CH_2; NCH_2), 59.91 (CH; CHNH), 103.32 (C-1′), 160.74 (C; CNH), 170.56 (C; CON), 203.21 ppm (C; C-2′); IR (ATR): $\tilde{\nu}$ = 2961 (m), 2935 (m), 2894 (m), 2838 (w), 2184 (br w), 1965 (br w), 1624 (vs), 1571 (vs), 1486 (m), 1453 (s), 1430 (s), 1379 (m), 1365 (m), 1341 (m), 1311 (m), 1289 (m), 1279 (m), 1250 (s), 1214 (s), 1179 (m), 1141 (m), 1123 (m), 1097 (s), 1067 (m), 1025 (m), 1007 (m), 947 (w), 877 (w), 835 (w), 778 (m), 756 (m), 726 (m), 683 cm^{-1} (w); MS (70 eV, EI): *m*/*z* (%): 308 (5) [M^+], 265 (1) [M^+−C_3H_7], 208 (100) [M^+−CONEt$_2$], 164 (3), 152 (1) [$C_9H_{14}NO^+$], 100 (3) [CONEt$_2^+$], 79 (1), 72 (5) [NEt$_2^+$], 55 (3); elemental analysis calcd (%) for $C_{18}H_{32}N_2O_2$ (308.46): C 70.09, H 10.46, N 9.08; found: C 69.85, H 10.45, N 9.21.

***N*-[1-(2-Oxocyclohexylidene)propyl]-L-valine diethylamide (4e)**: According to the general procedure, betaine **8e** (1.00 g, 4.95 mmol) and L-valine diethylamide (**2**, 1.00 g, 5.90 mmol) were reacted in MeCN (3 mL). Chromatography (alumina, PE/EA 1:1) furnished **3e** (451 mg, 1.46 mmol, 30%, R_f(silica gel) = 0.38). In a second fraction, **4e** (R_f(silica gel) = 0.14) was isolated as a colorless solid (789 mg, 2.56 mmol, 52%). M.p. 95°C; $[\alpha]_D^{20}$ = +268 (*c* = 12.2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.05 (d, ^3J = 6.8 Hz, 3H; CHCH_3), 1.08 (d, ^3J = 6.8 Hz, 3H; CHCH_3), 1.09 (t, ^3J = 7.7 Hz, 3H; CH_3), 1.12 (t, ^3J = 7.1 Hz, 3H; NCH_2CH_3), 1.19 (t, ^3J = 7.1 Hz, 3H; NCH_2CH_3), 1.63–1.73 (m, 4H; 4′-H and 5′-H), 2.11 (oct, ^3J = 6.5 Hz, 1H; CHCH$_3$), 2.33–2.49 (m, 6H; 3′-H, 6′-H, and CH_2Me), 3.21–3.54 (m, 4H; NCH_2), 4.19 (dd, ^3J = 8.5, ^3J = 6.0 Hz, 1H; CHNH), 12.80 ppm (br s, 1H; NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 12.26 (CH_3), 12.61 (CH_3; NCH_2CH_3), 14.15 (CH_3; NCH_2CH_3), 17.94 (CH_3; CHCH_3), 19.87 (CH_3; CHCH_3), 20.94 (CH_3), 22.71 (CH_2), 24.02 (CH_2), 25.42 (CH_2), 31.63 (CH; CHCH$_3$), 37.94 (CH_2; C-3′), 40.14 (CH_2; NCH_2), 41.28 (CH_2; NCH_2), 60.53 (CH; CHNH), 99.95 (C; C-1′), 166.64 (C; CNH), 170.03 (C; CON), 195.50 ppm (C-2′); IR (ATR): $\tilde{\nu}$ = 2962 (m), 2930 (s), 2874 (m), 1633 (s), 1584 (vs), 1560 (vs), 1452 (s), 1377 (m), 1343 (m), 1320 (m), 1274 (s), 1237 (s), 1217 (m), 1158 (m), 1082 (m), 1053 (m), 971 (m), 825 cm^{-1} (s); MS (70 eV, EI): *m*/*z* (%): 308 (8) [M^+], 265 (1) [M^+−C_3H_7], 208 (100) [M^+−CONEt$_2$], 190 (2), 164 (4), 150 (4), 72 (4) [NEt$_2^+$]; elemental analysis calcd (%) for $C_{18}H_{32}N_2O_2$ (308.47): C 70.09, H 10.46, N 9.08; found: C 70.15, H 10.52, N 9.04.

***N*-[1-(2-Oxocyclohexylidene)butyl]-L-valine diethylamide (4f)**: According to the general procedure, betaine **8f** (500 mg, 2.31 mmol) and L-valine diethylamide (**2**; 400 mg, 2.32 mmol) were reacted in CH_2Cl_2 (2 mL). Chromatography (alumina, PE/EA 1:2) afforded **3f** (117 mg, 0.36 mmol, 16%, R_f(PE/EA 1:1, silica gel) = 0.29). In a second fraction, **4f** (R_f(PE/EA 1:2, silica gel) = 0.11) was isolated as a colorless solid (253 mg, 0.79 mmol, 34%). M.p. 69°C; $[\alpha]_D^{20}$ = +25 (*c* = 0.5 in $CDCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.99 (t, ^3J = 7.3 Hz, 3H; CH_3), 1.04 (d, ^3J = 6.9 Hz, 3H; CHCH_3), 1.08 (d, ^3J = 6.7 Hz, 3H; CHCH_3), 1.11 (t, ^3J = 7.0 Hz, 3H; NCH_2CH_3), 1.19 (t, ^3J = 7.1 Hz, 3H; NCH_2CH_3), 1.42–1.51 (m, 2H), 1.63–1.69 (m, 4H), 2.06–2.15 (m, 2H), 2.21–2.27 (m, 1H; CHCH$_3$), 2.35 (t, ^3J = 6.2 Hz, 4H; 3′-H and CH_2Et), 3.27 (dt, ^2J = (−)13.9, ^3J = 6.6 Hz, 1H; NCH_2), 3.34–3.43 (m, 4H; NCH), 3.45 (dt, ^2J = (−)13.6, ^3J = 7.0 Hz, 1H; NCH_2), 4.16 (dd, ^3J = 8.4, ^3J = 6.0 Hz, 1H; CHNH), 12.89 ppm (br d, ^3J = 8.3 Hz, 1H; NH); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$): δ = 12.73 (CH_3; CHCH_3), 14.31 (CH_3; CHCH_3), 14.52 (CH_3), 18.05 (CH_3; NCH_2CH_3), 20.06 (CH_3; NCH_2CH_3), 20.72 (CH_2), 22.86 (CH_2), 24.17 (CH_2), 25.75 (CH_2), 30.16 (CH_2), 31.70 (CH; CHCH$_3$), 38.07 (CH_2; CH$_2$CO), 40.21 (CH_2; NCH_2), 41.34 (CH_2; NCH_2), 60.85 (CH; CHNH), 100.47 (C; C-1′), 165.71 (C; CNH), 170.15 (C; CON), 195.59 ppm (C; C-2′); IR (ATR): $\tilde{\nu}$ = 2964 (m), 2931 (s), 2870 (m), 2826 (w), 1737 (w), 1638 (s), 1588 (s), 1554 (vs), 1485 (m), 1451 (s), 1427 (m), 1376 (m), 1342 (m), 1319 (m), 1293 (s), 1270 (s), 1215 (m), 1157 (m), 1126 (s), 1104 (m), 1086 (s), 1066 (m), 1048 cm^{-1} (w); MS (70 eV, EI): *m*/*z* (%): 322 (8) [M^+], 279 (1) [M^+−C_3H_7], 222 (100) [M^+−CONEt$_2$], 178 (3), 156 (2) [$C_{10}H_{16}NO^+$], 124 (1), 72 (4) [NEt$_2^+$], 55 (3); HRMS (70 eV, EI): *m*/*z* calcd for $C_{19}H_{34}N_2O_2$: 322.2620; found: 322.2620.

General procedure for the preparation of racemic triketones 7: The respective β-diketone **1**, $FeCl_3$·6H_2O, and **5** were stirred in CH_2Cl_2 for 16 h at 23°C. After evaporation of all volatile materials, the residue was purified by column chromatography (silica gel, PE/EA).

General procedure for asymmetric Michael reactions: Cu(OAc)$_2$·H_2O and the respective enamine **3** or **4** were stirred in acetone for 1 h at 23°C. Then **5** was added and the mixture was stirred at 23°C for the time given. After evaporation of all volatile materials, hydrochloric acid (*c* = 1 mol dm^{-3}) was added and the solution was stirred for 3 h at 0°C. The mixture was then extracted three times with CH_2Cl_2, the combined organic layers were washed with H_2O, dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel, PE/EA).

***rac*-2-(3-Oxobutyl)-2-propionylcyclopentanone (*rac*-7b)**: According to the general procedure, 2-propionylcyclopentanone (500 mg, 3.57 mmol), $FeCl_3$·6H_2O (48 mg, 0.02 mmol), and **5** (500 mg, 7.13 mmol) were reacted in CH_2Cl_2 (3 mL). Chromatography (silica gel, PE/EA 2:1, R_f = 0.37) yielded **7b** as a colorless oil (557 mg, 2.65 mmol, 74%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.01 (t, ^3J = 7.2 Hz, 3H; CH_2CH_3), 1.68 (dt, ^2J = (−)13.1, ^3J = 7.3 Hz, 1H; 4-H), 1.81–2.02 (m, 3H), 2.12 (s, 3H; $COCH_3$),

2.13–2.23 (m, 1H), 2.28–2.40 (m, 4H), 2.52 (q, ^3J=7.2 Hz, 2H; CH_2Me), 2.51–2.60 ppm (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ=7.87 (CH_3; CH_2CH_3), 19.44 (CH_2), 27.63 (CH_2), 29.99 (CH_3), 31.75 (CH_2), 32.08 (CH_2), 38.49 (CH_2), 38.74 (CH_2), 66.99 (C; C-2), 207.30 (C), 207.43 (C), 216.45 ppm (C); IR (ATR): $\tilde{\nu}$=2970 (m), 1732 (s), 1699 (vs), 1456 (m), 1406 (m), 1354 (m), 1317 (w), 1274 (w), 1143 (s), 1099 (m), 1073 (m), 930 cm^{-1} (m); MS (70 eV, EI): *m/z* (%): 210 (5) [M^+], 154 (79) [$M^+-CO-C_2H_4$], 136 (47), 121 (12), 111 (17), 97 (100), 84 (31), 67 (5), 57 (92) [$COEt^+$], 43 (62) [$COMe^+$]; elemental analysis calcd (%) for $C_{12}H_{18}O_3$ (210.27): C 68.54, H 8.63; found: C 68.60, H 8.71.

(*S*)-2-(3-Oxobutyl)-2-propionylcyclopentanone ((*S*)-7b): According to the general procedure, $Cu(OAc)_2{\cdot}H_2O$ (3.4 mg, 0.02 mmol), enamine **3b** (100 mg, 0.34 mmol), and **5** (48 mg, 0.68 mmol) were reacted in acetone (1 mL) for 16 h. Chromatography (silica gel, PE/EA 2:1) yielded (*S*)-**7b** (61 mg, 0.28 mmol, 85%). GC: Bondex unβ; temperature program: 3 min at 80°C, then 2.5 K min^{-1} gradient; t_R((*S*)-**7b**)=26.60 min; 88% *ee*; $[\alpha]_D^{20}$=+95 (*c*=7.7 in $CHCl_3$).

(*R*)-2-(3-Oxobutyl)-2-propionylcyclopentanone ((*R*)-7b): According to the general procedure, $Cu(OAc)_2{\cdot}H_2O$ (12 mg, 0.06 mmol), enamine **4b** (360 mg, 1.22 mmol), and **5** (171 mg, 2.45 mmol) were reacted in acetone (2 mL) for 48 h. **5** (200 mg, 2.85 mmol) was added and the mixture was stirred at 23°C for a further 48 h. Chromatography (silica gel, PE/EA) yielded (*R*)-**7b** (78 mg, 0.37 mmol, 30%). GC: Bondex unβ; t_R((*R*)-**7b**)= 26.90 min; 13% *ee*; $[\alpha]_D^{20}$=−22 (*c*=12.5 in $CDCl_3$).

***rac*-2-Butyryl-2-(3-oxobutyl)cyclopentanone (*rac*-7c)**: According to the general procedure, 2-butyrylcyclopentanone (500 mg, 3.24 mmol), $FeCl_3{\cdot}6H_2O$ (44 mg, 0.02 mmol), and **5** (454 mg, 6.48 mmol) were reacted in CH_2Cl_2 (0.5 mL). Chromatography (silica gel, PE/EA 3:1, R_f=0.24) yielded **7c** as a colorless oil (668 mg, 2.98 mmol, 92%). ^1H NMR ($CDCl_3$, 300 MHz): δ=0.88 (t, ^3J=7.4 Hz, 3H; CH_2CH_3), 1.50 (sex, ^3J=7.3 Hz, 2H; CH_2Me), 1.67 (dt, ^2J=(−)13.1, ^3J=7.6 Hz, 1H; 4-H), 1.80–2.02 (m, 3H), 2.12 (s, 3H; $COCH_3$), 2.14–2.22 (m, 1H), 2.27–2.40 (m, 4H), 2.43–2.49 (m, 2H; CH_2Et), 2.50–2.59 ppm (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ=13.81 (CH_3), 17.29 (CH_2), 19.68 (CH_2), 27.68 (CH_2), 30.20 (CH_3; $COCH_3$), 32.06 (CH_2), 38.70 (CH_2), 38.88 (CH_2), 40.39 (CH_2), 67.36 (C; C-2), 206.86 (C), 207.43 (C), 216.54 ppm (C; C-1); IR (ATR): $\tilde{\nu}$=2965 (s), 1735 (s), 1704 (vs), 1407 (w), 1367 (m), 1277 (w), 1146 (m), 895 cm^{-1} (m); MS (70 eV, EI): *m/z* (%): 224 (2) [M^+], 154 (100) [$M^+-CO-C_3H_6$], 136 (45), 121 (14), 111 (18), 108 (10), 97 (100), 84 (43), 71 (90) [$COPr^+$], 55 (18), 43 (96) [$COMe^+$]; elemental analysis calcd (%) for $C_{13}H_{20}O_3$ (224.30): C 69.61, H 8.99; found: C 69.42, H 9.12; GC: Bondex unβ; 5 min at 80°C, then 1 K min^{-1} gradient; t_R((*S*)-**7c**)= 52.98 min; t_R((*R*)-**7c**)=53.49 min.

(*S*)-2-Butyryl-2-(3-oxobutyl)cyclopentanone ((*S*)-7c): According to the general procedure, $Cu(OAc)_2{\cdot}H_2O$ (6.5 mg, 0.03 mmol), enamine **3c** (200 mg, 0.65 mmol), and **5** (91.0 mg, 1.30 mmol) were reacted in acetone (1 mL) for 16 h. Chromatography (silica gel, PE/EA 3:1) yielded (*S*)-**7c** (100 mg, 0.45 mmol, 69%). GC: Bondex unβ; t_R((*S*)-**7c**)=53.15 min, t_R-((*R*)-**7c**)=53.69 min; 82% *ee*; $[\alpha]_D^{20}$=+120 (*c*=22.9 in $CDCl_3$).

(*R*)-2-Butyryl-2-(3-oxobutyl)cyclopentanone ((*R*)-7c): According to the general procedure, $Cu(OAc)_2{\cdot}H_2O$ (12.9 mg, 0.07 mmol), enamine **4c** (100 mg, 0.32 mmol), and **5** (45.0 mg, 0.63 mmol) were reacted in acetone (1 mL) for 5 d. Chromatography (silica gel, PE/EA 3:1) yielded (*R*)-**7c** (53 mg, 0.24 mmol, 73%). GC: Bondex unβ; t_R((*S*)-**7c**)=53.12 min, t_R-((*R*)-**7c**)=53.61 min; 39% *ee*; $[\alpha]_D^{20}$=−64 (*c*=7.3 in $CDCl_3$).

***rac*-2-(3-Oxobutyl)-2-propionylcyclohexanone (*rac*-7e)**: According to the general procedure, 2-propionylcyclohexanone (2.99 g, 13.0 mmol), $FeCl_3{\cdot}6H_2O$ (129 mg, 0.65 mmol), and **5** (1.80 g, 25.7 mmol) were reacted in CH_2Cl_2 (2 mL). Chromatography (silica gel, PE/EA 2:1, R_f=0.33) yielded **7e** as a colorless oil (2.60 g, 11.6 mmol, 89%). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.04 (t, ^3J=7.2 Hz, 3H; CH_3), 1.42–1.57 (m, 2H), 1.58–1.83 (m, 3H), 1.86–2.01 (m, 2H), 2.11 (s, 3H; $COCH_3$), 2.23–2.55 ppm (m, 7H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ=8.22 (CH_3; CH_2CH_3), 22.57 (CH_2), 27.44 (CH_2), 27.94 (CH_2), 30.35 (CH_3), 31.87 (CH_2), 35.19 (CH_2), 38.72 (CH_2), 41.77 (CH_2), 66.78 (C; C-2), 208.08 (C; COMe), 210.50 (C; CO), 210.61 ppm (C; CO); IR (ATR): $\tilde{\nu}$=2941 (s), 2870 (m), 1716 (vs), 1696 (s), 1453 (w), 1356 (w), 1169 (w), 1131 (w), 902 cm^{-1} (w); MS (70 eV, EI): *m/z* (%): 224 (5) [M^+], 206 (2), 168 (42) [$M^+-CO-C_2H_4$], 150 (56), 135 (12), 125 (12), 121 (7), 111 (100), 98 (50), 81 (7), 67 (8), 57 (73) [$COEt^+$], 43 (76) [$COMe^+$]; HRMS (70 eV, EI): *m/z* calcd for $C_{13}H_{20}O_3$: 224.1412; found: 224.1413; elemental analysis calcd (%) for $C_{13}H_{20}O_3$ (224.30): C 69.61, H 8.99; found: C 69.18, H 9.04; GC: Bondex unβ; 3 min at 80°C, then 2 K min^{-1} gradient; t_R((*S*)-**7e**)=34.47 min; t_R-((*R*)-**7e**)=34.81 min.

(*S*)-2-(3-Oxobutyl)-2-propionylcyclohexanone ((*S*)-7e): According to the general procedure, $Cu(OAc)_2{\cdot}H_2O$ (3.2 mg, 0.02 mmol), enamine **3e** (100 mg, 0.32 mmol), and **5** (45.0 mg, 0.65 mmol) were reacted in acetone (0.5 mL) for 16 h. Chromatography (silica gel, PE/EA 3:1) yielded (*S*)-**7e** (55 mg, 0.25 mmol, 76%). GC: Bondex unβ; t_R((*S*)-**7e**)=34.82 min; t_R-((*R*)-**7e**)=35.18 min; 97% *ee*; $[\alpha]_D^{20}$=+150 (*c*=6.4 in $CDCl_3$).

(*R*)-2-(3-Oxobutyl)-2-propionylcyclohexanone ((*R*)-7e): According to the general procedure, $Cu(OAc)_2{\cdot}H_2O$ (3.2 mg, 0.02 mmol), enamine **4e** (100 mg, 0.32 mmol), and **5** (45.0 mg, 0.65 mmol) were reacted in acetone (1 mL) for 5 d. Chromatography (silica gel, PE/EA 3:1) yielded (*R*)-**7e** (52 mg, 0.23 mmol, 72%). GC: Bondex unβ; t_R((*S*)-**7e**)=34.81 min; t_R-((*R*)-**7e**)=35.14 min; 67% *ee*; $[\alpha]_D^{20}$=−83 (*c*=6.5 in $CDCl_3$).

***rac*-2-Butyryl-2-(3-oxobutyl)cyclohexanone (*rac*-7f)**: According to the general procedure, 2-butyrylcyclohexanone (168 mg, 1.00 mmol), $FeCl_3{\cdot}6H_2O$ (13.5 mg, 0.05 mmol), and **5** (120 mg, 2.00 mmol) were reacted in CH_2Cl_2 (0.5 mL). Chromatography (silica gel, PE/EA 2:1, R_f=0.40) yielded **7f** as a colorless oil (224 mg, 0.94 mmol, 94%). ^1H NMR ($CDCl_3$, 300 MHz): δ=0.90 (t, ^3J=7.4 Hz, 3H; CH_3), 1.40–1.82 (m, 6H), 1.84–1.97 (m, 2H), 2.03–2.09 (m, 1H), 2.11 (s, 3H; $COCH_3$), 2.23–2.37 (m, 4H), 2.38–2.54 ppm (m, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ=13.55 (CH_3), 16.86 (CH_2), 22.06 (CH_2), 26.91 (CH_2), 27.40 (CH_2), 29.81 (CH_3; $COCH_3$), 34.48 (CH_2), 38.19 (CH_2), 40.04 (CH_2), 41.37 (CH_2), 66.38 (C; C-2), 207.46 (C), 209.15 (C), 210.00 ppm (C); IR (ATR): $\tilde{\nu}$=2937 (m), 2872 (w), 1713 (s), 1692 (vs), 1452 (m), 1358 (s), 1310 (w), 1272 (w), 1237 (w), 1168 (m), 1129 (m), 1030 (w), 1011 (w), 954 cm^{-1} (w); MS (70 eV, EI): *m/z* (%): 238 (3) [M^+], 168 (74) [$M^+-CO-C_3H_6$], 150 (75), 135 (10), 125 (7), 121 (5), 111 (100), 98 (53), 81 (5), 71 (56) [$COPr^+$], 55 (8), 43 (38) [$COMe^+$]; elemental analysis calcd (%) for $C_{14}H_{22}O_3$ (238.32): C 70.56, H 9.30; found: C 70.56, H 9.29; GC: Bondex unβ; 3 min at 80°C, then 2 K min^{-1} gradient; t_R((*S*)-**7f**)=38.18 min; t_R((*R*)-**7f**)=38.45 min.

(*S*)-2-Butyryl-2-(3-oxobutyl)cyclohexanone ((*S*)-7f): According to the general procedure, $Cu(OAc)_2{\cdot}H_2O$ (15.4 mg, 0.08 mmol), enamine **3f** (500 mg, 1.55 mmol), and **5** (217 mg, 3.10 mmol) were reacted in acetone (3 mL) for 16 h. Chromatography (silica gel, PE/EA 2:1) yielded (*S*)-**7f** (268 mg, 1.12 mmol, 73%). GC: Bondex unβ; t_R((*S*)-**7f**)=38.06 min; t_R-((*R*)-**7f**)=38.31 min; 98% *ee*; $[\alpha]_D^{20}$=+141 (*c*=16.2 in $CDCl_3$).

(*R*)-2-Butyryl-2-(3-oxobutyl)cyclohexanone ((*R*)-7f): According to the general procedure, $Cu(OAc)_2{\cdot}H_2O$ (0.9 mg, 0.01 mmol), enamine **4f** (30.0 mg, 0.09 mmol), and **5** (13.0 mg, 0.19 mmol) were reacted in acetone (1 mL) for 5 d. Chromatography (silica gel, PE/EA 2:1) yielded (*R*)-**7f** (5 mg, 0.02 mmol, 23%). GC: Bondex unβ; t_R((*S*)-**7f**)=38.07 min; t_R-((*R*)-**7f**)=38.34 min; 83% *ee*.

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