Regioselective Enamine Formation from Oxonia-Boranuida-Betaines and Their Application in Asymmetric Michael Reactions

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β-Diketonato borate betaines **2** are readily accessible by the reaction of β-dicarbonyl compounds **1** with $BF_3{\cdot}OEt_2$. Reaction of borates **2** with L-valine diethylamide (**3a**) gives almost exclusively the exocyclic enamines **4** as the kinetic products. In contrast, direct, acid catalyzed conversion of β-diketones **1** with the chiral auxiliary **3a** yield the endocyclic enamines **5** as the thermodynamic products. Both enamines **4** and **5** give products with quaternary stereocenters in high selectivity in copper-catalyzed asymmetric Michael reactions with methyl vinyl ketone (**8**). But interestingly, exo- and endocyclic enamines are complementary with respect to stereochemistry of the subsequent Michael reactions since they give stereocenters with opposite configurations.

Introduction

The stereoselective formation of quaternary stereocenters is still a challenging task and the definitive touchstone for every asymmetric C−C bond forming reaction.[1] The Michael reaction, the conjugate or 1,4-addition of enolates to acceptor-substituted olefins, is a fundamental C−C coupling reaction, being catalyzed not only by Brönstedt bases,[2] but also by a number of metal compounds.[3] Established methods for catalytic enantioselective Michael reactions often cannot prove their efficiency if quaternary stereocenters are the synthetic target.[4] In some cases, the use of chiral auxiliaries turns out to give superior results.[5] Recently, we have introduced a new procedure for the construction of quaternary stereocenters at ambient temperature applying L-valine diethylamide as the chiral auxiliary and copper(II) as the catalyst.[6] β-Oxo esters and β-diketones are typical substrates, which are initially converted with the auxiliary to form enamines. However, a considerable regioselectivity problem in the enamine forming step is observed when β-diketones are utilized as donors. Herein we report the preparation of β-diketonatoboron difluorides and their application as starting materials in the enamine formation, resulting in considerable regioselectivity in this step, at least in certain cases.

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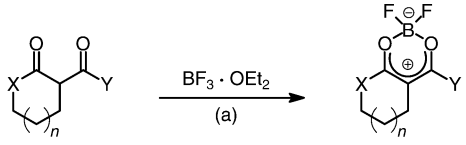
2. Results and Discussion

2.1 Formation of Borate Betaines

The boranuida cycles **2a**−**2g** were prepared by simply treating dicarbonyl compounds **1a**−**1g** with a small excess of $BF_3{\cdot}OEt_2$ at ambient temperature in an inert solvent (CH_2Cl_2) (Scheme 1).[7] The solid compounds (apart from **2e**) can be recrystallized from Et_2O to yield analytically pure, air-stable materials. The optically active derivative **2e** was obtained as an oil, which was pure by ^1H NMR spectroscopy. All products **2a**−**2g** have been fully characterized spectroscopically.[8] ^{19}F NMR resonances appear in the range of δ = −149 to −140 ppm. The quaternary ^{13}C resonances in the sp^2-region have been assigned by 2D-^1H,^{13}C



1a–g **2a–g**

1, 2	*n*	X	Y	yield (%)
a	0	CH_2	Me	81
b	1	CH_2	Me	85
c	2	CH_2	Me	93
d	1	$PhCH_2N$	Me	88
e	0	CH_2	O-menthyl	97
f	1	CH_2	OEt	63
g	2	CH_2	OMe	70

Scheme 1. Formation of oxonia-boranuida-betaines **2** from β-dicarbonyl compounds **1**; reagents and conditions: (a) 1. CH_2Cl_2, 23 °C, 16 h, 2. crystallization; for **2e**: yield without crystallization

correlation for all products **2** (COLOC experiments). In the cases of **2b**, **2c**, **2d**, and **2f** single crystals were obtained being suitable for X-ray structure analysis. While the structure of **2b** has already been published,[9] ORTEP representations of betaines **2c**, **2d** and **2f**[10] are given in Figure 1.

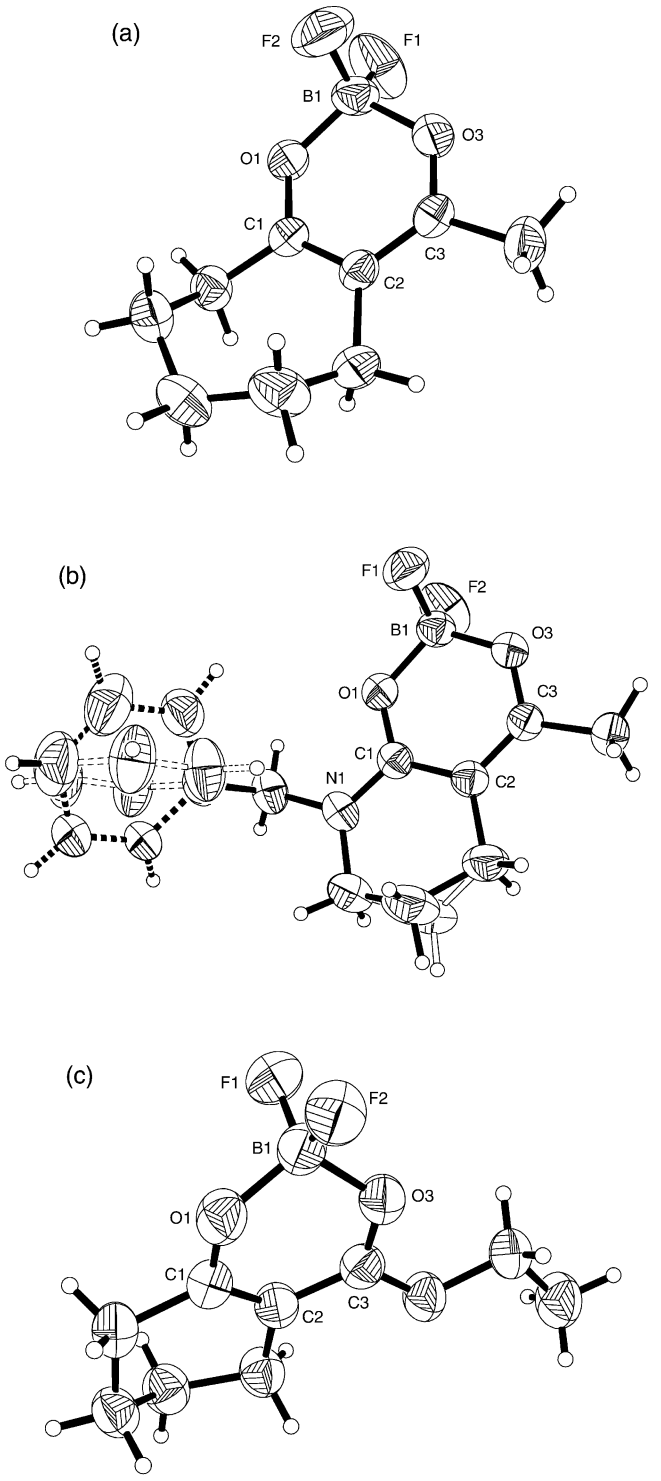


Figure 1. Molecular structures of **2c** (a), **2d** (b), **2f** (c) in the solid state (ORTEP-representations); selected bond lengths (Å): **2c**: 1.2964(16) (C1−O1), 1.3927(18) (C1−C2), 1.386(2) (C2−C3), 1.2999(18) (C3−O3); **2d**: 1.305(3) (C1−O1), 1.423(4) (C1−C2), 1.351(4) (C2−C3), 1.323(3) (C3−O3); **2f**: 1.333(4) (C1−O1), 1.357(4) (C1−C2), 1.407(4) (C2−C3), 1.293(3) (C3−O3)

In all solved structures the boranuida cycle is planar. In diketone-derived cycles **2b**, **c** both the C−O and the C−C bond length of the π-system are identical within the experimental error. The C−C bond lengths represent a bonding order of about 1.5, which can be rationalized by an average of both mesomeric structures **2** and **2′** shown in Figure 2. In contrast, the lactam and ester derived betaines **2d** and **2f** exhibit significantly different C−O and C−C bond lengths, thus, their bonding situation is represented only by one of the two structures **2** and **2′** (**2** for **2d**, **2′** for **2f**). Obviously, a ketene semi aminal/acetal structure is avoided in these cases.

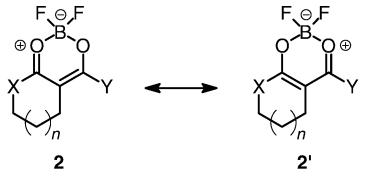
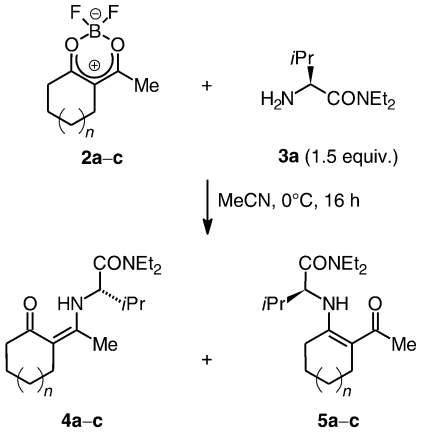


Figure 2. Mesomeric structures of betaines **2**

2.2 Reaction with Amines

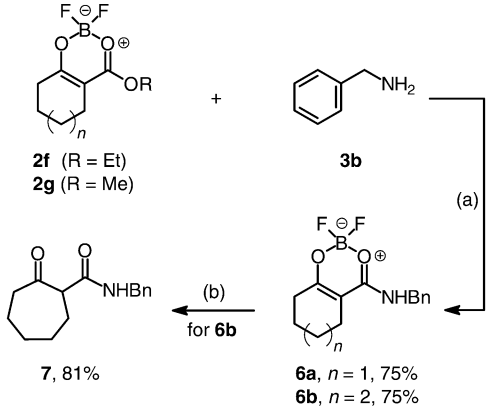
The regioselectivity of enamine formation from α-acetyl cycloalkanones was reported to be dependent on the ring size.[11] From our work, however, an endocyclic enamine **5** is known to be the thermodynamically favoured product in the cases of the α-acetylcyclopentanone (**1a**) and -hexanone (**1b**) (vide infra). Therefore we were pleased to find that boranuida cycles **2a** and **2b** smoothly reacted with the auxiliary **3a** to form almost exclusively the exocyclic enamines **4a** and **4b** as products. For the seven-membered ring **2c**, however, a mixture of exo- and endocyclic enamine (**4c**/**5c**, 70:30) was obtained (Scheme 2).



compd.	*n*	yield (%)	ratio **4** : **5**
2a	0	93	100 : 0
2b	1	87	97 : 3
2c	2	66	70 : 30

Scheme 2. Regioselective formation of exocyclic enamines **4** with the chiral auxiliary L-valine diethylamide (**3a**); starting material **2c** (5%) was recovered in case of **4c**/**5c**

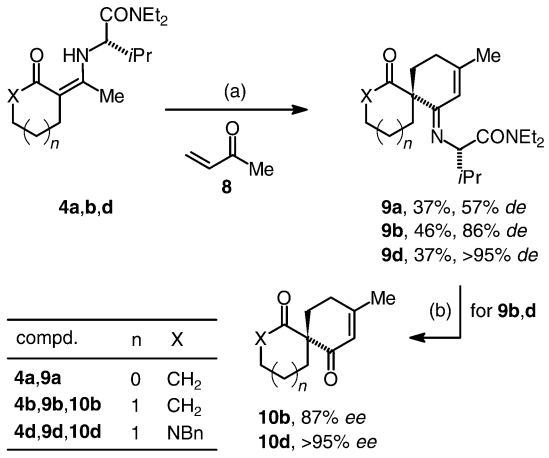
Compounds **2f** and **2g**, derived from β-oxo esters **1f** and **1g**, also react with primary amines such as benzylamine (**3b**). In contrast to the β-diketonato cogeners enamines are not formed as the products. The boronato difluoride moiety activates the ester carbonyl function towards an attack of the nucleophilic amine and the substitution products **6a** and **6b** are obtained. This reactivity can be explained by the fact that only the enol-borate resonance structure is found in the solid state as depicted in Scheme 3. Interestingly, the boronato moiety is retained during this conversion. Compounds **6a** and **6b** are found to be stable towards air and moisture and can even be chromatographed on SiO_2 without significant decomposition. In order to cleave the boronato chelate prolonged conversion with half concd. hydrochloric acid is required as shown for the formation of amide **7** from **6b** (Scheme 3). Lactam-derived **2d** also reacts with L-valine amide **3a**, however, the yield of enamine **4d** (Scheme 4) is not superior to the one achieved by direct, acid-catalyzed conversion of lactam **1d** with **3a** (48%). In the formation of the heterocyclic enamine **4d** a regioselectivity problem is of course not observed. Very recently, in situ formed β-diketonatoboron difluorides have been utilized for allylations.[12]



Scheme 3. Reaction of oxonia-boranuida-betaines **2f**, **g** with benzylamine (**3b**); reagents and conditions: (a) **3b** (1.2−20 equiv.), CH_2Cl_2, 23 °C, 16 h; (b) HCl−H_2O (6 mol/L), 23 °C, 16 h

2.3 Michael Reactions

The exocyclic enamines **4a**, **4b** and **4d** were treated with methyl vinyl ketone (**8**) in the presence of a catalytic amount of $Cu(OAc)_2 \cdot H_2O$ to give the spirocyclic imines **9a**, **9b**, and **9d** as the only isolable, unique products. Interestingly, the Michael reaction did not stop at the stage of the open-chain 1,5-dicarbonyl products, but subsequent Robinson annulation occurred. The auxiliary is retained in the product since an imine moiety in a neopentyl environment exhibits reasonable hydrolytic stability and therefore survives the workup procedure and purification by chromatography. Whereas only one diastereomer of lactam **9d** is obtained with a single signal set in the ^{1}H NMR spectrum (>95% *de*), compounds **9a** (57% *de*) and **9b** (86% *de*) additionally show a minor diastereomer in ^{1}H NMR spectra. To determine whether this diastereomer is the epimer regarding the



compd.	n	X
4a,**9a**	0	CH_2
4b,**9b**,**10b**	1	CH_2
4d,**9d**,**10d**	1	NBn

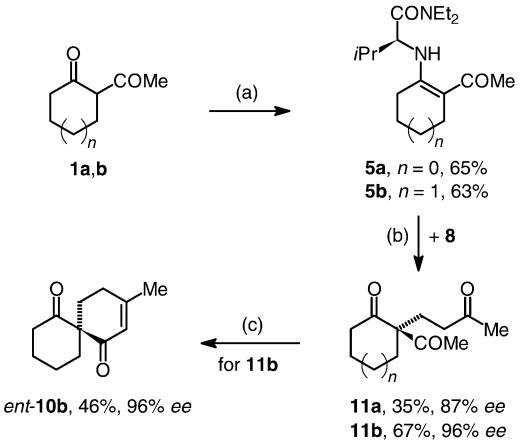
Scheme 4. Reaction of exocyclic enamines **4** with methyl vinyl ketone (**8**); reagents and conditions: (a) $Cu(OAc)_2 \cdot H_2O$ (10 mol%), **8** (2−3 equiv.), acetone, 23 °C, 16 h; (b) HCl−H_2O, 23 °C, 5 h; spirocycles **10b** and **10d** were isolated only on an analytical scale

spirocenter, imine **9b** was hydrolytically cleaved and the spirocycle **10b** analyzed by GLC on a chiral phase. Indeed, this material **10b** had an optical purity of 87% *ee*, which clearly relates to the 86% *de* of the parent imine **9b**. Analogously, **9d** was converted to **10d** with >95% *ee* determined by GLC on a chiral phase. Both spirocycles **10b** and **10d** were prepared only on an analytical scale, but their identity was without doubt proved by comparison with the racemic materials *rac*-**10b** and *rac*-**10d**, which were synthesized on larger scale to elucidate their constitutions and to develop GLC conditions for baseline resolution of the enantiomers (vide infra). Actually the 1,3-diketo constitution of **10b**[13] was confirmed by X-ray single crystal analysis,[9] whereas the β-oxolactam structure of **10d** was established by 2D-^{1}H, ^{13}C spectroscopy and by comparison with the regioisomeric δ-oxolactam **12**.

For comparison with these results we focused our attention in further studies on stereoselectivities and configurations of the products obtained from the regioisomeric endocyclic enamines **5a** and **5b**,[6b] which are accessible as the thermodynamic products in acid-catalyzed conversions of β-diketones **1a** and **1b** with L-valine amide **3a** (Scheme 5). The Michael reaction with methyl vinyl ketone (**8**) gave the open-chain 1,5-diketones **11a** and **11b** in good to excellent selectivity (87% *ee* for **11a** and 96% *ee* for **11b**). In contrast to conversions of the exocyclic compounds **4a**, **b**, **d** no spirocyclic products were detected. The five-membered ring product **11a** could be analyzed directly by GLC on a chiral phase, the homologue **11b**, however, gave no sufficient baseline resolution. We therefore performed spirocyclization to *ent*-**10b**,[6b] which turned out to be, as expected, the enantiomer of **10b** obtained from exocyclic enamine **4b**.

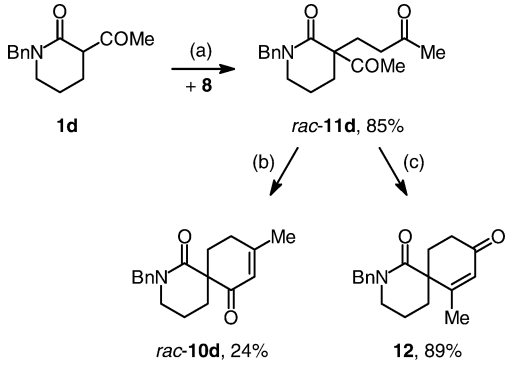
In summary, we conclude that control of endo- and exocyclic enamine formations enables the complementary preparation of either enantiomer of spirocycle **10a** with high selectivity applying the chiral auxiliary with the same absolute configuration.

Finally, we mention our efforts to prepare racemic spirolactam *rac*-**10d**, since we had to tackle again an interesting



Scheme 5. Formation of endocyclic enamines **5** and subsequent Michael reactions with methyl vinyl ketone (**8**); reagents and conditions: (a) for **5a**: toluene, 100 °C, 5 d, cat. HCl; for **5b**: see ref.[6b]; (b) 1. $Cu(OAc)_2 \cdot H_2O$ (5−10 mol%), **8** (3 equiv.), acetone, 23 °C, 16 h, 2. HCl−H_2O (2 mol/L), 3 h, 23 °C; (c) concd. H_2SO_4 (10 equiv.), 0 °C, 4 h, 2. H_2O (ice). Enamine **5a** was isolated as a mixture of **5a**:**4a**, 87:13, while **5b** was formed exclusively

regioselectivity problem. The open-chain precursor *rac*-**11d** was available by copper-catalyzed conversion of donor **1d** with methyl vinyl ketone (**8**). Cyclization under standard Robinson conditions (pyrrolidine, glacial acetic acid)[14] afforded the δ-oxolactam **12**, being the "wrong" regioisomer (Scheme 6). The constitution of **12** was established by the $^3J(^1H,^{13}C)$ correlation of the methyl protons to the spiro carbon atom in a 2D-$^1H,^{13}C$ NMR experiment. The β-oxolactam *rac*-**10d** was obtained under acidic conditions, and its signal sets in ^1H and ^{13}C NMR spectra are isomorphous to those of regioisomer **12**, however, $^3J(^1H,^{13}C)$ coupling constants are different and specifically fit to the constitution of **10d** shown in the Schemes.



Scheme 6. Preparation of racemic spirolactam derivatives *rac*-**10d** and **12**; reagents and conditions: (a) $Cu(OAc)_2 \cdot H_2O$ (5 mol%), **8** (1.5 equiv.), acetone, 23 °C, 16 h; (b) 1. concd. H_2SO_4, 23 °C, 16 h, 2. H_2O (ice); (c) pyrrolidine (0.5 equiv.), glacial acetic acid (0.5 equiv.), 23 °C, 16 h

Experimental Section

General: Melting points were measured on a Büchi 510 and are uncorrected. Starting materials **1a**, **1b** and **1f** are commercially available. $BF_3 \cdot OEt_2$ was purchased from Aldrich Chemical Co. Spectroscopic data of **1c** were identical with the literature.[15] The following compounds were prepared according to literature procedures: **1c**,[16] **1d**,[17] **1e**,[17] **3a**,[6b] **5b**,[6b] *rac*-**11a**,[18] and *rac*-**11b**.[19] Column chromatography was carried out by using Merck SiO_2 60 or Merck basic Alumina (act. I) with petroleum ether (PE, b.p. 40−60 °C) and ethyl acetate (EA) as eluents. ^{19}F NMR spectra were recorded on a Bruker ARX 300 (282 MHz) with TFA ($\delta^{19}F$ = −77 ppm) as internal standard. ^{13}C NMR multiplicities were determined with DEPT experiments or proton-coupled measurements, carbonyl carbon resonances were assigned with COLOC experiments. GC analysis was performed with a HRGC 5300 (Carlo−Erba Strumentazione) with FID, and a column Bondex unα/β (20 m × 0.3 mm) or Lipodex E (25 m × 0.3 mm) with hydrogen carrier gas (0.4 bar).

General Procedure for the Preparation of Boranuida Compounds 2: $BF_3 \cdot OEt_2$ (1.2 equiv.) was added to a solution of the respective β-dicarbonyl compound **1a**−**g** (1 equiv.) in CH_2Cl_2 (3−7 mol/L) at 23 °C, and the mixture was then stirred for 16 h or 21 h (for **2d**). After removal of all volatile materials under high vacuum, the residue was recrystallized twice from Et_2O.

3,3-Difluoro-5-methyl-4-oxa-2-oxonia-3-boranuidabicyclo[4.3.0]-nona-1,5-diene (2a): According to the General Procedure, **1a** (2.00 g, 15.8 mmol) and $BF_3 \cdot OEt_2$ (2.70 g, 19.0 mmol) in CH_2Cl_2 (5 mL) were converted to yield **2a** as a colorless solid (2.22 g, 12.7 mmol, 81%). M.p. 64 °C (58−60 °C[8c]). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.04−2.16 (m, 2 H), 2.27 (s, 3 H), 2.68 (dd, *J* = 7.6, *J* = 7.1 Hz, 2 H), 2.76 (t, *J* = 8.0 Hz, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 20.44 (CH_2), 22.72 (CH_3), 25.58 (CH_2), 34.90 (CH_2), 113.09 (C), 187.36 (C=O, endo), 199.55 (C=O, exo) ppm. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ = −141.32 (s) ppm. IR (ATR): $\tilde{\nu}$ = 2920 (m), 2880 (m), 1706 (m), 1600 (s), 1526 (vs), 1380 (s), 1345 (s), 1310 (s), 1191 (s), 1150 (s) cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 174 (36) [M^+], 159 (100) [$M^+ - CH_3$], 131 (13) 118 (11). $C_7H_9BF_2O_2$ (173.96): calcd. C 48.33, H 5.22; found C 48.31, H 5.15.

3,3-Difluoro-5-methyl-4-oxa-2-oxonia-3-boranuidabicyclo[4.4.0]-deca-1,5-diene (2b): According to the General Procedure, **1b** (10.0 g, 71.3 mmol) and $BF_3 \cdot OEt_2$ (12.2 g, 85.6 mmol) in CH_2Cl_2 (10 mL) were converted to yield **2b** as colorless crystals (11.4 g, 61.0 mmol, 85%). M.p. 79 °C (79−79.6 °C[8a]). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.75−1.85 (m, 4 H), 2.30 (s, 3 H), 2.38−2.41 (m, 2 H), 2.55−2.59 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 20.88 (CH_2), 21.90 (CH_2), 22.24 (CH_3), 23.12 (CH_2), 32.42 (CH_2), 108.92 (C), 190.01 (C=O, endo), 191.86 (C=O, exo) ppm. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ = −140.03 (s) ppm. IR (ATR): $\tilde{\nu}$ = 1583 (s), 1507 (vs), 1462 (m), 1405 (m), 1364 (s), 1350 (s), 1331 (s), 1304 (m), 1201 (m), 1138 (s), 1089 (m), 1041 (vs) cm^{-1}. HRMS for $C_8H_{11}BF_2O_2$ (70 eV, EI): calcd. 188.0820, found 188.0820. $C_8H_{11}BF_2O_2$ (187.98): calcd. C 51.11, H 5.90; found C 51.08, H 5.84.

9,9-Difluoro-11-methyl-10-oxa-8-oxonia-9-boranuidabicyclo-[5.4.0]undeca-7,11-diene (2c): According to the General Procedure, **1c** (5.00 g, 32.4 mmol) and $BF_3 \cdot OEt_2$ (5.00 g, 35.6 mmol) in CH_2Cl_2 (5 mL) were converted to yield **2c** as colorless crystals (6.09 g, 30.0 mmol, 93%). M.p. 86 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.62 (quint., *J* = 5.5 Hz, 2 H), 1.71−1.87 (m, 4 H), 2.33 (s, 3 H), 2.45−2.49 (m, 2 H), 2.70−2.74 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 22.51 (CH_3), 24.30 (CH_2), 26.05 (CH_2), 27.90 (CH_2), 31.24 (CH_2), 38.53 (CH_2), 113.73 (C), 188.71 (C=O, exo), 196.71 (C=O, endo) ppm. $^{19}F\{^1H\}$ NMR

(282 MHz, $CDCl_3$): δ = −141.45 (s) ppm. IR (ATR): ṽ = 2939 (m), 1574 (s), 1510 (vs), 1440 (s), 1370 (s), 1349 (s), 1308 (m), 1216 (m), 1179 (s), 1149 (vs), 1055 (s), 1028 (vs) cm^{-1}. MS (70 eV, EI): *m/z* (%) = 202 (100) [M^+], 187 (80) [$M^+ - CH_3$], 183 (47), 174 (30), 159 (71), 132 (28), 118 (11), 93 (29). $C_9H_{13}BF_2O_2$ (202.01): calcd. C 53.51, H 6.49; found C 53.28, H 6.45.

10-Benzyl-3,3-difluoro-5-methyl-10-aza-3-boranuida-4-oxa-2-oxoniabicyclo[4.4.0]deca-1,5-diene (2d): According to the General Procedure, **1d** (231 mg, 1.00 mmol) and $BF_3{\cdot}OEt_2$ (156 mg, 1.10 mmol) in CH_2Cl_2 (1 mL) were converted. After all volatile materials were removed at 50 °C under high vacuum, crystallization from CH_2Cl_2 gave **2d** (245 mg, 0.878 mmol, 88%) as a colorless solid. M.p. 119 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.89 (quint., *J* = 6.4 Hz, 2 H), 2.12 (s, 3 H), 2.47 (t, *J* = 6.4 Hz, 2 H), 3.36 (t, *J* = 6.4 Hz, 2 H), 4.74 (s, 2 H), 7.30−7.41 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 20.19 (CH_3), 21.15 (CH_2), 21.93 (CH_2), 47.26 (CH_2), 51.66 (CH_2), 92.84 (C), 128.31 (CH), 128.33 (CH), 128.97 (CH), 134.27 (C), 164.99 (C), 173.73 (C) ppm. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ = −146.79 (s) ppm. IR (ATR): ṽ = 1598 (s), 1577 (s), 1493 (s), 1453 (m), 1437 (m), 1310 (s), 1219 (m), 1134 (s), 1072 (s), 1051 (vs), 1004 (vs), 975 (m), 924 (m), 896 (m), 870 (s), 751 (m), 728 (m), 702 (m) cm^{-1}. $C_{14}H_{16}BF_2NO_2$ (279.09): calcd. C 60.19, H 5.78, N 5.02; found C 60.23, H 5.75, N 4.94.

(1′*R*,2′*S*,5′*R*)-3,3-Difluoro-5-menthyloxy-4-oxa-2-oxonia-3-boranuidabicyclo[4.3.0]nona-1,5-diene (2e): According to the General Procedure, **1e** (500 mg, 1.88 mmol) and $BF_3{\cdot}OEt_2$ (266 mg, 1.88 mmol) in CH_2Cl_2 (0.5 mL) were converted to yield **2e** as a brown oil (575 mg, 1.83 mmol, 97%, without recrystallization). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 1.34 (t, *J* = 7.1 Hz, 1 H), 1.49−1.59 (m, 2 H), 1.70−1.84 (m, 4 H), 1.97−2.13 (m, 4 H), 2.55 (t, *J* = 7.7 Hz, 2 H), 2.66 (t, *J* = 8.0 Hz, 2 H), 5.04 (td, *J* = 10.8, *J* = 4.5 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 16.45 (CH_3), 19.76 (CH_2), 20.54 (CH_3), 21.83 (CH_3), 23.51 (CH_2), 24.13 (CH_2), 26.59 (CH), 31.39 (CH), 33.82 (CH_2), 33.86 (CH_2), 40.59 (CH_2), 46.98 (CH), 81.37 (CH), 97.48 (C), 171.25 (C), 191.87 (C) ppm. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ = −141.97 (s), −142.03 (s) ppm. IR (ATR): ṽ = 2955 (m), 2928 (m), 1613 (s), 1529 (vs), 1478 (s), 1374 (m), 1216 (m), 1118 (s), 1043 (vs) cm^{-1}. HRMS for $C_{16}H_{25}BF_2O_2$ (70 eV, EI): calcd. 314.1865, found 314.1862.

3,3-Difluoro-5-ethoxy-4-oxa-2-oxonia-3-boranuidabicyclo[4.4.0]-deca-1,5-diene (2f): According to the General Procedure, **1f** (3.00 g, 17.6 mmol) and $BF_3{\cdot}OEt_2$ (2.50 g, 17.6 mmol) in CH_2Cl_2 (3 mL) were converted to yield **2f** as pale yellow crystals (2.43 g, 11.1 mmol, 63%). M.p. 64 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.2 Hz, 3 H), 1.66−1.80 (m, 4 H), 2.26 (t, *J* = 6.2 Hz, 2 H), 2.44 (t, *J* = 6.0 Hz, 2 H), 4.53 (q, *J* = 7.1 Hz, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 14.08 (CH_3), 20.40 (CH_2), 21.34 (CH_2), 21.57 (CH_2), 31.16 (CH_2), 66.17 (CH_2), 95.49 (C), 173.76 (C), 183.35 (C) ppm. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ = −142.76 (s) ppm. IR (ATR): ṽ = 2939 (m), 1604 (s), 1520 (vs), 1492 (vs), 1449 (s), 1374 (s), 1339 (vs), 1170 (s), 1041 (vs) cm^{-1}. HRMS for $C_9H_{13}BF_2O_3$ (70 eV, EI): calcd. 218.0926, found 218.0926. $C_9H_{13}BF_2O_3$ (218.01): calcd. C 49.58, H 6.01; found C 49.17, H 5.96.

9,9-Difluoro-11-methoxy-10-oxa-8-oxonia-9-boranuidabicyclo-[5.4.0]undeca-7,11-diene (2g): According to the General Procedure, **1g** (10.0 g, 58.4 mmol) and $BF_3{\cdot}OEt_2$ (12.4 g, 87.6 mmol) in CH_2Cl_2 (10 mL) were converted to yield **2g** as colorless crystals (8.86 g, 40.6 mmol, 70%). M.p. 79 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.53 (quint., *J* = 5.6 Hz, 2 H), 1.67−1.72 (m, 2 H), 1.75−1.79 (m, 2 H), 2.39−2.43 (m, 2 H), 2.61−2.65 (m, 2 H), 4.07 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 22.69 (CH_2), 24.20 (CH_2), 27.15 (CH_2), 31.53 (CH_2), 37.80 (CH_2), 55.96 (CH_3), 99.15 (C), 173.75 (C), 190.60 (C) ppm. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ = −142.98 (s) ppm. IR (ATR): ṽ = 2929 (m), 2859 (m), 1597 (s), 1498 (vs), 1388 (m), 1368 (s), 1042 (vs) cm^{-1}. MS (70 eV, EI): *m/z* (%) = 218 (62) [M^+], 199 (20) [$M^+ - F$], 176 (10), 138 (100), 110 (75), 82 (36), 67 (21), 55 (48). $C_9H_{13}BF_2O_3$ (218.01): calcd. C 49.58, H 6.01; found C 49.39, H 6.01.

General Procedure for the Preparation of Exocyclic Enamines 4: To a stirred solution of the respective diketonatoboron difluoride **2** in MeCN was added dropwise L-valine diethylamide (**3a**) at 0 °C. After being warmed up to 23 °C, the solution was stirred for a further 16 h. The solvent was evaporated and the residue purified by column chromatography (Al_2O_3, PE/EA).

***N*-[1-(2-Oxocyclopentylidene)ethyl]-L-valine Diethylamide (4a):** According to the General Procedure, from **2a** (100 mg, 0.57 mmol) and **3a** (295 mg, 1.71 mmol) in MeCN (2 mL) and chromatography [PE/EA, 1:1, $R_f(SiO_2)$ = 0.11] was obtained **4a** as colorless crystals (149 mg, 0.53 mmol, 93%), $[\alpha]_D^{20}$ = +220 (*c* = 7.7, $CDCl_3$). M.p. 72 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 7.0 Hz, 3 H), 1.04 (d, *J* = 7.0 Hz, 3 H), 1.12 (t, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.83 (quint., *J* = 7.0 Hz, 2 H), 1.88 (s, 3 H), 2.10 (oct., *J* = 6.4 Hz, 1 H), 2.33 (t, *J* = 7.9 Hz, 2 H), 2.52 (t, *J* = 7.1 Hz, 2 H), 3.17−3.24 (m, 1 H), 3.28−3.35 (m, 1 H), 3.39−3.47 (m, 1 H), 3.53−3.60 (m, 1 H), 4.16 (dd, *J* = 8.9, J = 6.4 Hz, 1 H), 10.67 (d, br., *J* = 8.4 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 12.88 (CH_3), 14.62 (CH_3), 16.39 (CH_3), 17.81 (CH_3), 19.87 (CH_3), 20.36 (CH_2), 28.00 (CH_2), 32.20 (CH), 39.15 (CH_2), 40.35 (CH_2), 41.61 (CH_2), 59.15 (CH), 103.25 (C), 156.38 (C), 170.06 (C), 202.14 (C) ppm. IR (ATR): ṽ = 2961 (s), 2874 (m), 1628 (vs), 1572 (vs), 1432 (s), 1379 (m), 1339 (m), 1247 (vs), 1216 (m), 1181 (m), 1125 (m), 1097 (m), 1070 (m) cm^{-1}. HRMS for $C_{16}H_{28}N_2O_2$ (70 eV, EI): calcd. 280.2151, found 280.2153. $C_{16}H_{28}N_2O_2$ (280.41): calcd. C 68.53, H 10.06, N 9.99; found C 68.53, H 10.00, N 9.87.

***N*-[1-(2-Oxocyclohexylidene)ethyl]-L-valine Diethylamide (4b):** According to the General Procedure, from **2b** (150 mg, 0.79 mmol) and **3a** (408 mg, 2.38 mmol) in MeCN (1 mL) and chromatography [PE/EA, 1:3, $R_f(SiO_2)$ = 0.14] was obtained **4b** as a pale yellow oil (202 mg, 0.69 mmol, 87%), $[\alpha]_D^{20}$ = +180 (*c* = 4.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.04 (d, *J* = 6.7 Hz, 3 H), 1.06 (d, *J* = 6.7 Hz, 3 H), 1.12 (t, *J* = 7.1 Hz, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.65−1.69 (m, 4 H), 1.89 (s, 3 H), 2.13 (q, *J* = 7.3 Hz, 1 H), 2.31−2.33 (m, 4 H), 3.17−3.60 (m, 4 H), 4.16 (t, *J* = 6.5 Hz, 1 H), 12.90 (d, br., *J* = 7.7 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 12.85 (CH_3), 14.50 (CH_3), 14.94 (CH_3), 18.02 (CH_3), 19.98 (CH_3), 22.77 (CH_2), 24.09 (CH_2), 26.57 (CH_2), 31.93 (CH), 38.01 (CH_2), 40.40 (CH_2), 41.59 (CH_2), 60.45 (CH), 100.97 (C), 162.51 (C), 169.94 (C), 194.76 (C) ppm. IR (ATR): ṽ = 2966 (m), 2931 (s), 2873 (m), 1642 (vs), 1590 (vs), 1557 (s), 1461 (m), 1272 (m) cm^{-1}. HRMS for $C_{17}H_{30}N_2O_2$ (70 eV, EI): calcd. 294.2307, found 294.2307.

***N*-[1-(2-Oxocycloheptylidene)ethyl]-L-valine Diethylamide (4c) and *N*-(2-Acetyl-1-cycloheptenyl)-L-valine Diethylamide (5c):** According to the General Procedure, from **2c** (1.00 g, 4.95 mmol) and **3a** (850 mg, 4.95 mmol) in MeCN (4 mL) and chromatography [PE/EA, 2:1, $R_f(SiO_2)$ = 0.11] was obtained a mixture **4c/5c** as a yellow oil (1.01 g, 3.29 mmol, 66%) in a ratio of 7:3 (determined from integrals of the NH protons in the ^1H NMR).

4c: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.7 Hz, 3 H), 1.03 (d, *J* = 7.8 Hz, 3 H), 1.11 (t, *J* = 7.1 Hz, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.58−1.85 (m, 6 H), 2.05−2.12 (m, 1 H), 2.35 (s, 3 H), 2.46−2.52 (m, 2 H), 2.70−2.74 (m, 2 H), 3.13−3.58 (m, 4 H), 4.11 (t, *J* = 8.0 Hz, 1 H), 12.42 (d, br., *J* = 8.0 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 12.86 (CH_3), 14.49 (CH_3), 15.85 (CH_3), 18.00 (CH_3), 19.84 (CH_3), 22.53 (CH_2), 25.10 (CH_2), 28.27 (CH_2), 28.31 (CH_2), 31.33 (CH_2), 31.67 (CH), 40.43 (CH_2), 44.08 (CH_2), 60.12 (CH), 105.88 (C), 159.61 (C), 170.23 (C), 200.81 (C) ppm. **5c:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.7 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 1.13 (t, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 1.49−1.55 (m, 2 H), 1.60−1.75 (m, 4 H), 1.97 (q, *J* = 6.9 Hz, 1 H), 2.02 (s, 3 H), 2.09−2.14 (m, 2 H), 2.48−2.52 (m, 2 H), 3.37 (q, *J* = 7.2 Hz, 1 H), 3.38 (q, *J* = 7.0 Hz, 1 H), 3.45−3.52 (m, 2 H), 4.76 (dd, *J* = 9.2, *J* = 6.9 Hz, 1 H), 12.14 (d, br., *J* = 7.7 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 12.86 (CH_3), 14.49 (CH_3), 18.01 (CH_3), 19.79 (CH_3), 19.80 (CH_3), 24.35 (CH_2), 25.95 (CH_2), 27.30 (CH_2), 28.27 (CH_2), 31.17 (CH_2), 32.08 (CH), 38.48 (CH_2), 41.65 (CH_2), 59.68 (CH), 106.47 (C), 167.93 (C), 170.18 (C), 193.86 (C) ppm. Isomeric mixture **4c/5c**: IR (ATR): ṽ = 3310 (m, br.), 2969 (s), 2930 (vs), 2856 (m), 1643 (s), 1584 (vs), 1512 (vs), 1438 (m), 1372 (m) cm^{-1}. HRMS for $C_{18}H_{32}N_2O_2$ (70 eV, EI): calcd. 308.2464, found 308.2461.

***N*-[1-(3-Benzyl-2-oxo-3-azacyclohexylidene)ethyl]-L-valine Diethylamide (4d):** Under exclusion of moisture and air, **1d** (1.40 g, 6.05 mmol) and **3a** (1.04 g, 6.03 mmol) were added to molecular sieves (5 g, 4 Å) in dry toluene (3.6 mL). After addition of 2 drops of concd. H_2SO_4, the reaction mixture was stirred at 60 °C for 16 h, then decanted, and the molecular sieves washed with toluene. The combined organic layers were evaporated and the residue chromatographed on Al_2O_3 (PE/EA, 2:1, R_f = 0.38) to yield **4d** (1.12 g, 2.89 mmol, 48%) as a colorless oil, $[\alpha]_D^{20}$ = +130 (*c* = 4.05, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 7.0 Hz, 3 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 1.12 (t, *J* = 7.0 Hz, 3 H), 1.18 (t, *J* = 7.0 Hz, 3 H), 1.73−1.79 (m, 2 H), 1.86 (s, 3 H), 2.04−2.13 (m, 1 H), 2.40 (t, *J* = 7.0 Hz, 2 H), 3.14 (t, *J* = 5.7 Hz, 2 H), 3.23−3.31 (m, 1 H), 3.40 (q, *J* = 7.0 Hz, 2 H), 3.46−3.54 (m, 1 H), 4.03 (t, *J* = 7.6 Hz, 1 H), 4.59 (d, *J* = 15.3 Hz, 1 H), 4.68 (d, *J* = 15.3 Hz, 1 H), 7.19−7.30 (m, 5 H), 10.63 (d, *J* = 8.3 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 12.73 (CH_3), 14.33 (CH_3), 15.08 (CH_3), 18.95 (CH_3), 19.93 (CH_3), 23.33 (CH_2), 26.20 (CH_2), 31.99 (CH), 40.19 (CH_2), 41.27 (CH_2), 46.89 (CH_2), 49.63 (CH_2), 61.65 (CH), 90.50 (C), 126.63 (CH), 127.73 (CH), 128.20 (CH), 138.68 (C), 154.56 (C), 169.03 (C), 171.27 (C) ppm. IR (ATR): ṽ = 2980 (vs), 2965 (vs), 2835 (m), 1650 (vs), 1610 (vs), 1600 (vs), 1485 (vs), 1460 (vs), 1450 (vs), 1430 (vs), 1412 (vs), 1380 (s), 1350 (vs), 1340 (vs), 1300 (vs), 1280 (vs), 1260 (vs), 1210 (s), 1195 (vs), 1170 (m), 1125 (m), 1090 (m), 1070 (m), 1020 (m), 720 (s), 680 (s) cm^{-1}. HRMS for $C_{23}H_{35}N_3O_2$ (70 eV, EI): calcd. 385.2729, found 385.2729.

***N*-(2-Acetyl-1-cyclopentenyl)-L-valine Diethylamide (5a):** To a mixture of β-diketone **1a** (1.00 g, 7.90 mmol) and **3a** (1.40 g, 8.20 mmol) in toluene (3 mL) were added 2 drops of concd. HCl. After stirring for 5 d at 100 °C, no further conversion was detected by GC. The mixture was evaporated and the residue chromatographed (Al_2O_3, PE/EA, 3:1, R_f = 0.18) to yield 1.45 g (5.14 mmol, 65%) of an isomeric mixture **5a/4a**, (87:13) as a yellow oil. $[\alpha]_D^{20}$ = +110 (*c* = 3.1, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 1.12 (t, *J* = 7.1 Hz, 3 H), 1.19 (t, *J* = 7.2 Hz, 3 H), 1.85 (dd, *J* = 7.4, *J* = 7.1 Hz, 2 H), 2.04 (s, 3 H), 2.06−2.13 (m, 1 H), 2.42−2.54 (m, 2 H), 2.59 (dd, *J* = 7.3, *J* = 5.9 Hz, 2 H), 3.11−3.62 (m, 4 H), 3.95 (t, *J* = 9.6 Hz, 1 H), 9.78 (d, br., *J* = 9.5 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 12.90 (CH_3), 14.70 (CH_3), 17.64 (CH_3), 19.80 (CH_3), 21.38 (CH_2), 28.09 (CH_3), 30.15 (CH_2), 32.19 (CH_2), 32.47 (CH), 40.33 (CH_2), 41.68 (CH_2), 60.56 (CH), 105.35 (C), 164.48 (C), 170.01 (C), 193.67 (C) ppm. IR (ATR): ṽ = 2966 (s), 2936 (m), 1624 (vs), 1555 (s), 1465 (m), 1282 (m) cm^{-1}. HRMS for $C_{16}H_{28}N_2O_2$ (70 eV, EI): calcd. 280.2151, found 280.2154.

5-(*N*-Benzylamino)-3,3-difluoro-4-oxa-2-oxonia-3-boranuidabicyclo[4.4.0]deca-1,5-diene (6a): 3b (295 mg, 2.75 mmol) was added dropwise to a solution of **2f** (500 mg, 2.29 mmol) in CH_2Cl_2 (1 mL), and the reaction mixture was stirred at 23 °C for 24 h. Evaporation of all volatile materials under high vacuum and chromatography (SiO_2, PE/EA, 3:1, R_f = 0.54) yielded **6a** (481 mg, 1.72 mmol, 75%) as a colorless solid. M.p. 141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71−1.76 (m, 4 H), 2.08−2.12 (m, 2 H), 2.37−2.41 (m, 2 H), 4.65 (d, *J* = 5.7 Hz, 2 H), 5.87 (s, br., 1 H), 7.30−7.43 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 21.00 (CH_2), 21.76 (CH_2), 22.08 (CH_2), 30.94 (CH_2), 45.05 (CH_2), 95.03 (C), 126.28 (CH), 128.57 (CH), 129.25 (CH), 136.25 (C), 168.16 (C), 175.35 (C) ppm. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ = −145.44 (s) ppm. IR (ATR): ṽ = 3395 (s), 1600 (vs), 1525 (vs), 1336 (m), 1195 (m), 1114 (s), 1027 (s) cm^{-1}. $C_{14}H_{16}BF_2NO_2$ (279.09): calcd. C 60.25, H 5.78, N 5.02; found C 60.27, H 5.81, N 4.93.

11-(*N*-Benzylamino)-9,9-difluoro-10-oxa-8-oxonia-9-boranuidabicyclo[5.4.0]undeca-7,11-diene (6b): 3b (4.9 g, 46 mmol) was added dropwise to **2g** (0.50 g, 2.3 mmol), and the reaction mixture was stirred at 23 °C for 24 h. Evaporation of all volatile materials under high vacuum and chromatography (SiO_2, CH_2Cl_2, R_f = 0.27) yielded **6b** (506 mg, 1.73 mmol, 75%) as a colorless solid. M.p. 107 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.53−1.59 (m, 2 H), 1.64−1.69 (m, 2 H), 1.73−1.78 (m, 2 H), 2.19−2.21 (m, 2 H), 2.53−2.55 (m, 2 H), 4.60 (d, *J* = 5.7 Hz, 2 H), 6.30 (s, br., 1 H), 7.30−7.39 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 23.99 (CH_2), 24.38 (CH_2), 26.62 (CH_2), 30.99 (CH_2), 36.81 (CH_2), 45.21 (CH_2), 98.11 (C), 128.27 (CH), 128.43 (CH), 129.08 (CH), 135.57 (C), 167.54 (C), 182.51 (C) ppm. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ = −149.74 (s) ppm. IR (ATR): ṽ = 3371 (m), 2927 (m), 1592 (vs), 1520 (s), 1331 (m), 1222 (s), 1189 (m), 1027 (s) cm^{-1}. HRMS for $C_{15}H_{18}BF_2NO_2$ (70 eV, EI): calcd. 293.1399, found 293.1399. $C_{15}H_{18}BF_2NO_2$ (293.12): calcd. C 61.46, H 6.19, N 4.78; found C 61.06, H 6.19, N 4.71.

***N*-Benzyl-2-oxocycloheptanecarboxamide (7):** A solution of **6b** (40 mg, 0.14 mmol) in 1,4-dioxane (1 mL) and hydrochloric acid (1 mL, 1 mol/L) was stirred at 23 °C for 16 h. The mixture was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were dried ($MgSO_4$). Evaporation of all volatile materials under high vacuum and chromatography (SiO_2, PE/EA, 1:1, R_f = 0.29) yielded **7** (29 mg, 0.11 mmol, 81%) as a colorless solid. M.p. 83−84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39−1.45 (m, 1 H), 1.49−1.68 (m, 2 H), 1.85−1.96 (m, 4 H), 2.17−2.22 (m, 1 H), 2.55−2.61 (m, 2 H), 3.41 (dd, *J* = 11.0, *J* = 4.0 Hz, 1 H), 4.41 and 4.48 (AB part of an ABX system, J_{AB} = 14.9, J_{AX} = 5.5, J_{BX} = 5.6 Hz, 2 H), 7.06 (s, br., 1 H), 7.24−7.38 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 23.36 (CH_2), 27.26 (CH_2), 28.14 (CH_2), 28.15 (CH_2), 42.51 (CH_2), 42.57 (CH), 58.21 (CH_2), 126.39 (CH), 126.56 (CH), 127.65 (CH), 137.06 (C), 167.93 (C), 211.76 (C) ppm. IR (ATR): ṽ = 3362 (m, br.), 2923 (m), 2854 (m), 1702 (s), 1640 (vs), 1559 (m), 1452 (m), 1317 (m), 1028 (s) cm^{-1}. HRMS for $C_{15}H_{19}NO_2$ (70 eV, EI): calcd. 245.1416, found 245.1416.

(*R*)-*N*-(9-Methyl-1-oxospiro[4.5]dec-8-en-7-ylidene)-L-valine Diethylamide (9a): A mixture of **2a** (200 mg, 0.71 mmol) and

$Cu(OAc)_2 \cdot H_2O$ (14 mg, 0.070 mmol) in acetone (1 mL) was stirred at 23 °C for 1 h. After addition of **8** (100 mg, 1.43 mmol), the mixture was stirred for a further 16 h. Evaporation of all volatile materials and chromatography (Al_2O_3, EA, R_f = 0.50) gave **9a** (91 mg, 0.27 mmol, 37%) as a pale yellow oil, 57% *de* (calcd. from integrals of olefinic protons in the ^1H NMR spectrum). Major diastereomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.5 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 1.03 (t, *J* = 7.1 Hz, 3 H), 1.05 (t, *J* = 7.1 Hz, 3 H), 1.18−1.23 (m, 4 H), 1.48−1.61 (m, 2 H), 1.67−1.81 (m, 1 H) 1.87 (s, 3 H), 2.10−2.23 (m, 4 H), 3.06−3.55 (m, 4 H), 3.88 (d, *J* = 9.9 Hz, 1 H), 6.21 (sext., *J* = 1.6 Hz, 1 H) ppm; minor diastereomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.3 Hz, 3 H), 4.04 (d, *J* = 8.9 Hz, 1 H), 6.15 (sext., *J* = 1.3 Hz, 1 H) ppm. All other signals overlap with resonances of the major diastereomer. Major diastereomer: $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 12.50 (CH_3), 14.10 (CH_3), 18.62 (CH_2), 19.53 (CH_3), 20.57 (CH_3), 24.24 (CH_3), 28.26 (CH_2), 29.93 (CH_2), 31.83 (CH), 34.88 (CH_2), 38.79 (CH_2), 39.55 (CH_2), 40.61 (CH_2), 55.71 (C), 73.37 (CH), 115.32 (CH), 151.66 (C), 168.84 (C), 171.43 (C), 220.59 (C) ppm. IR (ATR): ṽ = 2962 (s), 2933 (s), 2870 (m), 1702 (m), 1626 (vs), 1455 (s), 1379 (s), 1215 (s) cm^{-1}. HRMS for $C_{20}H_{32}N_2O_2$ (70 eV, EI): calcd. 332.2464, found 332.2454.

(*R*)-*N*-(3-Methyl-7-oxospiro[5.5]dec-2-en-1-ylidene)-L-valine Diethylamide (9b): As described for **9a**, enamine **4b** (711 mg, 2.41 mmol), $Cu(OAc)_2 \cdot H_2O$ (24 mg, 0.12 mmol) and **8** (508 mg, 7.24 mmol) were reacted in acetone (10 mL). Evaporation of all volatile materials and chromatography (Al_2O_3, EA, R_f = 0.78) yielded **9b** (380 mg, 1.09 mmol, 46%) as a yellow oil, 86% de (calcd. from integrals of olefinic protons in the ^1H NMR spectrum). Major diastereomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93−1.03 (m, 12 H), 1.58−1.72 (m, 4 H), 1.83 (s, 3 H), 1.93−2.04 (m, 1 H), 2.11−2.23 (m, 4 H), 2.30−2.49 (m, 4 H), 3.16−3.46 (m, 4 H), 3.96 (d, *J* = 9.6 Hz, 1 H), 6.15 (sext., *J* = 1.5 Hz, 1 H) ppm; minor diastereomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.4 Hz, 3 H), 4.07 (d, *J* = 8.4 Hz, 1 H), 6.08 (sext., *J* = 1.4 Hz, 1 H) ppm. All other signals overlap with resonances of the major diastereomer. Major diastereomer: $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 12.47 (CH_3), 14.12 (CH_3), 19.58 (CH_3), 20.80 (CH_3), 21.02 (CH_2), 23.85 (CH_3), 26.64 (CH_2), 27.71 (CH_2), 31.09 (CH_2), 31.86 (CH), 34.86 (CH_2), 39.53 (CH_2), 40.56 (CH_2), 42.11 (CH_2), 54.92 (C), 72.92 (CH), 115.34 (CH), 150.06 (C), 168.46 (C), 171.28 (C), 213.01 (C) ppm. IR (ATR): ṽ = 2966 (m), 2934 (s), 2969 (m), 1657 (s), 1637 (vs) cm^{-1}. HRMS for $C_{21}H_{34}N_2O_2$ (70 eV, EI): calcd. 346.2621, found 346.2620.

(*S*)-*N*-(8-Benzyl-3-methyl-7-oxo-8-azaspiro[5.5]undec-2-en-1-ylidene)-L-valine Diethylamide (9d): $Cu(OAc)_2 \cdot H_2O$ (46.4 mg, 0.232 mmol) and **8** (245 mg, 3.50 mmol) were added to a solution of **4d** (900 mg, 2.33 mmol) in acetone (4 mL), and the reaction mixture was stirred at 23 °C for 16 h. After evaporation of all volatile materials, the residue was chromatographed [SiO_2, gradient elution from PE/EA, 2:1 to EA, R_f (SiO_2, PE/EA, 1:1) = 0.29] to give **9d** (375 mg, 0.859 mmol, 37%) as a yellow oil, $[\alpha]_D^{20}$ = +115 (*c* = 4.15, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.4 Hz, 3 H), 1.02 (t, *J* = 7.0 Hz, 3 H), 1.04 (t, *J* = 7.0 Hz, 3 H), 1.06 (d, *J* = 6.4 Hz, 3 H), 1.64−1.73 (m, 2 H), 1.76 (ddd, *J* = 13.4, *J* = 5.1, *J* = 2.2 Hz, 1 H), 1.89 (s, 3 H), 2.02−2.34 (m, 5 H), 2.76 (ddd, *J* = 13.4, *J* = 12.1, *J* = 6.4 Hz, 1 H), 3.05−3.14 (m, 1 H), 3.16−3.26 (m, 2 H), 3.27−3.32 (m, 1 H), 3.34−3.42 (m, 1 H), 3.68−3.79 (m, 1 H), 3.85 (d, *J* = 15.3 Hz, 1 H), 3.92 (d, *J* = 10.2 Hz, 1 H), 5.43 (d, *J* = 15.3 Hz, 1 H), 6.26 (s, 1 H), 7.25−7.45 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 12.36 (CH_3), 14.00 (CH_3), 17.84 (CH_2), 19.32 (CH_3), 20.95 (CH_3), 23.86 (CH_3), 27.36 (CH_2), 30.06 (CH_2), 31.52 (CH), 32.39 (CH_2), 39.44 (CH_2), 40.84 (CH_2), 46.91 (C), 49.47 (C), 49.91 (CH_2), 73.60 (CH), 115.19 (CH), 126.55 (CH), 127.25 (CH), 127.95 (CH), 137.41 (C), 150.07 (C), 168.05 (C), 171.35 (C) 171.42 (C) ppm. IR (neat): ṽ = 2970 (m), 1640 (vs), 1635 (vs), 1450 (m), 1440 (m) cm^{-1}. HRMS for $C_{27}H_{39}N_3O_2$ (70 eV, EI): calcd. 437.3042, found 437.3042.

***rac*-3-Methylspiro[5.5]undec-2-ene-1,7-dione (*rac*-10b):** To *rac*-**11b** (997 mg, 4.74 mmol) was added dropwise concd. H_2SO_4 (2 mL), and the reaction mixture was stirred at 0 °C for 4 h. After dilution with ice (10 g), the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) and dried ($MgSO_4$). Evaporation of all volatile materials and chromatography (SiO_2, PE/EA, 5:1, R_f = 0.24) yielded **10** (420 mg, 2.18 mmol, 46%) as colorless crystals. Spectroscopic data were in accordance with the literature.[19] GC: Bondex unα/β, temperature program: 3 min at 100 °C, then 1 K min^{-1} gradient to 130 °C, t_R(*S*-**10b**) = 28.36 min, t_R(*R*-**10b**) = 29.11 min.

(*S*)-3-Methylspiro[5.5]undec-2-ene-1,7-dione (10b): $Cu(OAc)_2 \cdot H_2O$ (68.0 mg, 0.34 mmol) and **8** (810 mg, 10.19 mmol) were added to a solution of **4b** (1.00 g, 3.40 mmol) in acetone (10 mL), and the reaction mixture was stirred at 23 °C for 16 h. After evaporation of all volatile materials, hydrochloric acid (5 mL, 2 mol/L) was added, and the reaction mixture was stirred at 23 °C for 3 h. After extraction with CH_2Cl_2 (3 × 5 mL), the combined organic layers were dried ($MgSO_4$) and the solvents evaporated. The residue was chromatographed (SiO_2, PE/EA, 5:1) to give **10b** in analytical amounts. GC: Bondex unα/β, t_R(*S*-**10b**) = 28.24 min, 87% *ee*.

(*R*)-3-Methylspiro[5.5]undec-2-ene-1,7-dione (*ent*-10b): *ent*-**10b** was prepared as described for *rac*-**10b** (vide supra). GC: Bondex unα/β, t_R(*R*-**10b**) = 28.90 min, 96% *ee*.

***rac*-2-Benzyl-9-methyl-2-azaspiro[5.5]undec-8-ene-1,7-dione (*rac*-10d):** Ice-cold concd. H_2SO_4 (3 mL) was added to *rac*-**11d** (350 mg, 1.16 mmol), the reaction mixture was stirred at 23 °C for 16 h, and then hydrolyzed with ice (11 g). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with satd. $NaHCO_3$ solution (10 mL), dried ($MgSO_4$) and the solvents evaporated. The residue was chromatographed (SiO_2, PE/EA, 1:1, R_f = 0.14) to yield *rac*-**10d** (79.1 mg, 0.279 mmol, 24%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.72−1.82 (m, 2 H), 1.90−1.99 (m, 2 H), 2.01 (s, 3 H), 2.22−2.28 (m, 1 H), 2.37−2.48 (m, 2 H), 2.90−2.97 (m, 1 H), 3.20−3.27 (m, 1 H), 3.28−3.35 (m, 1 H), 4.50 (d, *J* = 14.8 Hz, 1 H), 4.86 (d, *J* = 14.8 Hz, 1 H), 5.90 (sext., *J* = 1.2 Hz, 1 H), 7.28−7.40 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 19.01 (CH_2), 24.59 (CH_3), 28.07 (CH_2), 29.91 (CH_2), 32.64 (CH_2), 47.56 (CH_2), 50.88 (CH_2), 53.00 (C), 125.25 (CH), 127.57 (CH), 128.14 (CH), 128.99 (CH), 137.50 (C), 161.74 (C), 170.56 (C), 199.12 (C) ppm. IR (ATR): ṽ = 1661 (vs), 1626 (vs), 1492 (m), 1452 (m), 1436 (m), 1355 (m), 1284 (m), 1220 (m), 1290 (s) cm^{-1}. HRMS for $C_{18}H_{21}NO_2$ (70 eV, EI): calcd. 283.1572, found 283.1572. GC: Bondex unα/β, temperature program: 3 min at 150 °C, then 2.5 K min^{-1} gradient to 220 °C, t_R(*S*-**10d**) = 30.94 min, t_R(*R*-**10d**) = 31.06 min.

(*S*)-2-Benzyl-9-methyl-2-azaspiro[5.5]undec-8-ene-1,7-dione (10d): Hydrochloric acid (1.5 mL, 3 mol/L) was added to a solution of **9d** (99.0 mg, 0.226 mmol) in acetone (1 mL), and the reaction mixture was stirred at 23 °C for 20 h. After extraction with CH_2Cl_2 (3 × 2 mL), the combined organic layers were washed with $NaHCO_3$ solution (1 mL), dried ($MgSO_4$) and the solvents evaporated. The residue was chromatographed [SiO_2, gradient elution from PE/EA,

Table 1. X-ray single-crystal analysis data for compounds **2c**, **2d**, and **2f**

	2c	**2d**	**2f**
Empirical formula	$C_9H_{13}BF_2O_2$	$C_{14}H_{16}BF_2NO_2$	$C_9H_{13}BF_2O_3$
Formula mass (g mol^{-1})	202.00	279.09	218.00
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/c$	$P2_1/c$
a (Å)	7.8825(10)	14.5604(5)	8.9963(5)
b (Å)	10.5116(13)	9.3357(5)	11.9601(5)
c (Å)	11.8363(11)	10.3842(4)	10.2611(6)
α (deg)	90	90	90
β (deg)	92.324(8)	101.586(4)	109.618(4)
γ (deg)	90	90	90
Z	4	4	4
V (Å^3)	979.9(2)	1382.78(10)	1039.97(9)
$d_{calcd.}$ (g cm^{-3})	1.369	1.341	1.392
T (K)	293	293	293
λ (Å)	0.71073	1.54178	1.54178
μ (mm^{-1})	0.117	0.893	1.064
R_w (F^2)	0.1324	0.2551	0.2622
$R(F)$ [$I > 2\sigma(I)$]	0.0527	0.0721	0.0758
Goodness-of-fit on F^2	1.035	1.151	1.156

2:1 to EA, R_f (PE/EA) = 0.14] to yield **10d** in analytical amounts only. GC: Bondex unα/β, t_R(*S*-**10d**) = 30.94 min, >95% *ee*.

(*S*)-2-Acetyl-2-(3-oxobutyl)cyclopentanone (11a): $Cu(OAc)_2·H_2O$ (10 mg, 0.05 mmol) was added to **5a** (150 mg, 0.53 mmol) in acetone (2 mL), and the reaction mixture was stirred at 23 °C for 1 h. Then **8** (112 mg, 1.60 mmol) was added, and the mixture stirred at 23 °C for 20 h. After all volatile materials were evaporated, hydrochloric acid (2 mL, 2 mol/L) was added to the residue and stirred for 3 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL), dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 with PE/EA, 1:1 (R_f = 0.34) gave **11a** (36 mg, 0.18 mmol, 35%) as a pale yellow oil. GC: Lipodex E, temperature program: 20 K min^{-1} gradient from 40 °C to 100 °C, then 120 min isothermic, finally 1 K min^{-1} gradient to 120 °C, t_R(*S*-**11a**) = 156.22 min, t_R(*R*-**11a**) = 157.46 min, 87% *ee*.

(*S*)-2-Acetyl-2-(3-oxobutyl)cyclohexanone (11b): $Cu(OAc)_2·H_2O$ (13.4 mg, 0.07 mmol) was added to **5b** (395 mg, 1.34 mmol) in acetone (5 mL), and the reaction mixture was stirred at 23 °C for 1 h. Then **8** (212 mg, 2.68 mmol) was added, and the mixture stirred at 23 °C for 16 h. After all volatile materials were evaporated, hydrochloric acid (5 mL, 0.5 mol/L) was added to the residue and stirred for 1 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL), dried ($MgSO_4$) and concentrated. Chromatography on SiO_2 with PE/EA, 1:1 (R_f = 0.42) gave **11b** (188 mg, 0.89 mmol, 67%) as a colorless oil, 96% *ee* (determined by GLC after derivatization to **10**).

***rac*-3-Acetyl-1-benzyl-3-(3-oxobutyl)-2-piperidone (*rac*-11d):** $Cu(OAc)_2·H_2O$ (10 mg, 0.050 mmol) and **8** (105 mg, 1.50 mmol) were added to a solution of **1d** (231 mg, 1.00 mmol) in acetone (1 mL), and the reaction mixture was stirred at 23 °C for 16 h. All volatile materials were removed under vacuum, and the residue was chromatographed on Al_2O_3 (PE/EA, 1:1, R_f = 0.37) to yield *rac*-**11d** (255 mg, 0.85 mmol, 85%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.56 (ddd, J = 13.3, J = 9.5, J = 3.5 Hz, 1 H), 1.65−1.74 (m, 1 H), 1.79−1.87 (m, 1 H), 2.11 (s, 3 H), 2.12−2.19 (m, 3 H), 2.21 (s, 3 H), 2.47 (ddd, J = 17.8, J = 9.5, J = 6.0 Hz, 1 H), 2.56 (ddd, J = 17.8, J = 9.5, J = 6.0 Hz, 1 H), 3.19−3.27 (m, 2 H), 4.40 (d, J = 14.6 Hz, 1 H), 4.76 (d, J = 14.6 Hz, 1 H), 7.23−7.34 (m, 5 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 19.65 (CH_2), 26.79 (CH_3), 29.25 (CH_2), 29.26 (CH_2), 29.99 (CH_3), 39.10 (CH_2), 47.39 (CH_2), 50.65 (CH_2), 59.14 (C), 127.54 (CH), 128.07 (CH), 128.67 (CH), 136.94 (C), 169.58 (C), 206.99 (C), 207.97 (C) ppm. IR (ATR): $\tilde{\nu}$ = 1714 (vs), 1633 (vs), 1494 (m), 1453 (m), 1356 (s), 1168 (m) cm^{-1}. HRMS for $C_{18}H_{23}NO_3$ (70 eV, EI): calcd. 301.1678, found 301.1676.

2-Benzyl-7-methyl-1,9-dioxo-2-azaspiro[5.5]undec-7-ene (12): To *rac*-**11d** (200 mg, 0.66 mmol) were successively and dropwise added pyrrolidine (40 mg, 0.56 mmol) and glacial acetic acid (34 mg, 0.56 mmol), the reaction mixture stirred at 23 °C for 16 h, and then directly chromatographed on SiO_2 (EA, R_f = 0.36) to give **12** (170 mg, 0.59 mmol, 89%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.86−2.09 (m, 4 H), 1.94 (s, 3 H), 2.17 (ddd, J = 13.5, J = 5.0, J = 3.8 Hz, 1 H), 2.43 (ddd, J = 17.5, J = 13.0, J = 4.9 Hz, 1 H), 2.48 (ddd, J = 17.5, J = 5.3, J = 3.8 Hz, 1 H), 2.61 (dddd, J = 13.4, J = 13.1, J = 5.4, J = 1.1 Hz, 1 H), 3.24−3.37 (m, 2 H), 4.55 (d, J = 14.6 Hz, 1 H), 4.71 (d, J = 14.6 Hz, 1 H), 5.93 (q, J = 1.4 Hz, 1 H), 7.25−7.34 (m, 5 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 19.83 (CH_2), 20.82 (CH_3), 28.72 (CH_2), 31.36 (CH_2), 32.44 (CH_2), 47.53 (C), 48.27 (CH_2), 50.94 (CH_2), 127.65 (CH), 128.21 (CH), 128.63 (CH), 128.74 (CH), 137.02 (C), 163.63 (C), 171.79 (C), 197.82 (C) ppm. IR (ATR): $\tilde{\nu}$ = 1665 (s), 1620 (vs), 1492 (m), 1452 (m), 1352 (m), 1265 (m), 1232 (m), 1196 (s), 737 (m), 608 (m) cm^{-1}. HRMS for $C_{18}H_{21}NO_2$ (70 eV, EI): calcd. 283.1572, found 283.1572.

Single-Crystal X-ray Analysis: Single-crystal X-ray diffraction data were collected for difluoroborates **2c**, **2d** and **2f** (Table 1). For each structure the data were collected either on a Nicolet P3 diffractometer by using a graphite monochromator with Mo-K_α radiation (λ = 0.71073 Å) (**2c**) or on a Siemens P4 diffractometer by using Cu-K_α radiation (λ = 1.54178 Å). The structures were solved by direct methods and refined[20] against F^2.

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