Synthesis and Aldol Stereoselectivity of 2-Oxazolidinones Derived from L-Histidine

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The regiospecific synthesis of the 2-oxazolidinones **5b**, **7**, **12a**, and **12b** starting from L-histidine **1a** is described. The stereoselectivity in the dibutyl(trifluoromethylsulfonyloxy)borane promoted aldol condensation between the chiral imides **13a** and **13b** and benzaldehyde was also studied. The formation of a cationic imidazole-boron complex, **14a**, occurs before the aldol condensation between **13a** and benzaldehyde takes place. However, the condensation between **13b** and benzaldehyde occurs without the formation of any boron complex. The steric hindrance of the substituent at C-4 may account for this difference in behavior.

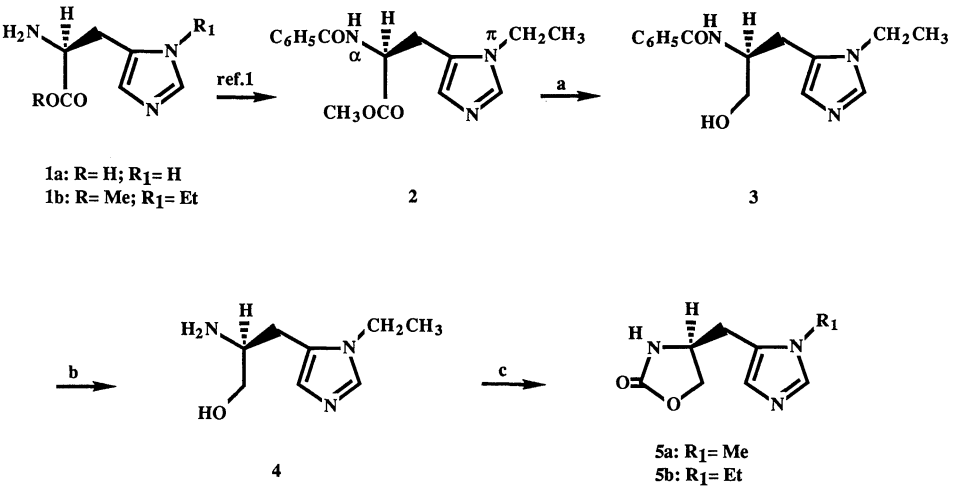
As part of a program aimed at the discovery and development of novel drugs with potential muscarinic activity, our laboratory has examined the preparation of 2-oxazolidinones derived from the naturally occurring amino acid L-histidine **1a**.

As far as we know, the preparation of N^{π}- and N^{τ}-alkyl-substituted 2-oxazolidinones (The N-2 and N-4 positions in the imidazolyl group are tentatively denoted as N^{π} and N^{τ}-, respectively) derived from L-histidine has no precedents in the literature, even though the regiospecific functionalization on the imidazole moiety has been previously resolved.[1-6] We now wish to report our first results on this topic. Our interest in the potential aldol diastereoselectivity exhibited by chiral imides such as **13a** and **13b** lay in the previously announced feature of the amine-boron complexation.[7] These imides display a very different behavior when treated with dibutyl(trifluoromethylsulfonyloxy)borane. While **13a** leads to the formation of a cationic imidazole-boron complex **14a** before the aldol condensation with benzaldehyde takes place, the chiral imide **13b** undergoes aldol condensation without complexing; the steric hindrance at C-4[8] may account for this different behavior. However, since the stereoselectivity obtained in both cases is remarkable, we assume that an important role of the boron complexation on the aldol steroselectivity in the former case seems unlikely.

Results and Discussion

Preparation of the N^{π}-Ethyl 2-Oxazolidinone Derived from L-Histidine 5b. Preparation of the N^{π}-ethyl-substituted 2-oxazolidinone **5b** was achieved using the same synthetic sequence that we have recently reported for the preparation of the N^{π}-methyl-substituted 2-oxazolidinone, **5a**, in the course of the synthesis of some (+)-pilocarpine analogs[9] (Scheme 1).

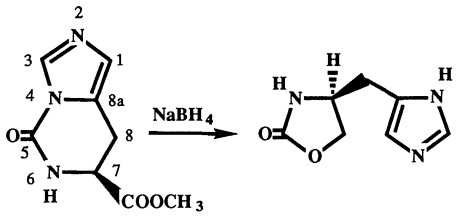
The reaction of N^{α}-benzoyl-N^{π}-ethyl-L-histidine



a: LAH(4 eq,), THF, 0 °C, 45 min. (90%); b: 1) 6N HCl, 80 °C, 6h.; 2) 1N KOH (EtOH) (95%); c: $(EtO)_2CO$ (1.2 equiv), CH_3OH reflux, $NaCH_3O$ (2 equiv), 1h. (70%)

Scheme 1.

(**2**)[1a] with 4 equiv of LAH in freshly distilled THF at 0 °C (45 min.) yielded a crude material from which the reduction product **3** was isolated by flash chromatography (90%). Hydrolysis of **3** by treatment with 6 M HCl (1 M=mol dm^{-3}) at 80—90 °C afforded the N^{π}-ethyl-L-histidinol dihydrochloride **4·2HCl**. Neutralization of **4·2HCl** with 1 M ethanolic KOH led to the free base **4**, after removal of the KCl and evaporation of the solvent. The structural change was confirmed by the upfield displacement of the signals corresponding to the two aromatic protons from δ H_2^{im}=8.81 and δ H_5^{im}=7.39 in **4·2HCl** to δH_2^{im}=7.51 and δH_5^{im}=6.69 in **4**. Reaction of **4** with 1.2 equiv of diethyl carbonate in refluxing methanol, using CH_3ONa as a base, afforded a crude material from which it was possible to isolate the 2-oxazolidinone **5b** by flash chromatography (70%). The presence of a signal at δ=161.8 in the ^{13}C NMR spectrum confirmed the presence of the cyclic carbamate functionality.

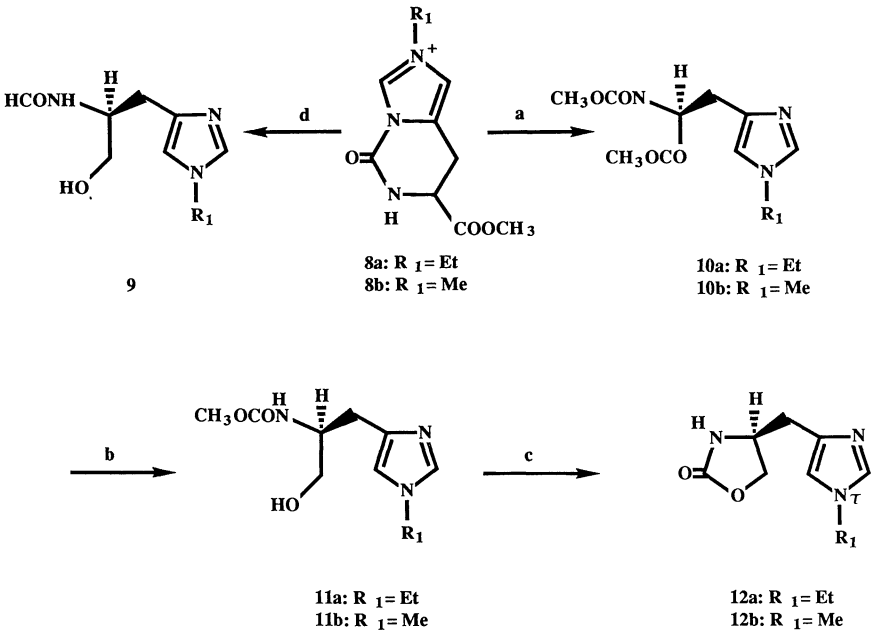


6 **7**

Scheme 2.

Preparation of the 2-Oxazolidinone 7. The starting material to obtain our next target molecule was the oxoimidazo[1,5-*c*]pyrimidine **6**[2] (Scheme 2). Reduction of **6** with an excess of $NaBH_4$[10] afforded the 2-oxazolidinone **7** (80%) (Scheme 2). We assumed that the carbonyl group belonging to the cyclic urea function of **6** undergoes nucleophilic attack by the alkoxide resulting from the reduction of the ester function. The acyl migration is helped by the good leaving character of the imidazole ring. The structural change was confirmed by the displacement of the ^{13}C NMR signals corresponding to the carbonyl groups from δ=149 in the urea **6** to δ=162 in the cyclic carbamate **7**. This result provides a very interesting alternative to the previously reported LAH reduction of **6**.[11]

Preparation of the N^{τ}-Alkyl-Substituted 2-Oxazolidinones Derived from L-Histidine 12a and 12b. The experience gained on the reduction of the oxoimidazo-[1,5-*c*]pyrimidine **6** prompted us to prepare the imidazolium iodides **8a** and **8b**[2] (Scheme 3) and to attempt the cyclization under the conditions described for **6** in an effort to prepare **12a** and **12b**. We expected that the imidazolinium functionality of both molecules would accelerate the process, due to the increased leaving character of the aromatic moiety. However, $NaBH_4$ reduction of **8a** led to a complicated mixture from which the hydroxy-substituted formamide **9** was isolated by flash chromatography (65%). The spectroscopic properties obtained for the new reduction product provided enough evidence for the presence of



9

8a: R 1= Et
8b: R 1= Me

10a: R 1= Et
10b: R 1= Me

11a: R 1= Et
11b: R 1= Me

12a: R 1= Et
12b: R 1= Me

a: $NaCH_3O$ (1.1 equiv), CH_3OH, 24 °C, 2h. (95%); **b**: $NaBH_4$ (5 equiv), CH_3OH, 0 °C, 5h. (70%); **c**: $NaCH_3O$ (2 equiv), CH_3OH, 24 °C, 5h. (87%); **d**: $NaBH_4$

Scheme 3.

the hydroxy (^{13}C NMR: δ=63.95; ^{1}H NMR: δ=3.50 (d, J=7.5 Hz, 2H)) and the formamide moieties (^{13}C NMR: δ=163.8 (CH); ^{1}H NMR: δ=7.95 (s, 1H)). We were able to detect traces of the desired 2-oxazolidinone **12a** by ^{1}H NMR analysis of some of the minor components, but the yield was unacceptable.

This disappointing result led us to attempt the transformation of **8a** into the carbamate **10a**.[6] Treatment of **8a** with 1.1 equiv of CH_3ONa in absolute methanol at room temperature afforded a crude product from which it was possible to isolate the carbamate **10a** by flash chromatography (95%). The presence of two singlets at δ=3.63 and 3.60 in the ^{1}H NMR spectrum together with the appearance of two signals at δ=172 and 156 in the ^{13}C NMR spectrum allowed us to confirm the presence of the two desired functionalities; the methyl ester and the methyl carbamate.

$NaBH_4$ reduction of **10a** led to the isolation of the hydroxy-substituted carbamate **11a** by flash chromatography (70%). The ^{13}C NMR spectrum of **11a** showed only one carbonyl absorption at δ=156 together with a new methylene absorption at δ=64.14 corresponding to the hydroxymethyl group; this allowed us to confirm the chemoselective reduction of the methyl ester functionality.

Base-promoted cyclization of **11a** was successfully achieved with an excellent yield. The treatment of the hydroxy carbamate **11a** with CH_3ONa in methanol at room temperature led to the isolation of the N^{τ}-ethyl-substituted 2-oxazolidinone **12a** (87%). The structural change was confirmed by the displacement of the signals corresponding to the absorption of the carbonyl and hydroxymethyl groups in the ^{13}C NMR spectrum from δ=156 and 64 in **11a** to δ=159 and 68 in **12a**, respectively. Application of the same three-step sequence to the imidazolium iodide **8b** afforded the N^{τ}-methyl-substituted 2-oxazolidinone **12b** with 63% overall yield.

In summary, the effective regioselective synthesis of **12a** and **12b** proceeded in five steps from the methyl ester of L-histidine **1b** with 60% and 58% overall yields, respectively.

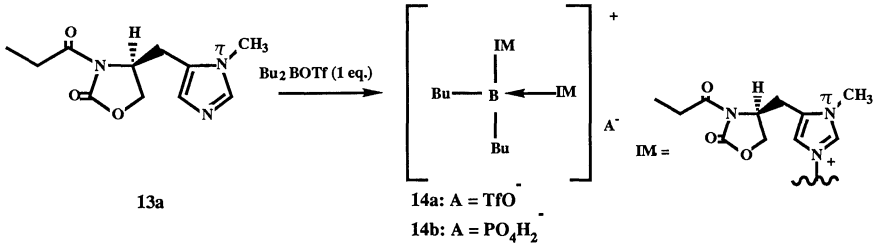
Stereoselection in the Aldol Condensation between the Chiral Imides 13a and 13b with Benzaldehyde. In order to test the induction of the stereoselectivity of these 2-oxazolidinones in the aldol condensation with aldehydes and to see what role the imidazole moiety might play in this type of process, we decided to analyze the reaction of the N-acyl-2-oxazolidinones **13a** and **13b** with benzaldehyde via the boron enolate.

Treatment of **5a**[9] and **12b** with HaH (1.1 equiv) in DMF followed by addition of propionyl chloride (1.1 equiv) led to the imides **13a** (80%) and **13b** (85%), respectively.

Treatment of the chiral imide **13a** with 1 equiv of dibutyl(trifluoromethylsulfonyloxy)borane, followed by addition of benzaldehyde under the conditions described by Evans[7] led to the isolation of a white solid **14b** (Scheme 4), which was soluble in chloroform and could be purified by crystallization in dry THF; flash chromatography of the crude product led also to pure **14b** with partial decomposition. Spectroscopic analysis (IR, ^{1}H NMR, and ^{13}C NMR) clearly showed that the condensation reaction did not take place. The ^{13}C NMR spectrum of the new product exhibited two signals corresponding to two carbonyl groups (δ=174.30 and 153.16) and three upfield signals corresponding to three methyl groups (δ=33.23, 13.93, and 8.14), one of them belonging to a butyl moiety, as the presence of three new methylene signals (δ=26.76, 26.06, and 21.03) seemed to confirm. The ^{1}H NMR spectrum exhibited the presence of the three methyl groups (signals at δ=3.81 (s), 1.11 (t), and 0.80 (t)) and pointed to a structural change in the imidazole ring by the downfield displacement of the aromatic protons from δ H_2^{im}=7.35 and δ H_5^{im}=6.76 in **13a** to δ H_2^{im}=8.02 and δ H_5^{im}=6.85 in **14b**.

According to the assumption of Evans that the ineffectiveness of bases such as pyridine in the enolization process of this type of chiral imides can be attributed to the irreversible amine-boron complexation,[7] we first thought of the formation of an sp^3-hybridized cationic boron complex **14a**;[12] which under the usual workup conditions would undergo metathesis to the phosphate **14b**.[13] The obtained MS (FAB) spectrum for **14b** comfirmed our assumption. The presence of two peaks at m/z: 599 (45%) and 362 (100%) proved the presence of the boron cation in the complex and the loss of an imide fragment, respectively.

Treatment of the imide **13a** with 1 equiv of dibutyl(trifluoromethylsulfonyloxy)borane at 0 °C gave **14b** (80%) after quenching the reaction with phosphate buffer. Apparently, the formation of the boron complex occurred prior to any condensation process.



13a

14a: A = TfO$^-$

14b: A = $PO_4H_2^-$

Scheme 4.

Since the imidazole base present in **13a** scavenged half of one equiv of the triflate, the use of al least 1.5 equiv of the reagent was necessary to promote the aldol condensation with benzaldehyde. Treatment of **13a** with 2 equiv of dibutyl(trifluoromethylsulfonyloxy)-borane followed by addition of benzaldehyde led to the condensation product **15** (Scheme 5) after the usual work up conditions.

Spectroscopic analysis of the aldol product **15a** excluded the presence of threo isomers and confirmed the formation of the imidazol-boron complex by the downfield shifts obtained for the imidazole protons (δ H_2^{im}=7.98 and δ H_5^{im}=6.84) by comparison with the above-mentioned values exhibited by **13a**.[16]

Transformation of the crude aldol product into the possible mixture of erythro isomers of methyl 3-hydroxy-2-methyl-3-phenylpropionate **16a** by the classical procedure[7] allowed us to obtain an optical value of $[\alpha]_D^{24}$=−18.1° (*c* 1.74, $CHCl_3$), which led us to establish the absolute configuration of the major erythro isomer as (2*S*, 3*S*) **16a** and to determine the optical puriry of the aldol condensation product as >94% in accordance with the data in the literature.[17,18]

Treatment of the chiral imide **13b** (Scheme 6) with 1 equiv of dibutyl(trifluoromethylsulfonyloxy)borane followed by addition of benzaldehyde led to the aldol product **15b** (86%) whose spectroscopic properties excluded the existence of threo isomers in the reaction product. However, in this case the chemical shifts obtained for the imidazole protons at δ H_5^{im}=6.69 and δ H_2^{im}=7.41 excluded the imidazol-boron complexation. We assume that the steric hindrance at C-4 may account for the difficulties of the chiral imide **13b** in undergoing the imidazole-boron complexation.

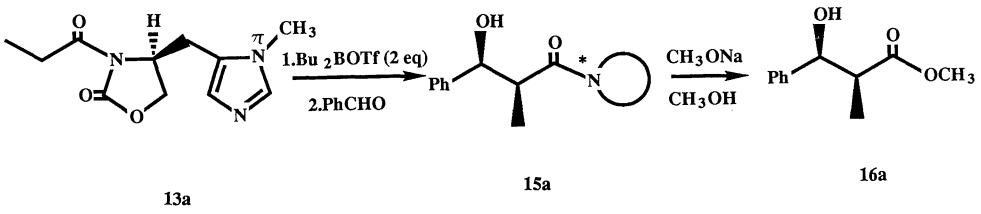
Transformation of **15b** into **16b** by the reported procedure[7] led us to obtain an optical value of $[\alpha]_D^{21}$=−17.3° and enabled us to determine the optical purity of the aldol product as >90%, in agreement with the data in the literature.[17]

Conclusion

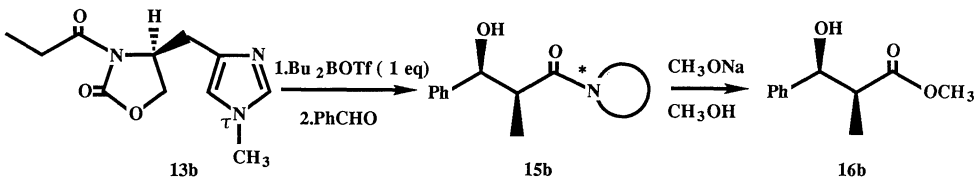
The synthesis of **5b**, **7**, **12a**, and **12b** from L-histidine was successfully achieved. These compounds are useful chiral auxiliaries from which imides such as **13a** and **13b** can be prepared and used in aldol reactions. Since the imidazole base present in the histidine-derived auxiliary **13a** scavenged half of one equiv of the triflate reagent, the use of 1.5 equiv of dibutyl(trifluoromethylsulfonyloxy)borane to promote the aldol condensation between **13a** and benzaldehyde was necessary. However, the chiral imide **13b** led to the aldol product **15b** by treatment with 1 equiv of the boron triflate followed by addition of benzaldehyde. Since the aldol stereoselectivity was remarkable in both cases we assume that the imidazole-boron complexation displayed by **13a** plays no significant role in the high stereoselectivity observed with this chiral imide.

Experimental

Organic extracts were dried with commercially dried Na_2SO_4 and evaporated under reduced pressure below 40 °C. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined on a digital Perkin-Elmer 241 polarimeter in a 1-dm cell. The ^1H and ^{13}C NMR spectra were recorded on a Bruker WP-200-SY spectrometer operating at 200 MHz and 50.3 MHz respectively. All ^{13}C NMR spectra were obtained using deuteriochloroform as solvent unless otherwise stated; for ^{13}C NMR spectra in D_2O, 1,4-dioxane (δ=67.6) was used as the internal standard. The IR spectra were determined on a Beckman 33-IR spectrophotometer as indicated in each case. Mass spectra were recorded on a Kratos MS-25 instrument operating with either EI (70 eV) or FAB ionization (8 kV, using Xe and $(HOCH_2CH_2S)_2$ as matrix). Elemental analyses were carried out using a Perkin-Elmer 240 B Analyzer. Conductimetric measurements were made on a Crison 522 conductimeter. All compounds discussed in this paper were obtained in a chromatographically homogeneous state.



Scheme 5.



Scheme 6.

N^{α}-Benzoyl-N^{π}-ethyl-L-histidinol: (3). A solution of **2**[1] (5 g, 16.6 mmol) in freshly distilled THF (100 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.3 g, 33.2 mmol) in anhydrous THF (100 mL) under a nitrogen atmosphere. After 45 min of stirring the reaction was worked up as usual to obtain a residue (4.2 g) which was fractionated by flash chromatography on silica gel. Elution with chloroform-methanol (80:20) yielded **3** (4.1 g, 90%); $[\alpha]_D^{20}$ −49.3° (*c* 1.02, CH_3OH); IR ν_{max} ($CDCl_3$) 3600—3000, 2950, 1640, 1540, 1230, 1040, 940, and 710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.39 (3H, t, *J*=7 Hz, $NCH_2\underline{CH_3}$), 2.94 (2H, m, $\underline{CH_2}Ar$), 3.68 (2H, m, $\underline{CH_2}OH$), 4.06 (2H, q, *J*=7 Hz, $N\underline{CH_2}CH_3$), 4.14 (1H, m, CH), 6.73 (1H, s, CCHN), 7.36 (3H, m, Ar), 7.44 (1H, s, NCHN), 7.72 (2H, m, Ar); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=16.54 (q, $NCH_2\underline{CH_3}$), 26.30 (t, $\underline{CH_2}Ar$), 40.63 (t, $N\underline{CH_2}CH_3$), 52.53 (d, CH), 64.25 (t, CH_2OH), 127.49 (d, Ar), 128.24 (d, Ar), 129.39 (d, Ar), 130.00 (s, C_4^{im}), 132.51 (d, C_5^{im}), 135.89 (s, Ar), 138.00 (d, C_2^{im}) 170.28 (s, Ar$\underline{CO}$). Anal. Calcd for $C_{15}H_{19}N_3O_2$ (M. W. 273): C, 65.93; H, 6.96; N, 15.38%. Found: C, 65.87; H, 6.90; N, 15.32%.

N^{π}-Ethyl-L-histidinol Dihydrochloride: (4·2HCl) and N^{π}-Ethyl-L-histidinol: (4). A solution of **3** (5 g, 18.3 mmol) in 6 M HCl (350 mL) was heated under reflux for 6 h in a nitrogen atmosphere. The volume of water was reduced (to 50 mL) by evaporation of the solvent. Benzoic acid was removed by extraction of the aqueous solution with ether (3×15 mL). The aqueous solution was evaporated to dryness to afford **4·2HCl** (4 g, 90%); $[\alpha]_D^{21}$ 3.3° (*c* 1.6, CH_3OH); IR ν_{max} (Nujol) 3300, 3030, 2950, 1540, 1470, 1380, 1060, and 860 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ=1.35 (3H, t, *J*=7 Hz, $NCH_2\underline{CH_3}$), 3.0 (2H, m, $\underline{CH_2}Ar$), 3.48 (1H, m, CH), 3.58 (2H, m, $\underline{CH_2}OH$), 4.11 (2H, q, *J*=7 Hz, $N\underline{CH_2}CH_3$), 7.39 (1H, s, CCHN), 8.81 (1H, s, NCHN); ^{13}C NMR (50.3 MHz, CD_3OD) δ=15.48 (q, $NCH_2\underline{CH_3}$), 24.27(t, $\underline{CH_2}Ar$), 43.63 (t, $N\underline{CH_2}CH_3$), 52.79 (d, CH), 61.18 (t, CH_2OH), 119.98 (d, C_5^{im}), 130.70 (s, C_4^{im}), 136.22 (d, C_2^{im}). Anal. Calcd for $C_8H_{15}N_3O\cdot 2HCl\cdot 2H_2O$ (M. W. 278): C, 34.53; H, 7.55; N, 15.11%. Found: C, 34.49; H, 7.50; N, 15.06%.

Treatment of **4·2HCl** (4 g, 16.5 mmol) with 1 M ethanolic KOH (33 mL) led to the isolation of the free base **4** (2.8 g, 100%); $[\alpha]_D^{20}$ −15.1° (*c* 1.44, CH_3OH), after filtration of the KCl and evaporation of the solvent; IR ν_{max} (film) 3600—3000, 2900, 1490, 1050 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ=1.30 (3H, t, *J*=7 Hz, $NCH_2\underline{CH_3}$), 2.62 (2H, m, $\underline{CH_2}Ar$), 2.97 (1H, m, CH), 3.41 (2H, m, $\underline{CH_2}OH$), 3.92 (2H, q, *J*=7 Hz, $N\underline{CH_2}CH_3$), 6.71 (1H, s, CCHN), 7.53 (1H, s, NCHN); ^{13}C NMR (50.3 MHz, D_2O) δ=16.7 (q, $NCH_2\underline{CH_3}$), 28.57 (t, $\underline{CH_2}Ar$), 40.62 (t, $N\underline{CH_2}CH_3$), 53.27 (d, CH), 66.38 (t, CH_2OH), 127.32 (d, C_5^{im}), 129.98 (s, C_4^{im}), 137.87 (d, C_2^{im}). Anal. Calcd for $C_8H_{15}N_3O$ (M. W. 169): C, 56.80; H, 8.88; N, 24.85%. Found: C, 56.76; H, 8.79; N, 24.81%.

(4*S*)-4-[(3-Ethyl-3*H*-imidazol-4-yl)methyl]-2-oxazolidinone: (5b). Diethyl carbonate (4.3 mL, 35.5 mmol) and 1.78 g (59.2 mmol) of NaH (80%) were added to a solution of **4** (5 g, 29.6 mmol) in absolute methanol (20 mL) under a nitrogen atmosphere. When addition had finished, the reaction mixture was heated to 100 °C for 1 h. Evaporation of the solvent at reduced pressure afforded a residue which was fractionated by flash chromatography on silica gel. Elution with chloroform-methanol (70:30) afforded **5b** (4 g, 70%); mp 111—113 °C (CH_3OH); $[\alpha]_D^{21}$−12.8° (*c* 1.31, CH_3OH); IR ν_{max} (Nujol) 2950, 1750, 1450, 1360, 1050 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ=1.32 (3H, t, *J*=7 Hz, $NCH_2\underline{CH_3}$), 2.82 (2H, d, *J*=6.2 Hz, $\underline{CH_2}Ar$), 3.93 (2H, q, *J*=7 Hz, $N\underline{CH_2}CH_3$), 4.07 (2H, m, CH_2OCO), 4.45 (1H, m, CH), 6.74 (1H, s, CCHN), 7.57 (1H, s, NCHN); ^{13}C NMR (50.3 MHz, CD_3OD) δ=16.56 (q, $NCH_2\underline{CH_3}$), 30.40 (t, $\underline{CH_2}Ar$), 40.74 (t, $N\underline{CH_2}CH_3$), 52.81 (d, CH), 71.01 (t, $\underline{CH_2}OCO$), 127.35 (d, C_5^{im}), 128.21 (s, C_4^{im}), 138.24 (d, C_2^{im}), 161.81 (s, CO); MS *m/z*, (%) 196 (M^++1, 1.5), 195 (4.9), 111 (9), 110 (100), 109 (96.7), 86 (6.3), 82 (43.3), 81 (58.0). Anal. Calcd for $C_9H_{13}N_3O_2$ (M. W. 195): C, 55.38; H, 6.67; N, 21.54%. Found: C, 55.30; H, 6.64; N, 21.50%.

(4*S*)-4-[(4-Imidazolyl)methyl]-2-oxazolidinone: (7). A solution of **6**[2] (5 g, 25.6 mmol) in absolute methanol (100 mL) at 0 °C under a nitrogen atmosphere was added dropwise to a suspension of $NaBH_4$ (4.8 g, 130 mmol) in absolute methanol (100 mL). The reaction mixture was stirred for 30 min at room temperature and was quenched by addition of an aqueous saturated NH_4Cl solution (30 mL). The reaction volume was then reduced (to ca. 50 mL) by evaporation of the solvent at reduced pressure and the aqueous solution was extracted with mixtures of chloroform-methanol (30:10) (5×25 mL). Evaporation of the organic solvent led to the isolation of **7** (3.4 g, 80%); mp 150—152 °C (Hexane); $[\alpha]_D^{23}$−7.2° (*c* 1.5, CH_3OH); IR ν_{max} (film) 3600—3000, 1750, 1540, 1410, 1240, 1020, 760 cm^{-1}; ^1H NMR (200 MNz, D_2O) δ=2.73 (2H, d, *J*=5.5 Hz, $\underline{CH_2}Ar$), 4.05 (2H, m, CH_2OCO), 4.35 (1H, m, CH), 6.95 (1H, s, CCHN), 7.89 (1H, s, NCHN); ^{13}C NMR (50.3 MHz, D_2O) δ=31.11 (t, $\underline{CH_2}Ar$), 52.45 (d, CH), 70.73 (t, $\underline{CH_2}OCO$), 118.02 (d, C_5^{im}), 131.47 (s, C_4^{im}), 135.80 (d, C_2^{im}), 162.19 (s, CO); MS *m/z* (%) 168 (M^++1, 10), 136 (12), 123 (80), 96 (75), 82 (100). Anal. Calcd for $C_7H_9N_3O_2$ (M. W. 167): c, 50.30; H, 5.39; N, 25.15%. Found: C, 50.26; H, 5.32; N, 25.08%.

N^{π}-Ethyl-N^{α}-methoxycarbonyl-L-histidine Methyl Ester: (10a). A solution of imidazolium iodide **8a**[2] (5 g, 14.2 mmol) in absolute methanol (35 mL) was added dropwise to a suspension of CH_3ONa (842.4 mg, 15.6 mmol) in absolute methanol at 0 °C under a nitrogen atmosphere. The reaction was stirred for 2h at room temperature and was quenched by addition of an aqueous saturated NH_4Cl solution (50 mL). Evaporation of the methanol at reduced pressure and extraction of the aqueous solution with chloroform led to the isolation of crude **10a** after evaporation of the solvent. Fractionation of the crude was performed by flash chromatography on silica gel. Elution with chloroform-methanol (90:10) yielded **10a** (3.6g, 100%); $[\alpha]_D^{24}$+1.0° (*c* 1.04, $CHCl_3$); IR ν_{max} (film) 3600—3000, 2950, 1720, 1500, 1450, 1050, and 780 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.35 (3H, t, *J*=7 Hz, $NCH_2\underline{CH_3}$), 2.98 (2H, m, $\underline{CH_2}Ar$), 3.60 (3H, s, $NHCOO\underline{CH_3}$), 3.63 (3H, s, $COO\underline{CH_3}$), 3.85 (2H, q, *J*=7 Hz, $N\underline{CH_2}CH_3$), 4.5 (1H, m, CH), 6.62 (1H, s, CCHN), 7.3 (1H, s, NCHN); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=15.72 (q, $NCH_2\underline{CH_3}$), 29.67 (t, $\underline{CH_2}Ar$), 41.34 (t, $N\underline{CH_2}CH_3$), 51.64 (q, $COO\underline{CH_3}$+q, $NHCOO\underline{CH_3}$), 53.90 (d, CH), 115.76 (d, C_5^{im}), 135.98 (d, C_2^{im}), 137.08 (s, C_4^{im}), 156.35 (s, $\underline{CO}N$), 171.98 (s, $\underline{CO}OCH_3$). Anal. Calcd for $C_{11}H_{17}N_3O_4$ (M. W. 255): C, 51.76; H, 6.67; N, 16.47%. Found: C, 51.70; H, 6.61; N, 16.43%.

N^{α}-Methoxycarbonyl-N^{π}-methyl-L-histidine Methyl Ester: (10b). Prepared under the same conditions as described for **10a**. Flash chromatography on silica gel. Eluent chloroform-methanol (90:10); **10b** (3.4 g, 96%); $[\alpha]_D^{22}$+2.3° (*c* 1.03, $CHCl_3$); IR ν_{max} (film) 3600—3000, 1725, 1500, 1450, 1050, and 760 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=2.96 (2H, m,

$\underline{CH_2}Ar$), 3.54 (3H, s, NCH_3), 3.59 (3H, s, $NHCOO\underline{CH_3}$), 3.63 (3H, s, $COO\underline{CH_3}$), 4.48 (1H, m, CH), 6.57 (1H, s, CCHN), 7.24 (1H, s, NCHN) ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=29.91 (t, $\underline{CH_2}Ar$), 33.02 (q, NCH_3), 51.91 (q, $NHCOO\underline{CH_3}$+q, $COO\underline{CH_3}$), 53.95 (d, CH), 117.59 (d, C_5^{im}), 137.45 (d, C_2^{im}+*s*, C_4^{im}), 156.59 (s, NCO), 172.11 (s, $\underline{CO}OCH_3$). Anal. Calcd for $C_{10}H_{15}N_3O_4$ (M. W. 241): C, 49.79; H, 6.22; N, 17.43%. Found: C, 49.76; H, 6.18; N, 17.39%.

N^{τ}-Ethyl-N^{α}-methoxycarbonyl-L-histidinol: (11a). A solution of **10a** (5 g, 19.6 mmol) in absolute methanol (50 mL) at 0 °C under a nitrogen atmosphere was added to a suspension of $NaBH_4$ (3.7 g, 98 mmol) in absolute methanol (25 mL). The reaction mixture was stirred for 5 h at room temperature. The reaction was then quenched by addition of an aqueous saturated NH_4Cl solution (30 mL). The organic solvent was evaporated at reduced pressure and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and evaporated to afford a crude **11a** which was fractionated by flash chromatography on silica gel. Elution with chloroform-methanol (90:10) afforded **11a** (3.1 g, 70%); $[\alpha]_D^{24}$+3.4° (*c* 1.6, $CHCl_3$); IR ν_{max} (film) 3600—3000, 2950, 1700, 1520, 1260, and 1060 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.4 (3H, t, *J*=7 Hz, $NCH_2\underline{CH_3}$), 2.8 (2H, m, $\underline{CH_2}Ar$), 3.60 (3H, s, OCH_3), 3.65 (2H, m, $\underline{CH_2}OH$), 3.85 (1H, m, CH), 3.88 (2H, q, *J*=7 Hz, $N\underline{CH_2}CH_3$), 6.70 (1H, s, CCHN), 7.35 (1H, s, NCHN); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=16.03 (q, $NCH_2\underline{CH_3}$), 30.23 (t, $\underline{CH_2}Ar$), 41.77 (t, $N\underline{CH_2}CH_3$), 51.84 (q, OCH_3), 52.24 (d, CH), 64.14 (t, CH_2OH), 116.46 (d, C_5^{im}), 135.79 (d, C_2^{im}), 138.17 (s, C_4^{im}), 156.89 (s, CO). Anal. Calcd for $C_{10}H_{17}N_3O_3$ (M. W. 227): C, 52.86; H, 7.49; N, 18.50%. Found: C, 52.82; H, 7.41; N, 18.48%.

N^{α}-Methoxycarbonyl-N^{τ}-methyl-L-histidinol: (11b). Prepared under the same conditions as described for **11a**. Flash chromatography on silica gel. Eluent: chloroform-methanol (90:10); **11b** (3.1 g, 70%); $[\alpha]_D^{22}$+10° (*c* 1.2, $CHCl_3$); IR ν_{max} (film) 3550—3000, 1724, 1480, 1450, 1050, and 760 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=2.76 (2H, m, $\underline{CH_2}Ar$), 3.54 (3H, s, NCH_3), 3.55 (3H, s, $NHCOO\underline{CH_3}$), 3.83 (2H, m, $\underline{CH_2}OH$), 4.10 (1H, m, CH), 6.63 (1H, s, CCHN), 7.27 (1H, s, NCHN); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=29.78 (t, $\underline{CH_2}Ar$), 33.02 (q, NCH_3), 51.60 (q, $NHCOO\underline{CH_3}$), 52.29 (d, CH), 63.64 (t, CH_2OH), 117.92 (d, C_5^{im}), 136.94 (d, C_2^{im}), 138.28 (s, C_4^{im}), 156.74 (s, CO). Anal. Calcd for $C_9H_{15}N_3O_3$ (M. W. 213): C, 50.70; H, 7.04; N, 19.72%. Found: C, 50.74; H, 7.07; N, 19.69%.

(4*S*)-4-[(1-Ethyl-1*H*-imidazol-4-yl)methyl]-2-oxazolidinone: (12a). Sodium methoxide (2.4 g, 44 mmol) was added to a solution of **11a** (5 g, 22 mmol) in absolute methanol (40 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 5 h at room temperature. The reaction was then quenched by addition of aqueous saturated NH_4Cl solution (15 mL). The aqueous phase was extracted with $CHCl_3$ (3×25 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to afford **12a** (3.7 g, 87%); mp 102 °C (Hexane); $[\alpha]_D^{24}$−44.3° (*c* 1.05, $CHCl_3$); IR ν_{max} (film) 3600—3000, 2950, 1750, 1500, 1400, 1250, 1020 940, and 760 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.38 (3H, t, *J*=7 Hz, $NCH_2\underline{CH_3}$), 2.74 (2H, d, *J*=6 Hz, $\underline{CH_2}Ar$), 3.90 (2H, q, *J*=7 Hz, $N\underline{CH_2}CH_3$), 4.14 (2H, m, CH_2OCO), 4.47 (1H, m, CH), 6.27 (1H, s, NH), 6.69 (1H, s, CCHN), 7.34 (1H, s, NCHN); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=15.39 (q, $NCH_2\underline{CH_3}$), 32.99 (t, $\underline{CH_2}Ar$), 41.05 (t, $N\underline{CH_2}CH_3$), 51.86 (d, CH), 68.97 (t, $\underline{CH_2}OCO$), 115.65 (d, C_5^{im}), 135.63 (d, C_2^{im}), 136.49 (s, C_4^{im}), 159.13 (s, CO); MS *m/z* (%) 196 (M^++1, 1), 195 (0.4), 111 (7.2), 110 (100), 109 (33.3), 95 (1.6), 82 (5.8), 81 (59.6). Anal. Calcd for $C_9H_{13}N_3O_2$ (M. W. 195): C, 55.38; H, 6.67; N, 21.50%. Found: C, 55.32; H, 6.61; N, 21.50%.

(4*S*)-4-[(1-Methyl-1*H*-imidazol-4-yl)methyl]-2-oxazolidinone: (12b). Prepared under the same conditions as described for **12a**. (92%); mp 132—134 °C (Hexane); $[\alpha]_D^{22}$−9.8° (*c* 1.6, $CHCl_3$); IR ν_{max} (film) 3600—3000, 1750, 1420, 1240, 1010, and 756 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=2.76 (2H, d, *J*=6 Hz, $\underline{CH_2}Ar$), 3.61 (3H, s, NCH_3), 4.13 (2H, m, CH_2OCO), 4.46 (1H, m, CH), 6.1 (1H, s, NH), 6.68 (1H, s, CCHN), 7.32 (1H, s, NCHN); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=32.84 (q, NCH_3), 33.14 (t, $\underline{CH_2}Ar$), 52.11 (d, CH), 69.22 (t, $\underline{CH_2}OCO$), 117.61 (d, C_5^{im}), 136.66 (s, C_4^{im}), 137.20 (d, C_2^{im}), 159.33 (s, CO); MS *m/z* (%) 182 (M^++1, 10), 181 (12), 150(10), 137 (25), 121 (20), 109 (30), 96 (100), 81 (30). Anal. Calcd for $C_8H_{11}N_3O_2$ (M. W. 181): C, 53.04; H, 6.08; N, 23.20%. Found: C, 53.09; H, 6.02; N, 23.23%.

(4*S*)-4-[(3-Methyl-3*H*-imidazol-4-yl)methyl]-3-propionyl-2-oxazolidinone: (13a). A solution of **5a** (5 g, 27.6 mmol) in DMF (100 mL) was added to a suspension of NaH (80%) (0.9 g, 30.4 mmol) in anhydrous DMF (6 mL) at room temperature under nitrogen atmosphere.

The reaction mixture was stirred for 30 min at the same temperature; it was then chilled at 0 °C and propionyl chloride (2.6 mL, 30.4 mmol) was added dropwise.

The reaction mixture was stirred at room temperature for 15 h. Then, a sat. NH_4Cl solution (25 mL) was added. The organic layer was separated, dried and evaporated under reduced pressure to give a crude residue which was fractionated by flash chromatography on silica gel. By elution with chloroform-methanol (80:20) a pale yellow solid **13a** (5.2 g, 80%), was obtained; mp 110—111 °C ($CHCl_3$); $[\alpha]_D^{20}$+76.9° (*c*, 1.52, CH_3OH); IR ν_{max} (film) 3100, 2950, 1780, 1770, 1680, 1440, 1360, 1050, 1010, 990, 940, 910, and 740 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.11 (3H, t, *J*=7 Hz, $COCH_2\underline{CH_3}$), 2.72 (1H, dd, J_1=15 Hz, J_2=10 Hz, $\underline{CH_2}Ar$), 2.88 (2H, dq, J_1=3 Hz, J_2=7 Hz, $CO\underline{CH_2}CH_3$), 3.17 (1H, dd, J_1=15 Hz, J_2=3 Hz, $\underline{CH_2}Ar$), 3.60 (3H, s, NCH_3), 4.14 (1H, dd, J_1=3 Hz, J_2=9 Hz, CH_2OCO), 4.23 (1H, t, *J*=7 Hz, CH_2OCO), 4.46 (1H, m, CH), 6.76 (1H, s, CCHN), 7.35 (1H, s, NCHN); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=7.75 (q, $COCH_2\underline{CH_3}$), 26.45 (t, $CO\underline{CH_2}CH_3$), 28.53 (t, $\underline{CH_2}Ar$), 30.91 (q, NCH_3), 52.51 (d, CH), 66.22 (t, $\underline{CH_2}OCO$), 125.49 (s, C_4^{im}), 127.54 (d, C_5^{im}), 138.41 (d, C_2^{im}), 152.72 (s, $N\underline{CO}O$), 173.66 (s, $\underline{CO}N$); MS *m/z* (%) 238 (M^++1, 10), 181 (80), 96 (100), 77 (40), 64 (80). Anal. Calcd for $C_{11}H_{15}N_3O_3$ (MW. 237): C, 55.69; H, 6.32; N, 17.72%. Found: C, 55.61; H, 6.27; N, 17.69%.

(4*S*)-4-[(1-Methyl-1*H*-imidazol-4-yl)methyl]-3-propionyl-2-oxazolidinone: (13b). Prepared under the same conditions as described for **13a** (85%). $[\alpha]_D^{22}$+72.4° (*c* 1.04, $CHCl_3$); IR ν_{max} (film) 3600—3000, 2900, 1780, 1700, 1380, 1020, and 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.15 (3H, t, *J*=7 Hz, $NCOCH_2\underline{CH_3}$), 2.95 (3H, m, CHAr+$CO\underline{CH_2}CH_3$), 3.05 (1H, dd, J_1=15 Hz, J_2=3 Hz, CHAr), 3.92 (3H, s ,NCH_3), 4.29 (1H, t, *J*=8 Hz, CHOCO), 4.54 (1H, dd, J_1=7 Hz, J_2=3 Hz, CHOCO), 4.65 (1H, m, CH), 6.68 (1H, s, CCHN), 7.38 (1H, s, NCHN); ^{13}C NMR ($CDCl_3$) δ=8.27 (q, $COCH_2\underline{CH_3}$), 29.01 (t, $CO\underline{CH_2}CH_3$), 30.17 (t, CH_2Ar), 41.72 (q, NCH_3), 54.13 (d, CH), 66.66 (t, CH_2OCO), 116.50 (s, C_5^{im}), 136.34 (d, C_2^{im}+s, C_4^{im}), 153.76 (s, $N\underline{CO}O$), 173.98 (s, $\underline{CO}CH_2CH_3$). Anal.

Calcd for $C_{15}H_{15}N_3O_3$ (M. W. 237): C, 55.69; H, 6,32: N, 17.72%. Found: C, 55.61; H, 6.28; N, 17.65%.

Formation of the Cationic Boron Complex: (14b). A 1 M solution of dibutyl(trifluoromethylsulfonyloxy)borane (4.2 mL, 4.2 mmol) in dichloromethane was added drpwise to a stirred solution of triethylamine (0.6 mL, 4.2 mmol) in dichloromethane (5 mL). Then, a solution of **13a** (1 g, 4.2 mmol) in dichloromethane (5 mL) was added dropwise at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 1 h and then quenched by addition to pH=7 phosphate buffer. The mixture was extracted twice with dichloromethane and the combined extracts were washed with brine and concentrated in vacuo. The crude oil was then dissolved in methanol (15 mL) at 0 °C and 30% hydrogen peroxide (4.5 mL) was added. After the mixture had been stirred at room tempetrature for 2h, water (20 mL) was added; the mixture was concentrated and extracted twice with dichloromethane. The combined organic layers were washed with 5% aqueous sodium hydrogencarbonate and brine, dried (Na_2SO_4), and concentrated in vacuo to afford 1.30 g of crude product. By digestion in ethyl acetate, a white solid (mp 131—134 °C) was separated which was recrystallized in THF to give **14b** (1.16 g, 80%); mp 135—136 °C (THF); $[\alpha]_D^{20}$+42.4° (*c*, 1.13, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3600—3200, 3180, 2980, 1790, 1720, 1600, 1550, 1460, 1400, 1280, 1160, 1100, 1020, 770, and 460 cm^{-1}; ^1H NMR (200 NHz, $CDCl_3$) δ=0.81 (3H, t, J=7 Hz, $(CH_2)_3\underline{CH_3}$), 1.11 (3H, t, J=7 Hz, $COCH_2\underline{CH_3}$), 2.86 (3H, m, $CO\underline{CH_2}CH_3$+$\underline{CH}Ar$), 3.17 (1H, dd, J_1=15 Hz, J_2=3 Hz, $\underline{CH}Ar$), 3.81 (3H, s, NCH_3), 4.13 (1H, dd, J_2=2 Hz, J_2=10 Hz, CH_2OCO), 4.37 (1H, t, J=8 Hz, CH_2OCO), 4.66 (1H, m, CH), 6.85 (1H, s, CCHN), 8.02 (1H, s, NCHN); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=8.14 (q, $COCH_2\underline{CH_3}$), 13.93 (q, $(CH_2)_3\underline{CH_3}$), 21.03 (t, BCH_2), 26.06 and 27.27 (dt, $BCH_2(\underline{CH_2})_2CH_3$), 26.76 (t, $CO\underline{CH_2}CH_3$), 28.92 (t, $\underline{CH_2}Ar$), 33.23 (q, NCH_3), 52.39 (d, CH), 66.89 (t, $\underline{CH_2}OCO$), 121.47 (d, C_5^{im}), 129.00 (s, C_4^{im}), 137.57 (d, C_2^{im}), 153.18 (s, $N\underline{C}OO$), 174.20 (s, $\underline{C}ON$); MS (FAB) *m/z* (%) 599 (45), 362 (100), 250 (90); MS (EI) *m/z* (%) 237 (60), 138 (90), 96 (100). Anal. Calcd for $C_{30}H_{50}O_{10}N_6BP$ (MW: 696): C, 51.73; H, 7.18; N, 12.07%. Found: C, 51.69; H, 7.09; N, 11.96%.

Condensation of 13a with Benzaldehyde via the Formation of the Cationic Boron Complex: (15a). A 1 M solution of dibutyl(trifluoromethylsulfonyloxy)borane (6.3 mL, 6.3 mmol) in dichloromethane was added dropwise to a stirred solution of triethylamine (0.9 mL, 6.3 mmol) in dichloromethane (4 mL) was added dropwise. Then, a solution of **13a** (0.75 g, 3.15 mmol) in dichloromethane (5 mL) was dropwise added at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 1 h, cooled to −78 °C and a solution of benzaldehyde (0.30 mL, 3.15 mmol) in dichloromethane (5 mL) was added. This mixture was stirred for 30 min at −78 °C and 1 h at 0 °C. The reaction was quenched by addition to pH=7 phosphate buffer. The mixture was extracted twice with dichloromethane and the combined extracts were washed with brine and concentrated in vacuo. The crude was then dissolved in methanol (10 mL) at 0 °C and 30% hydrogen peroxide (4.5 mL) was added. After the mixture had been stirred at room temperature for 2 h, water (20 mL) was added; the mixture was concentrated and extracted twice with dichloromethane. The combined organic layers were washed with 5% aqueous sodium hydrogencarbonate and brine, dried (Na_2SO_4) and concentrated in vacuo to afford **15a** (1.14 g, 80%); mp 95—97 °C (EtOAc); $[\alpha]_D^{20}$+69.1° (*c* 1.38, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ=0.81 (3H, t, J=7 Hz, $(CH_2)_3\underline{CH_3}$), 1.06 (3H, d, J=7 Hz, $CH\underline{CH_3}$),2.81 (1H, dd, J_1=15 Hz, J_2=10 Hz, $\underline{CH}Ar$), 3.12 (1H, dd, J_1=15 Hz, J_2=3 Hz, $\underline{CH}Ar$), 3.79 (3H, s, NCH_3), 4.02 (2H, m, $\underline{CH}OCO$+$\underline{CH}CH_3$), 4.22 (1H, dd, J_1=7 Hz, J_2=9 Hz, $\underline{CH}OCO$), 4.59 (1H, m, $\underline{CH}CH_2Ar$), 5.03 (1H, d, J=3.8 Hz, $Ar\underline{CH}OH$), 6.83 (1H, s, CCHN), 7.3 (5H, m, Ar), 7.98 (1H, s, NCHN); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=10.51 (q, $\underline{CH_3}CH$), 13.96 (q, $(CH_2)_3\underline{CH_3}$), 21.07 (t, BCH_2), 26.06 and 26.85 (dt, $BCH_2(\underline{CH_2})_2CH_3$), 27.30 (t, $\underline{CH_2}Ar$), 33.29 (q, NCH_3), 44.88 (d, $CH_3\underline{CH}$), 52.70 (d, $\underline{CH}CH_2Ar$), 66.90 (t, $\underline{CH_2}OCO$), 73.52 (d, $Ar\underline{CH}OH$), 121.52 (d, C_5^{im}), 125.98 (d, Ar), 127.48 (d, Ar), 128.21 (d, Ar), 129.04 (s, C_4^{im}), 137.40 (d, C_2^{im}), 141.58 (s, Ar), 152.87 (s, $N\underline{C}OO$), 176.29 (s, $\underline{C}ON$); MS (EI) *m/z* (%) 889 (M^++1−H_2O, 10), 739 (30), 614 (50), 475 (85), 237 (100), 107 (80). Anal. Calcd for $C_{44}H_{62}O_{12}N_6BP$ (MW. 908): C, 58.14; H, 6.82; N, 9.25%. Found: C, 57.96; H, 6.76; N, 8.97%.

Condensation of 13b with Benzaldehyde: (15b). Prepared under the same conditions as described for **15a** using one equiv of the boron triflate (86%). $[\alpha]_D^{21}$+75° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.14 (3H, d, J=7 Hz, $CH\underline{CH_3}$), 2.95 (2H, m, CH_2Ar), 3.90 (3H, s, NCH_3), 2.95 (2H, m, CH_2Ar), 3.90 (3H, s, NCH_3), 4.55 (1H, dq, J_1=7 Hz, J_2=3.8 Hz, $CHOH\underline{CH}CH_3$), 4.17 (1H, t, J=8.5 Hz, CH_2OCO), 4.59 (1H, m, $N\underline{CH}(CH_2O)CH_2$), 5.05 (1H, d, J=3.8 Hz, CHOH), 6.69 (1H, s, CCHN), 7.4 (5H, m, Ar), 7.41 (1H, s, NCHN); ^{13}C NMR ($CDCl_3$) δ=15.79 (q, $CH\underline{CH_3}$), 29.74 (t, $\underline{CH_2}Ar$), 42.19 (q, NCH_3), 44.54 (q, $CH\underline{CH_3}$), 54.07 (t, $NCH\underline{CH_2}$), 66.66 (t, $\underline{CH_2}OCO$), 73.62 (d, CHOH), 116.98 (d, C_5^{im}), 136.22 (d, C_2^{im}), 141.64 (s, C_4^{im}), 153.17 (s, $N\underline{C}OO$), 176.57 (s, $\underline{C}ONCOO$). Anal. Calcd for $C_{18}H_{21}O_4N_3$ (M. W. 343) C, 62.97; H, 6.12; N, 12.24%. Found C, 62.92; H, 6.16; N, 12.26%.

Methyl (2*S*,3*S*)-3-Hydroxy-2-methyl-3-phenylpropanoate: (16a). Sodium hydride (180 mg, 80%) was carefully added to methanol (10 mL) under an argon atmosphere. Then, a solution of **15b** (1.4 g, 2 mmol) in methanol (50 mL) was added dropwise at 0 °C. The reaction mixture was stirred 15 min at 0 °C. Addition of an aqueous sat. NH_4Cl solution (25 mL) was followed by extraction with chloroform. The combined organic layers were dried evaporated to afford a crude which was purified by flash chromatography. Elution with hexane-ethyl acetate (80:20) gives **16b** (760.5 mg, 98%); $[\alpha]_D^{20}$−18.1° (*c* 1.7, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$), δ=1.10 (3H, d, J=7 Hz, $CH\underline{CH_3}$), 2.78(1H, m, $\underline{CH}CH_3$), 3.65 (3H, s, $COO\underline{CH_3}$), 5.08 (1H, d, J=3.6 Hz, $\underline{CH}OH$), 7.31 (5H, m, Ar); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ=10.81 (q, $CH\underline{CH_3}$), 46.51 (d, $\underline{CH}CH_3$), 51.71 (q, $COO\underline{CH_3}$), 73.76 (d, CHOH), 125.97 (d, Ar), 127.47 (d, Ar), 128.22 (d, Ar), 141.57 (s, Ar), 175.97 (s, CO). Anal. Calcd for $C_{11}H_{14}O_3$ (MW. 194): C, 68.04; H, 7.21%. Found: C, 68.06; H, 7.15%.

Compound **16b** was prepared under the same conditions as described for **16a** staring from **15b** (97%). $[\alpha]_D$−17.3° (*c* 1.89, $CHCl_3$) with identical spectroscopic properties as those described for **16a**.

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