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Conjugate Addition of Chloride to α,β-Unsaturated Chiral Imides Promoted by BCl_3-derivatives. Part II.

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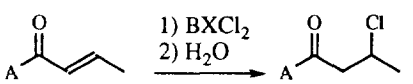
Abstract. The diastereoselective hydrochlorination of α,β-unsaturated chiral imides by reaction with BCl_2OR or $BCl(OR)_2$ type reagents is described. Complete diastereoselectivity is achieved through the use of new oxazolidin-2-ones *ad hoc* prepared for this purpose from (*S*)-tryptophan. An hypothesis on the donor-acceptor interactions, between the substrate and the Lewis acids, that drive the attack of the chloride preferentially to one face of the alkenoyl chain is reported.

Nucleophilic 1,4 addition to chiral α,β-unsaturated carbonyl equivalents is the most common method of synthesizing optically active β-substituted carbonyl compounds.[1] During our recent research on the addition of *O*-benzylhydroxylamine to chiral imides promoted by Lewis acids,[2] we observed a parallel reaction when BCl_2(O-*i*Pr) was used. Indeed, the chloride migration from the four-coordinated boron to the unsaturated system delivers a β-halogenated carboxylic acid derivative [3] (Scheme 1).

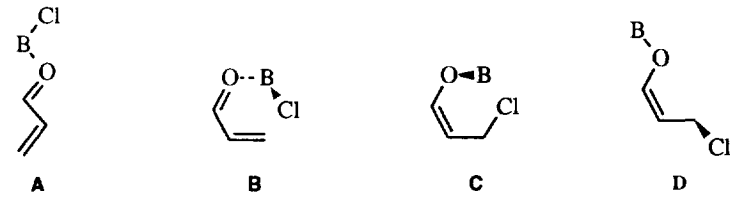
Scheme 1



A = chiral auxiliary
X = OPr^i, Cl

A deeper investigation into the mechanism shows that the reaction is geometrically possible and energetically favored. Indeed, the chlorine atom's attack on the double bond can be assumed to happen through a [1,5]-sigmatropic rearrangement with formation of the corresponding enolate. The reaction path was investigated by semiempirical AM1 calculations.[4] Both the geometry and orbital coefficients were in agreement, confirming the reliability of such calculations for this system. The complex between acrolein and BCl_3 was chosen as a simple model, and calculations showed the existence of two minima **A** and **B** for the complex and two minima **C** and **D** for the enolate as reported in Figure 1. In the *syn* form **B** the B-Cl bond is out of the acrolein plane with the s orbital roughly parallel to the p^* orbitals of the diene system, thus the two orbitals can interact and the chlorine atom can shift from boron to carbon. The enolate **C** is favored by the formation of a real B-O bond (1.37 Å compared to 1.81 Å in the complex) which is further stabilized by a p donation of the oxygen lone pair to the vacant boron orbital (bond order = 1.16 e^-).

Figure 1

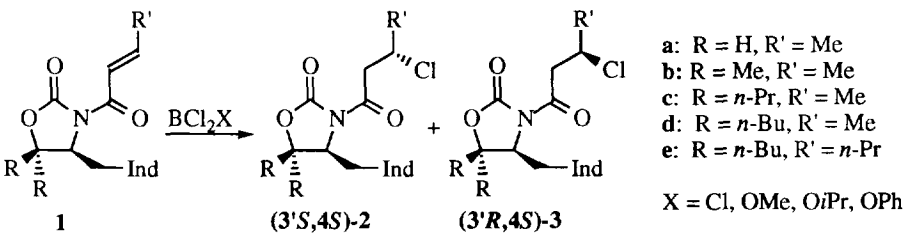


A **B** **C** **D**

DH_f = -119.2 Kcal/mol DH_f = -115.4 Kcal/mol DH_f =-117.5 Kcal/mol DH_f =-121.3 Kcal/mol

The complexes formed by Lewis acids and carbonyl groups are of great importance in organic synthesis, even though their properties are not fully understood.[5] Lewis acids of the type L_2BX have been utilized in enantio- and diastereoselective aldol reaction and in the enantioselective reduction of carbonyl groups,[6] but only one example of halogen migration from boron has been reported, to our knowledge.[7,8]

Since the introduction of a stereogenic centre to the β position of a carboxylic acid represents a challenging approach in synthetic organic chemistry, we wish to report here our efforts to achieve complete diastereoselectivity through the use of indolyl auxiliaries *ad hoc* prepared for this purpose from (*l*)-tryptophan. The high stereoselectivity has been achieved by utilising as Michael acceptors the hindered oxazolidin-2-ones (*S*)-4-(1H-indol-3-ylmethyl)-5,5-dialkyl-3-(1-oxo-but-2-enyl)-oxazo-lidin-2-ones **1**, as we have previously demonstrated that the selectivity of this reaction greatly depends on the kind of chiral auxiliary utilized.[3] The preparation and the conformational analysis of these new Michael acceptors is described in the preceding paper.



a: R = H, R' = Me
b: R = Me, R' = Me
c: R = *n*-Pr, R' = Me
d: R = *n*-Bu, R' = Me
e: R = *n*-Bu, R' = *n*-Pr

X = Cl, OMe, O*i*Pr, OPh

1 **(3'*S*,4*S*)-2** **(3'*R*,4*S*)-3**

Scheme 2

Thus the imides **1** were hydrochlorinated under a variety of conditions, including solvent, reaction temperature, reaction time and equivalent of the BCl_3-derivatives (Scheme 2). Best results were obtained when the reaction was carried out in anhydrous CH_2Cl_2 by addition of 3 equivalents of BCl_2OR in CH_2Cl_2 under an argon atmosphere at -78 °C. Indeed, when the reaction was performed with 1 equivalent of BCl_2OR, the same diastereomeric ratios were obtained together with a low yield (20-30%). The most interesting results are reported in Table 1.

The data in Table 1 confirm our hypothesis that diastereoselectivity depends on the substituents R at C_4. We observe a constant increase in diastereoselection on going from R = H to R = *n*-Bu (entries 1-4). Entries 4-8 report the results obtained with R = *n*-Bu. The reaction proceeds with high yield and diastereoselectivity and shows that the diastereomeric ratio also depends on the boron ligands and on the substituent R' of the unsaturated alkenoyl chain. Indeed, higher diastereomeric ratios were obtained with smaller boron ligands (entry 5 *versus* entry 4) and the larger R' group (entries 7 and 8). In contrast, the phenoxy boron ligand yields very low stereoselectivity (entry 6).

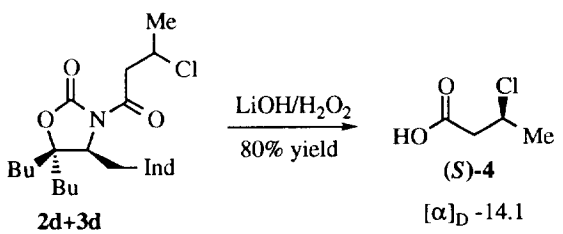
Table 1. Hydrochlorination of imides **1a-1e** with BCl_2OR type reagents.

Entry	Substrate	R	R'	Lewis acid (3 equiv.)	Reaction temp. (°C)	Reaction time (h)	Yield (%)	d.r.[a] **2/3**
1	**1a**	H	Me	BCl_2O-*i*Pr	-78	7	30	50 : 50
2	**1b**	Me	Me	BCl_2O-*i*Pr	-78	7	98	75 : 25
3	**1c**	*n*-Pr	Me	BCl_2O-*i*Pr	-78	3	80	83 : 17
4	**1d**	*n*-Bu	Me	BCl_2O-*i*Pr	-78	7	90	86 : 14
5	**1d**	*n*-Bu	Me	BCl_2OMe	-78	17	98	92 : 8
6	**1d**	*n*-Bu	Me	BCl_2OPh	-78	18	50	45 : 55
7	**1e**	*n*-Bu	*n*-Pr	BCl_2O-*i*Pr	-78	6	80	>99 : 1
8	**1e**	*n*-Bu	*n*-Pr	BCl_2OMe	-78	6	80	>99 : 1

[a] Determined by means of ^{13}C NMR and HPLC analysis.

The absolute configuration of the newly formed stereogenic centre was assigned by the hydrolysis of the 86:14 mixture of **2d** and **3d** (entry 4) with H_2O_2 and LiOH in water (Scheme 3).[9] The 3-chlorobutanoic acid **4** was isolated after the usual work-up and a value of $[\alpha]_D^{20}$ -14.1 (c 0.4, ether) was obtained.[8a] Thus the absolute configuration of the major product **2d** was unequivocally established as the (*S*)-form. This surprising result shows that the preferential attack occurs on the *si* face which is the most hindered one.

Scheme 3



2d+3d **(*S*)-4** $[\alpha]_D$ -14.1

In order to test the reactivity of $BCl(OR)_2$ derivatives, the imides **1a-1e** were submitted to hydrochlorination under the conditions described above (Table 2).

Table 2. Hydrochlorination of imides **1a-1e** with $BCl(OR)_2$ type reagents.

Entry	Substrate	R	R'	Lewis acid (equiv.)	Reaction temp. (°C)	Reaction time (h)	Yield (%)	d.r.[a] **2/3**
1	**5a**	H	Me	$BCl(O$-*i*$Pr)_2$ (3)	-78 - rt	72	15	50 : 50
2	**5b**	Me	Me	$BCl(O$-*i*$Pr)_2$ (3)	-78 - rt	72	50	27 : 73
3	**5c**	*n*-Pr	Me	$BCl(O$-*i*$Pr)_2$ (3)	-78 - rt	72	30	25 : 75
4	**5c**	*n*-Pr	Me	$BCl(O$-*i*$Pr)_2$ (10)	-78 - rt	48	40	33 : 67
5	**5d**	*n*-Bu	Me	$BCl(O$-*i*$Pr)_2$ (3)	-78 - rt	72	60	20 : 80
6	**5d**	*n*-Bu	Me	$BCl(OMe)_2$ (3)	-78 - rt	72	60	40 : 60
7	**5e**	*n*-Bu	*n*-Pr	$BCl(O$-*i*$Pr)_2$ (3)	-78 - rt	72	38	46 : 54
8	**5e**	*n*-Bu	*n*-Pr	$BCl(OMe)_2$ (3)	-78 - rt	72	27	43 : 57

[a] Determined by means of ^{13}C NMR and HPLC analysis.

With these kinds of reagents the diastereomeric ratio is also a function of R, R' and the boron ligands, but we observed opposite face selectivity and low diastereoselectivity. Moreover the yields were low even in the presence of 10 equivalents of reactant (entry 4). The best yield and diastereomeric ratio were obtained with R = *n*-Bu and R' = Me (entry 5). Indeed the diastereomeric ratio is higher with larger boron ligands (entry 5 *versus* entry 6) and smaller R' groups (entry 5 *versus* entry 7).

Thus we suppose that due to the orientation of the unsaturated chain and the indolyl group, an electron-rich channel suitable for a donor-acceptor interaction is formed (Figure 2). Whether the BCl_3-derivative is admitted or not depends on the hindrance of the substituents of the boron atom. Indeed when the species BCl_2OR are utilized, the reactants can enter the channel and the *si*-face is attacked by the chlorine. Moreover by replacing the isopropyl group with the smaller methyl group, steric hindrance of the ligands is reduced. This facilitates the entry of the reactant into the channel, therefore increasing diastereoselectivity. In contrast when the $BCl(OR)_2$ species are utilized, low yields are obtained and opposite face selectivity predominates. Indeed a preferential attack from the *re* face is observed as a consequence of the bulkiness of the Lewis acid of type $BCl(OR)_2$ which can not enter the channel.

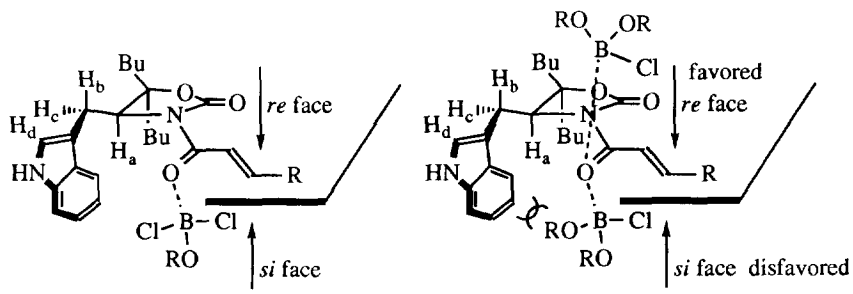


Figure 2

To summarize, the hydrochlorination of chiral imides of type **1** with BCl_2OR and $BCl(OR)_2$ can be explained by the mechanism proposed in this study. The fact that diastereoselectivity greatly depends on both the chiral auxiliary and the BCl_3-derivative utilized was confirmed.

EXPERIMENTAL SECTION

General Methods. ^1H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively. Chemical shifts are reported in ppm relative to the solvent peak of $CHCl_3$, defined to be δ 7.27. Infrared spectra were recorded with an FT-IR spectrometer. Melting points were determined in open capillaries and are uncorrected. Flash chromatography was performed with Merck silica gel 60 (230-400 mesh). Dichloromethane was distilled from P_2O_5. $BCl_2(OR)$ (R= Me, *i*-Pr, Ph) was obtained as a solution in anhydrous CH_2Cl_2, by mixing purchased BCl_3 (1M solution in CH_2Cl_2, 1 mmol, 1 mL) and pure $B(OR)_3$ (R= Me, *I*Pr, Ph) (0.5 mmol) in anhydrous CH_2Cl_2 (3 mL). The mixture was stirred for 30 min at rt. $BCl(OR)_2$ (R= Me, *i*-Pr, Ph) was obtained likewise, by varying the stiochiometry of the reaction.

AM1 calculations were performed on a Microwax 3500 using the integrated package MOPAC 6.0.[10] Geometry was fully optimised with the use of the option 'precise' and minima were checked by 'force' calculations.

General procedure for the synthesis of 3-chlorobutanoyl derivatives (2) and (3)

BCl_2OR (or $BCl(OR)_2$) in anhydrous CH_2Cl_2 was added dropwise under inert atmosphere to a stirring solution of **(1)** (0.5 mmol) in anhydrous CH_2Cl_2 (10 mL) (for the equivalents of boron derivatives and reaction temperature and time see Tables 1 and 2). When the reaction was complete, water and aqueous 0.05M $NaHCO_3$ were added until the aqueous layer reached pH 7 and the two layers were separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified if necessary, by silica gel chormatography (cyclohexane/ethyl acetate 8:2 as eluant).

(3'*S*,4*S*)-2a and **(3'*R*,4*S*)-3a**: (mixture of diastereoisomers): ^1H NMR ($CDCl_3$) δ 1.65 (d, 3H, J=6.7 Hz), 2.98 (dd, 1H, J=9.6, 14.3 Hz), 3.24 and 3.25 (dd, 1H, J=4.9, 17.3 Hz), 3.48 (dd, 1H, J=3.4, 14.3 Hz), 3.67 and 3.70 (dd, 1H, J=8.4, 17.3 Hz), 4.22 (m, 2H), 4.61 (m, 1H), 4.82 (m, 1H), 7.75 (d, 1H, J=7.8 Hz), 8.19 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 24.7 and 25.2, 45.7 and 45.8, 53.4, 68.5, 85.7, 109.8, 110.2, 120.2, 122.5, 122.7, 127.4, 136.3, 153.5 and 153.6, 169.8. Anal. Calcd. for $C_{16}H_{17}N_2O_3Cl$: C, 60.0; H, 5.4; N, 8.8. Found: C, 60.1; H, 5.5; N, 9.0.

(3'*S*,4*S*)-2b: IR (film) 3410, 1772, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H, C*H*$_3$-CHO), 1.46 (s, 3H, C*H*$_3$-CHO), 1.61 (d, 3H, J=6.6 Hz, C*H*$_3$-CHCl), 3.08-3.25 (m, 2H, C*H*$_2$-Ind), 3.27 (dd, 1H, J=5.1 Hz, J=16.9 Hz, C*H*H-CHCl), 3.57 (dd, 1H, J=8.3 Hz, J=16.9 Hz, CH*H*-CHCl), 4.53 (m, 1H, CHCl), 4.62 (dd, 1H, J=3.1 Hz, J=9.5 Hz, CHN), 7.04 (s, 1H, Ind), 7.14-7.30 (m, 2H, Ind), 7.37 (d, 1H, J=8.2 Hz, Ind), 7.86 (d, 3H, J=7.5 Hz, Ind), 8.16 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.9, 25.2, 28.6, 45.9, 52.5, 62.5, 82.6, 110.8, 111.2, 119.1, 119.8, 122.4, 122.6, 127.2, 136.1, 152.7, 170.0.

(3'*R*,4*S*)-3b: IR (film) 3410, 1772, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 3H, C*H*$_3$-CHO), 1.47 (s, 3H, C*H*$_3$-CHO), 1.55 (d, 3H, J=6.6 Hz, C*H*$_3$-CHCl), 3.08-3.25 (m, 3H, C*H*$_2$-Ind), 3.24 (dd, 1H, J=4.5 Hz, J=16.8 Hz, C*H*H-CHCl), 3.59 (dd, 1H, J=8.9 Hz, J=16.8 Hz, CH*H*-CHCl), 4.53 (m, 1H, CHCl), 4.62 (dd, 1H, J=3.1 Hz, J=9.5 Hz, CHN), 7.04 (s, 1H, Ind), 7.14-7.30 (m, 2H, Ind), 7.37 (d, 1H, J=8.2 Hz, Ind), 7.82 (d, 1H, J=7.0 Hz, Ind), 8.15 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.9, 25.3, 28.5, 45.6, 52.5, 62.5, 82.7, 110.8, 111.2, 119.1, 119.8, 122.4, 122.6, 127.2, 136.1, 152.7, 170.0. Anal. Calcd. for $C_{18}H_{21}N_2O_3Cl$: C, 62.1; H, 6.1; N, 8.0. Found: C, 61.9; H, 6.2; N, 7.9.

(3'*S*,4*S*)-2c: IR 3350, 1774, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, 6H, J=7.2 Hz, C*H*$_3$-CH$_2$-CH$_2$), 1.15 (m, 4H, CH$_3$-C*H*$_2$-CH$_2$), 1.55 (m, 4H, CH$_3$-CH$_2$-C*H*$_2$), 1.58 (d, 3H, J=6.4 Hz, C*H*$_3$-CHCl), 3.20 (m, 2H, C*H*$_2$-Ind), 3.24 (dd, 1H, J=5.2 Hz, J=16.9 Hz, C*H*H-CHCl), 3.52 (dd, 1H, J=8.2 Hz, J=16.9 Hz, CH*H*-CHCl), 4.48 (m, 1H, CHCl), 4.71 (dd, 1H, J=4.9 Hz, J=7.7 Hz, CHN), 7.04 (s, 1H, Ind), 7.13-7.28 (m, 2H, Ind), 7.35 (d, 1H, J=7.1 Hz, Ind), 7.80 (d, 1H, J=7.6 Hz, Ind), 8.15 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.3, 16.4, 16.8, 24.9, 25.2, 34.1, 39.3, 45.8, 52.4, 61.0, 86.8, 110.8, 111.2, 119.0, 119.7, 122.2, 122.3, 122.5, 127.2, 136.0, 146.3, 153.0, 169.7.

(3'*R*,4*S*)-3c: IR 3350, 1774, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, 6H, J=7.2 Hz, C*H*$_3$-CH$_2$-CH$_2$), 1.15 (m, 4H, CH$_3$-C*H*$_2$-CH$_2$), 1.53 (d, 1H, J=6.3 Hz, C*H*$_3$-CHCl), 1.58 (m, 4H, CH$_3$-CH$_2$-C*H*$_2$), 3.04 (dd, 1H, J=4.8 Hz, J=16.8 Hz, C*H*H-CHCl), 3.22 (m, 2H, C*H*$_2$-Ind), 3.53 (dd, 1H, J=8.7 Hz, J=16.8 Hz, CH*H*-CHCl), 4.46 (m, 1H, CHCl), 4.71 (dd, 1H, J=4.8 Hz, J=7.7 Hz, CHN), 7.04 (s, 1H, Ind), 7.12-7.28 (m, 3H, Ind), 7.35 (d, 1H, J=7.1 Hz, Ind), 7.77 (d, 1H, J=7.4 Hz, Ind), 8.15 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.3, 16.4, 16.8, 24.9, 25.2, 34.1, 39.0, 45.5, 52.7, 61.1, 86.8, 110.8, 111.1, 119.0, 119.7, 122.2, 122.3, 122.5, 127.2, 136.0, 146.3, 153.0, 169.7. Anal. Calcd. for $C_{22}H_{29}N_2O_3Cl$: C, 65.3; H, 7.2; N, 6.9. Found: C, 65.5; H, 7.1; N, 6.9.

(3'*S*,4*S*)-2d: IR (film) 3310, 1773, 1734, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (t, 3H, J=7.1 Hz, CH_3-CH_2-CH_2-CH_2), 0.82 (t, 3H, J=7.1 Hz, CH_3-CH_2-CH_2-CH_2), 1.25 (m, 8H, CH_3-CH_2-CH_2-CH_2), 1.57 (d, 3H, J=6.6 Hz, CH_3-CHCl), 1.65 (m, 4H, CH_3-CH_2-CH_2-CH_2), 3.19 (m, 2H, CH_2-Ind), 3.23 (dd, 1H, J=5.1 Hz, J=17.0 Hz, CHH-CHCl), 3.49 (dd, 1H, J=8.2 Hz, J=17.0 Hz, CHH-CHCl), 4.48 (m, 1H, CHCl), 4.71, (dd, 1H, J=5.5 Hz, J=7.1 Hz, CHN), 7.04 (s, 1H, Ind), 7.13-7.30 (M, 2H, Ind), 7.36 (d, 1H, J=7.2 Hz, Ind), 7.79 (d, 1H, J=7.2 Hz, Ind), 8.06 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.7, 13.9, 22.7, 22.9, 24.7, 25.2, 25.4, 26.9, 29.7, 30.2, 31.7, 36.7, 45.8, 52.4, 61.0, 86.9, 111.2, 119.0, 119.8, 122.3, 122.5, 123.8, 127.3, 136.1, 153.0, 169.7.

(3'*R*,4*S*)-3d: IR 3310, 1773, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (t, 3H, J=7.1 Hz, CH_3-CH_2-CH_2-CH_2), 0.82 (t, 3H, J=7.1 Hz, CH_3-CH_2-CH_2-CH_2), 1.25 (m, 8H, CH_3-CH_2-CH_2-CH_2), 1.48 (d, 3H, J=6.6 Hz, CH_3-CHCl), 1.65 (m, 4H, CH_3-CH_2-CH_2-CH_2), 3.02 (dd, 1H, J=4.6 Hz, J=17.0 Hz, CHH-CHCl), 3.21 (m, 2H, CH_2-Ind), 3.55 (dd, 1H, J=8.8 Hz, J=17.0 Hz, CHH-CHCl), 4.47 (m, 1H, CHCl), 4.71 (dd, 1H, J=5.5 Hz, J=7.7 Hz, CHN), 7.04 (s, 1H, Ind), 7.13-7.30 (m, 2H, Ind), 7.36 (d, 1H, J=7.2 Hz, Ind), 7.75 (d, 1H, J=7.2 Hz, Ind), 8.23 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.7, 13.9, 22.7, 22.9, 24.7, 25.2, 25.4, 26.9, 29.7, 30.2, 31.7, 36.7, 45.5, 52.7, 61.1, 86.9, 110.9, 119.0, 119.8, 122.3, 122.5, 123.8, 127.3, 136.1, 153.0, 169.7. Anal. Calcd. for $C_{24}H_{33}N_2O_3Cl$: C, 66.6; H, 7.7; N, 6.5. Found: C, 66.4; H, 7.7; N, 6.4.

(3'*S*,4*S*)-2e: IR (film) 3350, 1772, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80-1.98 (m, 25H, CH_3-CH_2-CH_2-CH_2 + CH_3-CH_2-CH_2-Cl), 3.21 (d, 2H, J=6.3 Hz, CH_2-Ind), 3.26 (dd, 1H, J=4.4 Hz, J=17 Hz, CHH-CHCl), 3.51 (dd, 1H, J=9.0 Hz, J=17.0 Hz, CHH-CHCl), 4.39 (m, 1H, CHCl), 4.72 (m, 1H, CHN), 7.05 (s, 1H, Ind), 7.16-7.38 (m, 3H Ind), 7.81 (d, 1H, J=7.5 Hz, Ind), 8.08 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.4, 13.8, 19.6, 22.7, 22.9, 24.8, 25.0, 25.5, 31.7, 36.7, 40.2, 44.4, 57.2, 61.0, 86.9, 111.2, 119.1, 119.8, 122.3, 122.5, 127.3, 136.0, 151.0, 170.0.

(3'*R*,,4*S*)-3e: IR (film) 3350, 1772, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80-1.98 (m, 25H, CH_3-CH_2-CH_2-CH_2 + CH_3-CH_2-CH_2-CHCl), 3.01 (dd, 1H, J=3.9 Hz, J=16.9 Hz, CHH-CHCl), 3.21 (d, 2H, J=6.3 Hz, CH_2-Ind), 3.57 (dd, 1H, J=9.6 Hz, J=16.9 Hz, CHH-CHCl), 4.40 (m, 1H, CHCl), 4.72 (m, 1H, CHN), 7.05 (s, 1H, Ind), 7.16-7.38 (m, 3H, Ind), 7.77 (d, 1H, J=7.6 Hz, Ind), 8.17 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.4, 13.8, 14.1, 19.6, 22.7, 22.9, 24.8, 25.0, 29.7, 31.7, 36.5, 40.1, 44.0, 57.6, 86.9, 111.1, 119.1, 119.8, 122.3, 122.5, 127.3, 136.0, 151.1, 153.1, 170.0. Anal. Calcd. for $C_{26}H_{37}N_2O_3Cl$: C, 67.8; H, 8.1; N, 6.1. Found: C, 67.6; H, 8.2; N, 6.0.

3-Chlorobutanoic acid (4)

H_2O_2 (4.36 mmol, 0.74 mL) and, after 5 min, LiOH (1.6 mmol, 73 mg) in H_2O (5 mL) were added at 0 °C under inert atmosphere to a stirring solution of a 86:14 mixture of **(2d+3d)** (Table 2, entry 4) (1.11 mmol, 0.48 g) in THF (10 mL) and H_2O (2.5 mL). The mixture was stirred for 1 h at rt then a solution of Na_2SO_3 (4 mmol, 0.5 g) in H_2O (5mL) was added. The THF was removed under reduced pressure and the aqueous solution was extracted three times with CH_2Cl_2. The organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure and the chiral auxiliary (*S*)-4-(1H-indol-3-ylmethyl)-5,5-dibutyl-oxazolidin-2-one was obtained nearly pure in 91% yield (1 mmol, 0.39 g). To the aqueous layer, 1M HCl was added at 0 °C until the solution reached pH 2, then the mixture was extracted three times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, the product **(4)** was obtained pure in 80% yield.^1H NMR ($CDCl_3$) δ 1.60 (d, 3H, J=6.6 Hz, CH_3-CHCl), 2.80 (m, 2H, OC-CH_2-CHCl), 4.43 (m,

1H, CHCl); ^{13}C ($CDCl_3$) δ 24.9, 44.8, 52.4, 174.2; $[\alpha]_D^{20}$ -14.1 (c 0.4, ether); lit.[8a] for the (*R*) form: $[\alpha]_D$ +21.5 (c 0.4, ether).

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