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N-(Chloroacetyl)- and *N*-(dichloroacetyl)-*N*-(xylyl)alanine esters: assignment of the absolute configurations and enantiodifferentiation by the dirhodium method

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This work is dedicated to Professor András Lipták, Hungarian Academy of Science, Carbohydrate Research Group, Debrecen, Hungary, on the occasion of his 70th birthday.

Abstract—Four chlorinated *N*-acylalanine methylesters (metalaxyl® derivatives) containing either stereogenic centres alone as in **1** and **3** or stereogenic centres plus chiral axes as in **2** and **4** were investigated. The latter have been examined in terms of the absolute configurations of the diastereomers in unresolvable mixtures, which were determined by evaluating NOE contacts in preferred conformations. Although these ligands are weak donors in **Rh*** adducts, it is easily possible to monitor their enantiomeric purity by the 'dirhodium method'. Surprisingly, only the monochloro derivatives **1** and **2** gave satisfactory results in chirality recognition experiments under standard dirhodium method conditions (including one drop of acetone-d_6 for enhancing the solubility of **Rh***). The dichloro derivatives **3** and **4** failed. However, they developed significant dispersion effects in the absence of acetone-d_6. It turns out that the preferred complexation site in the monochloro derivatives **1** and **2** is primarily the amide carbonyl oxygen, whereas this group is hardly available in the case of the dichloro derivatives **3** and **4** so that the ester group appears to be the complexation site.

1. Introduction

Alanine esters **1**–**4** belong to the acylaniline family and are derivatives of metalaxyl® whose structure is similar to that of **1** (Scheme 1) with the chlorine atom in **1** replaced by OCH_3. Metalaxyl® is a fungicide used for seed, soil or foliar treatment against fungi of the *Peronosporales* order, and was placed on the market by Ciba-Geigy in 1977.[1] Moser and Vogel[2] and Hubele et al.[3] reported that the (*R*)-enantiomer, also known as Metalaxyl-M®, is the biologically most active agent against fungi whereas the (*S*)-isomer shows very low biological activity.

Halogenated derivatives have also been prepared[4] and shown to possess fungicidal properties as well.[5] It has been claimed that the *transoid* orientation of the xylyl ring and the amide carbonyl group (cf. Fig. 1) is essential for the activity.[6] Hence, a detailed stereochemical and spectroscopic analysis of alanine esters **1**–**4** (Scheme 1) appeared desirable.

Over the last decade, the dirhodium method of chirality recognition has been introduced in which the chiral

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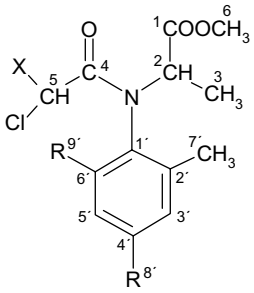
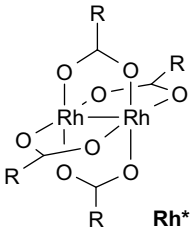
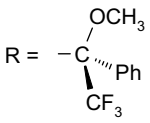


	1	2	3	4
X	H	H	Cl	Cl
$R^{8'}$	H	CH_3	H	CH_3
$R^{9'}$	CH_3	H	CH_3	H





Scheme 1. Structures of the *N*-acylalanine esters **1**–**4** and the enantiopure auxiliary (+)-(*R*)-**Rh***.

enantiopure dirhodium complex $Rh_2^{(II)}$[(*R*)-(+)-MTPA$_4$][7] (**Rh***:MTPA-H = methoxytrifluoromethylphenylacetic acid ≡ Mosher's acid; see Scheme 1) is added to a $CDCl_3$ solution of a chiral substrate and a ^{1}H NMR spectrum of this sample is recorded. Over the course of this project, it turned out that soft-base functionalities[8] are particularly suitable for forming rather stable adducts with **Rh***. Thus, the dirhodium method can be regarded as complementary to the application of chiral lanthanide shift reagents (CLSR),[9] which is optimal for hard-base functionalities. On the other hand, hard Lewis-bases can be subjected to **Rh*** as well, although the corresponding adducts are thermodynamically labile. However, even multifunctional substrates of this type can provide satisfactory results, in particular, since **Rh*** shows a remarkable selectivity in adduct formation. This has been demonstrated in the case of some xanthine derivatives.[10] Therefore, we were interested in extending this method to other multifunctional hard-base compounds and decided to investigate title compounds **1**–**4** as prototypes for the important acylamino acid/acylaniline family having at least three possible binding sites, two carbonyl oxygens and one nitrogen atom.

2. Results and discussion

2.1. Stereochemical and NMR signal assignment of the alanine ester derivatives 1–4

The ^{1}H and ^{13}C chemical shifts of compounds **1**–**4**, assigned on the basis of their DEPT, COSY, HMQC and HMBC spectra, are listed in Table 1. Compounds **1**–**4** all possess a stereogenic centre (α carbon of the alanine, C-2), the absolute configuration of which is known from their synthesis (cf. Experimental, Section 4.1). The molecules possess a high barrier in the rotation of the bond between the nitrogen and the aryl group (atropisomerism) giving rise to an additional chirality axis in **2** and **4**. This has already been discussed for a number of similarly substituted anilines, among them alanine[11] and metalaxyl® derivatives.[12] Thus, **1** and **3**—with their symmetrical xylyl group (2′,6′-dimethylphenyl)—exist as enantiomeric mixtures with pairs of diastereotopic atoms and groups in the aryl moiety, whereas **2** and **4** form two diastereomeric pairs of enantiomers. As a consequence of these stereochemical properties, the NMR spectra show only one signal set for **1** and **3** but two for **2** and **4** in ratios of **2A**:**2B** = 72:28 and **4A**:**4B** = 70:30 as determined from ^{1}H signal intensities. It should be noted that a preparative separation of the diastereomers in the samples of **2** and **4** was not possible; for details see Experimental. However, due to restricted internal mobility, it is possible to assign prochiral atoms

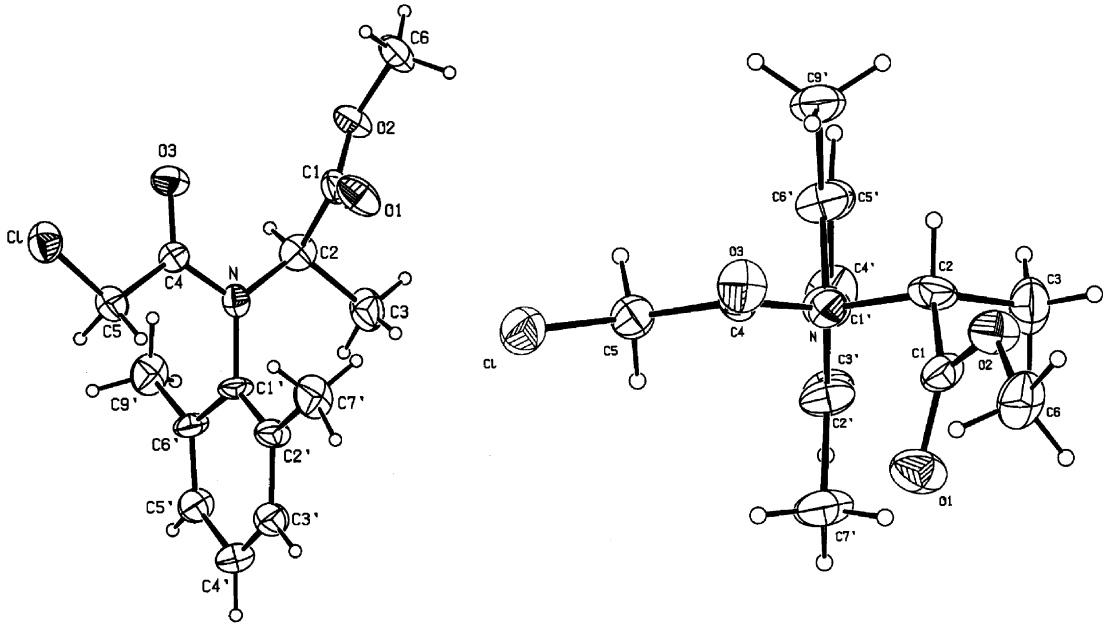


Figure 1. Structure of (2*R*)-**1** as determined by X-ray diffraction; right: view along the N–C-1′ bond.

Table 1. ^{1}H and ^{13}C chemical shifts of **1**–**4** in $CDCl_3$ with a drop of acetone-d_6 (in parts per million; see Experimental);[a] stereochemical assignment of the two diastereotopic H-5 protons in **1** and **2** was not performed

	1	2A/2B	3	4A/4B
H-2	4.52 (q)	4.79/4.24 (q)	4.53 (q)	4.78/4.24 (q)
H-3	1.04 (d)	1.15/1.49 (d)	1.10 (d)	1.18/1.54 (d)
H-5a	3.73 (d)	3.78 d/3.76 (d)	5.67 (s)	5.70 s/5.71 (s)
H-5b	3.64 (d)	3.71 d/3.72 (d)		
H-6	3.81 (s)	3.79/3.78 (s)	3.82 (s)	3.80/3.79 (s)
H-3′	7.14 (d)	7.13/n.d. (s)	7.16 (d)	7.15/n.d. (s)
H-4′	7.24 (t)	—	7.27 (t)	—
H-5′	7.18 (d)	7.07/n.d. (d)	7.20 (d)	7.10/n.d. (d)
H-6′	—	7.36/7.22 (d)	—	7.37/7.26 (d)
H-7′	2.18 (s)	2.23/2.34 (s)	2.22 (s)	2.25/2.34 (s)
H-8′	—	2.36/2.35 (s)	—	2.37/2.37 (s)
H-9′	2.48 (s)	—	2.49 (s)	—
C-1	172.38 (s)	172.33/171.46 (s)	171.58 (s)	171.59/170.74 (s)
C-2	55.85 (s)	55.62/59.14 (s)	56.38 (s)	56.07/59.80 (s)
C-3	14.80 (s)	14.28/15.40 (s)	14.76 (s)	14.18/15.19 (s)
C-4	166.83 (s)	166.72/166.49 (s)	164.82 (s)	164.56/164.18 (s)
C-5	41.87 (s)	42.18/42.15 (s)	63.30 (s)	63.60/63.71 (s)
C-6	52.21 (s)	52.30/52.30 (s)	52.36 (s)	52.45/n.d. (s)
C-1′	135.86 (s)	134.26/136.76 (s)	135.27 (s)	133.51/136.23 (s)
C-2′	137.36 (s)	136.44/136.03 (s)	137.56 (s)	136.47/135.93 (s)
C-3′	128.86 (s)	132.10/132.23 (s)	129.15 (s)	132.32/132.43 (s)
C-4′	129.45 (s)	139.49/139.25 (s)	129.72 (s)	140.06/139.81 (s)
C-5′	129.29 (s)	128.11/128.21 (s)	129.66 (s)	128.29/128.43 (s)
C-6′	138.47 (s)	129.66/128.95 (s)	138.51 (s)	129.60/128.88 (s)
C-7′	18.27 (s)	17.76/17.96 (s)	18.35 (s)	17.88/18.05 (s)
C-8′	—	20.98/20.95 (s)	—	21.05/21.01 (s)
C-9′	18.54 (s)	—	18.68 (s)	—

[a] The ^{1}H NMR data in the absence of acetone-d_6 are the same within the experimental error limits; signal multiplicities: s, singlet; d doublet; t, triplet; q, quartet.

and groups in **1** and **3** as well as the respective diastereomers in the mixtures of **2** and **4**.

Apart from the N–Ar moieties, there are two flexible groups in the molecule: (a) the C(=O)–N bond and (b) the carbon residue of the alanine [–$CH(CH_3)$–$COOCH_3$]. The existence of only one single signal set in **1** and **3** clearly proves that the amide adopts only one single configuration, namely the *E*-configuration as displayed in Scheme 1; the X-ray diffraction reveals this configuration in the crystal, too (Fig. 1). In addition, an analogous configuration and conformation has been published for a related phenylacetanilide derivative.[13]

The –$CH(CH_3)$–$COOCH_3$ group can rotate about the C-2–N bond at room temperature although some of the respective conformations are energetically disfavoured, especially those with the bulky ester residues directed towards the xylyl ring. The conformation in the solid state (Fig. 1) is in excellent accordance with our results extracted from the 2D NOESY spectrum of **1**: there is a strong NOE contact between the methine proton H-2 and only one of the methyl protons at the phenyl group, namely H-7′ (Fig. 2, left), whereas the methyl H-3 signal shows NOE responses with both H-7′ and H-9′. Under the assumption that the ester group is stretched outwards (Figs. 1 and 2, left), the NOEs are compatible with a conformation (Fig. 2, left) where the torsion angle H-2–C-2–N–C-1′ is around 100 ± 20°. Simultaneously, this provides—in combination with

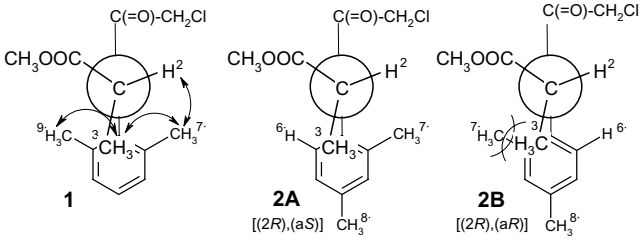


Figure 2. Preferred conformations of **1** and **2**; the double arrows in formular **1** (left) indicate NOE contacts; only the major enantiomers with the (2*R*)-configuration are depicted.

the HMQC and HMBC evidence—a stereochemical assignment for the pairs of diastereotopic methyl and aromatic CH protons and carbons of **1** (see Table 1): pro-(a*S*) for H-7′/C-7′ and pro-(a*R*) for H-9′/C-9′; assignments for the atom pairs H-3′/H-5′, C-2′/C-6′ and C-3′/C-5′ are analogous. Dichloro derivative **3** shows spectra, which are very similar to those of **1** except for H-5, C-5 and the amide carbon C-4 (Table 1). Therefore, we assume that its stereochemical features correspond to those of **1**.

As noted above, **2** and **4** form diastereomers due to the asymmetric substitution of the xylyl group (2′,4′-dimethylphenyl). Again, both compounds show spectra totally analogous to each other (Table 1) except for H-5, C-5 and C-4. Hence, the following configurational assignment is described only for **2** but holds true for

both **2** and **4**. It is based on a conformational analysis by inspecting NOE contacts (here: selective 1D NOESY experiments, Fig. 3).

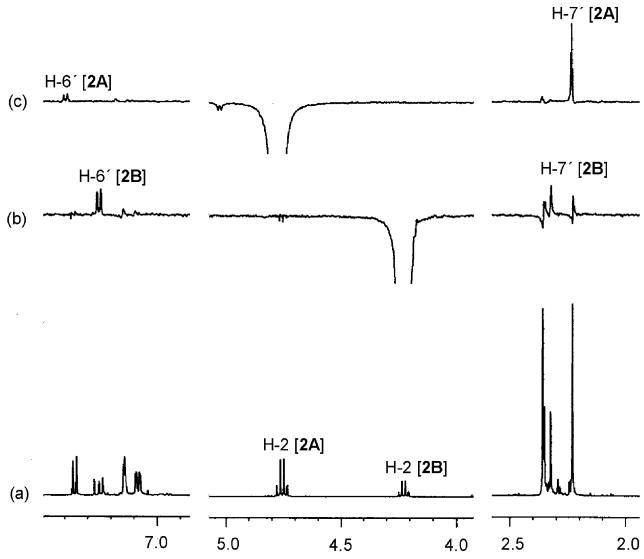


Figure 3. Trace (a): sections of the 500 MHz 1D ^{1}H NMR spectrum of **2**; trace (b): 1D NOESY with irradiation at H-2 of **2B**, trace (c): 1D NOESY with irradiation at H-2 of **2A**.

Sample **2** consists of a major diastereomer **2A** (72%) and a minor one **2B** (28%). This was deliberately prepared as a non-racemic mixture [(2*R*):(2*S*) = 2:1] from enantiomerically pure material with an already known absolute configuration at C-2 (see below). For each diastereomer **2A** (Fig. 2, centre) and **2B** (Fig. 2, right), we found a preferred conformation (compare discussion of **1** above). Irradiation on the signal of H-2 (Fig. 3c; $\delta = 4.79$), belonging to the major diastereomer **2A**, produces a strong NOE contact with H-7′ (short distance) whereas the distance of H-2 to the aromatic proton H-6′ is large (weak NOE response). This is in accordance with the conformation depicted in Figure 2 (centre). However, when the signal of H-2 of **2B** is irradiated (Fig. 3b; $\delta = 4.24$), the sequence of NOE intensities is reversed (Fig. 3c; strong for H-6′ but weak for H-7′) fitting to the geometry of structure **2B** in Figure 2 (right). It should be noted that all other NOE effects observed in further 1D NOESY spectra of **2** (not depicted) are in agreement with this assignment.

Thus, we have correlated the two chirality elements in each stereoisomer. The major enantiomer of the major diastereomer **2A** is (2*R*,a*S*), while the minor enantiomer of **2A** is (2*S*,a*R*)-configured. Conversely, the major enantiomer of the minor diastereomer **2B** is (2*R*,a*R*)- and the minor enantiomer of **2B** is (2*S*,a*S*)-configured.

Simultaneously, this conformational and configurational assignment provided an explanation as to why **2A** is the major diastereomer and **2B** the minor one. The ratio of these diastereomers (ca. 70:30) indicates a ground state energy difference $\Delta G_0 \approx 2$–2.5 kJ/mol. There is always a rather close proximity of two methyl groups 3 and 7 in the conformation of **2B** causing a steric repulsion, whereas there is no similar congestion in **2A** whose methyl groups are further apart (Fig. 2).

2.2. Ligand—Rh* complexation modes—effect of acetone

Ligand molecules **L** can form 1:1- and/or 2:1-adducts with the enantiopure dirhodium complex $Rh_2^{(II)}$[(*R*)-(+)-MTPA$_4$][7] (**Rh***) depending on the relative molar ratio of **L** versus **Rh***.[8,10] All adducts—except those of phosphane ligands—are kinetically labile so that room-temperature NMR signals are averaged. NMR signals may be shifted to some extent as compared to those of the free ligands. In general, such complexation shifts $\Delta\delta$ are small or even negligible. Only if the complexation site is close-by can noticeable deshielding $\Delta\delta$-values be observed because the inductive effect of the ligand's functional group is enhanced. Thus, complexation shifts are good indicators for the preferred complexation site if the donor is strong enough.

We started our investigation on the chirality recognition of **1**–**4** under standard 'dirhodium method' conditions, that is, one drop of acetone-d_6 (ca. 4 μl; ca. 0.053 mmol corresponding to 1–1.5 mol equiv relative to **Rh***) was added in order to enhance the solubility of **Rh***.[14] Thereby, a concentration can be achieved, which allows an easy NMR measurement of ^{13}C and other low-sensitivity-nuclei with a reasonable amount of spectrometer time. If the functional groups used for adduct formation are strong donors, such a small quantity of acetone-d_6—being a weak donor by itself—cannot compete and has practically no effect on the complexation shifts and dispersions in molecules with such atoms or groups. However, if the donor ability of the ligands is comparable to that of acetone-d_6, one has to expect that acetone-d_6 may 'dilute', or in the worst case even annihilate chirality recognition effects.

This latter situation occurs, indeed, in the case of **1**–**4**, as can be seen from Table 2. Only a few ^{1}H (H-3 and H-5) and ^{13}C (C-1 and C-4, the two carbonyl carbons) of the monochloro compounds **1** and **2** showed significant complexation shifts in the standard dirhodium method experiment (with acetone-d_6), while there was not even a single atom in the dichloro derivatives **3** and **4** with a significant $\Delta\delta$-value. If, however, acetone-d_6 is excluded, the ^{1}H complexation shifts of **1** and **2** increase considerably (Table 2). Corresponding $\Delta\delta(^{1}H)$-values of **3** and **4** are still negligible without acetone-d_6, but the existence of significant dispersion effects (Table 3) proves adduct formation. ^{13}C complexation shifts in the absence of acetone-d_6 were recorded only for one representative, ligand **2**, due to the low solubility of **Rh*** and the long spectrometer time, and here again clear enhancements were observed, particularly for the carbonyl atoms C-1 and C-4 (Table 2).

These observations lead to the following conclusions:

(a) Acetone-d_6 is a serious competitor in the adduct formation for hard ligands, such as the protected amino acid ligands **1**–**4**. This was shown from a temperature-dependent ^{13}C NMR experiment with

Table 2. Complexation shifts $\Delta\delta$ of selected ^{1}H and ^{13}C NMR resonances in **1**–**2**;[a] in parts per million

	1		**2A/2B**	
	With	Without	With	Without
	Acetone-d_6		Acetone-d_6	
H-2	+0.04	+0.06	+0.05/0.07	+0.14/+0.04
H-3	+0.08	+0.25	+0.02/+0.07	+0.12/+0.26
H-5a	+0.12	+0.32	+0.12/n.d.[b]	+0.36/+0.52
H-5b	+0.14	+0.33	+0.09/n.d.	+0.26/+0.19
H-6	−0.06	−0.11	−0.04/−0.04	−0.10
C-2	+0.9	[c]	+0.5/+0.9	+1.3/+2.3
C-4	+2.2		+1.6/n.d.	+4.5 to +5
C-5			−0.7/−1.0	−1.8/−2.3
C-2′			−0.7/n.d.	−0.3/−1.6
C-4′			−0.1/−2.0	

All samples contained an equimolar amount of **Rh***. Values are averaged if different for the enantiomers due to dispersion (see text). Data are listed only for atoms with at least one $\Delta\delta(^{1}H)$-value of ca. 0.1 ppm and larger or a $\Delta\delta(^{13}C)$-value of ca. 1 ppm and larger. Samples were non-racemic mixtures with an enantiomeric ratio of (2*R*)/(2*S*) = 3:2 for **1** and 2:1 for **2** (see text).

[a] Complexation shifts $\Delta\delta$ of **3** and **4** are negligible irregardless of the presence or absence of acetone-d_6.

[b] 'n.d.' means: not detectable safely.

[c] Not recorded due to low concentration.

1, which will be discussed below (subsection d), showing a coalescing carbonyl signal of acetone-d_6.

(b) The complexation site in **1** and **2** is primarily the amide carbonyl group (C-4). The $\Delta\delta$-values of the ester carbonyl carbons (C-1) are much smaller; that is, this carbonyl group is not the major binding site although some minor contribution in the adduct formation equilibria cannot be ignored. The introduction of the second chlorine atom, however, prohibits any effective adduct formation at the amide group so that only the ester carbonyl is available for ligation. This reveals a remarkable selectivity in the adduct formation of multifunctional ligands (see Section 2.3).

(c) Adduct formation equilibria involving weak donor ligands always contain a substantial proportion of free ligand molecules, that is, the complexation constants are low (presumably $K < 1$).[8,15,16] This can easily be monitored by the ^{1}H chemical shift of the MTPA methoxy group (δ ca. 3.17 ppm) in the experiments described,[15] which is a typical value for weak ligands with a low donor ability, that is, for hard-base functionalities. Recently, we found corresponding results for iodine atoms[15] and phosphoryl groups (P = O).[16] This is in sharp contrast to soft-base functionalities, which give rise to equilibria strongly biased in favour of the adducts (MTPA–OCH_3: $\delta < 3.0$).[8,16d]

(d) This conclusion is confirmed by temperature-dependent ^{13}C NMR experiments: only the C-1 (ester carbonyl), the C-4 (amide carbonyl) and the C-5 (CH_2Cl) signals approach coalescence on lowering the temperature of the NMR sample of **1** down to 203 K (**1**:**Rh*** = 1:1); all other ^{13}C and ^{1}H signals did not show any significant line broadening. This coalescence indicates an equilibrium between free ligands and ligands in the adducts.[8,15,16] Therefore, those minute coalescence effects along with the low complexation shifts are clear proof that a weak complexation exists.

As a consequence, it is advisable to refrain completely from adding acetone-d_6 if the ligand investigated is a weak donor (hard base). This, however, may result in rather low sample concentrations (for details see Experimental) and recording a ^{1}H NMR spectrum with a good signal-to-noise ratio may last for one or even more hours. Moreover, ^{13}C NMR spectroscopy may even be impossible under such conditions.

2.3. Chirality recognition

Some signals of the chiral ligands **1**–**4** are split into two due to the formation of diastereomeric adducts (chirality

Table 3. Dispersion effects $\Delta\nu[= \nu(2R) - \nu(2S)]$ of the ^{1}H NMR resonances in **1**–**4** in Hertz, recorded at 400 MHz in the presence an equimolar amount of **Rh***, with and without acetone-d_6

	1		**2A/2B**		**3**		**4A/4B**	
	With	Without	With	Without	With	Without	With	Without
	Acetone-d_6		Acetone-d_6		Acetone-d_6		Acetone-d_6	
H-2	−4.4	−2.4	−3.5/−4.6	−2.9/−10.7	0	−2.3	0/−1.7	−2.2/−5.6
H-3	−0.6	−5.7	+4.0/−1.7	+6.2/−8.9	0	0	0	+2.0/−2.6
H-5a	0	+7.0	+9.2/n.d.[a]	−4.1/+20.9	0	−1.0	0	−1.4/−0.8
H-5b	−6.8	−7.0	+5.9/n.d.	+6.0/+17.1				
H-6	+6.9	+12.2	+5.9/+5.9	+11.7/+10.0	0	+0.7	0	0/−1.6
H-3′	n.d.	—	n.d.	—	0	—	0	—
H-4′	n.d.	—	—	—	0	—	0	—
H-5′	n.d.	0	n.d.	0	0	—	0	—
H-6′	—	—	−6.5/n.d.	−24.1/+12.8	—	—	—	—
H-7′	+10.3	+25.0	+6.3/−8.4	+5.1/−44.4	0	−4.0	0	−2.4/n.d.
H-8′	—	—	0/n.d.	—	—	—	0	0/0
H-9′	−9.6	−22.8	—	—	0	0	—	—

All samples were non-racemic mixtures with an enantiomeric ratio of (2*R*)/(2*S*) = 3:2 for **1** and 2:1 for **2**–**4**.

[a] 'n.d.' means: not detectable safely.

recognition). The difference (in Hertz) between the individual lines in such duplicated signals is the diastereomeric dispersion $\Delta\nu$ (in Hertz), while their relative intensities reflect the enantiomeric composition of the ligand. Herein, mixtures with ratios (2*R*)/(2*S*) = 3:2 for **1** and 2:1 for **2**–**4** were prepared for the experiments described (see Experimental). This allowed us to attribute sets of NMR signals to the respective enantiomers.

In the standard dirhodium method experiment (with acetone-d_6),[8,15,16] noticeable dispersion effects $\Delta\nu$ [= $\nu(2R) - \nu(2S)$] could be found for ^{1}H and ^{13}C NMR signals of **1** and **2**; they range up to ca. 25 Hz for both sorts of nuclei. Signs can be attributed to these values because the signals belonging to each enantiomer in the non-racemic mixtures can be identified easily from their relative intensities. All $\Delta\nu$-values obtained are shown in Tables 3 and 4.

There is no general pattern of smaller or larger $\Delta\nu$-values with respect to the position of the nuclei involved; protons of *ortho*-methyl groups attached to the phenyl (H-7′, H-9′) seem to be particularly sensitive.

The potential of the dirhodium method for chirality recognition in this compound family is exemplified in Figure 4 for the H-6 (left) and the C-5 signals (right) of **2**. Moreover, the beneficial effect of recording ^{1}H NMR spectra in the absence of acetone-d_6 is demonstrated in Figure 5.

Table 4. Dispersion effects $\Delta\nu$[= $\nu(2R) - \nu(2S)$] of the observable ^{13}C NMR resonances in **1**–**4**, in Hertz, recorded at 100.6 MHz in the presence of an equimolar amount of **Rh***, with acetone-d_6

	1	**2A**[a]		**2B**		**3**	**4A**	**4B**
C-1	−1.3	−4.2	(−10.7)	−2.5	(−6.7)	+1.5	−1.7	−1.3
C-2	−3.1	+2.9	(+3.3)	+3.8	(+4.6)	0	0	0
C-3	+1.7	−1.0	(−1.9)	−1.5	(−3.8)	0	0	0
C-4	−25.5	−4.2	(4.5–5)[a]	0–1[a]	(n.d.)[b]	0	0	0
C-5	+10.2	+2.7	(+2.9)	+2.3	(+0.8)	0	0	0
C-6	−1.0	+1.2	(+2.5)	+1.0	(+1.5)	0	+1.9	−1.7
C-1′	+0.8	+3.1	(+7.5)	0	(+0.8)	−0.6	+1.0	0
C-2′	+1.2	0	(+14.4)	0	(+10.5)	−0.8	0	0
C-3′	+1.3	+1.7	(+5.4)	0	(n.d.)	0	0	0
C-4′	0	+24.0	(−1.0)	+5.4	(n.d.)	0	0	0
C-5′	0–1	+3.6	(−29.5)	n.d.	(n.d.)	0	0	0
C-6′	0–1	−2.1	(−3.8)	−5.2	(n.d.)	+1.0	0	0
C-7′	+1.1	+1.0	(+2.1)	+1.3	(+2.1)	0	+0.6	+0.6
C-8′	—	+3.1	(+2.3)	0	(n.d.)	—	+1.0	+1.0
C-9′	+0.6	—	—	—	—	0	—	—

The values in parentheses (for **2A** and **2B**) have been determined in the absence of acetone-d_6. All samples were non-racemic mixtures with an enantiomeric ratio of (2*R*)/(2*S*) = 3:2 for **1** and 2:1 for **2**–**4**.

[a] A sign of this $\Delta\nu$-value could not be determined safely due to the low signal-to-noise ratio.

[b] 'n.d.' means: not detectable safely.

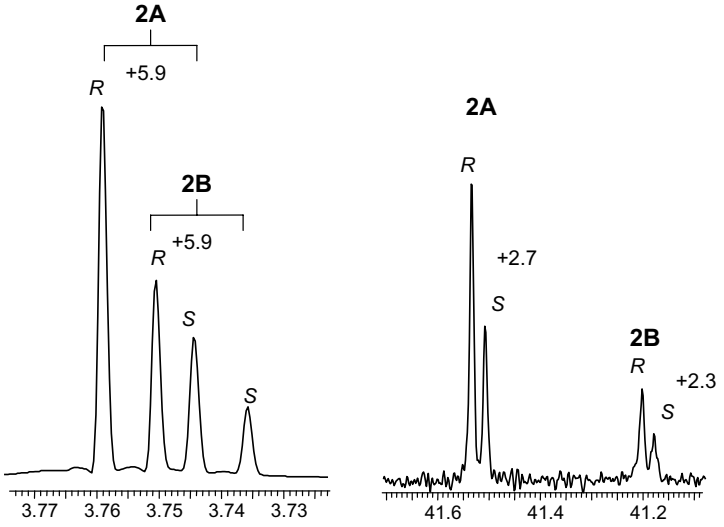


Figure 4. Signals of methoxy atoms H-6 (left) and the chlorinated C-5 (right) of **2A**/**2B**, recorded at 400 MHz and 100.6 MHz, respectively, in the presence of an equimolar amount of **Rh*** and one drop of acetone-d_6. The letters '*R*' and '*S*' refer to the absolute configurations at C-2. The numbers on top of the signals are dispersions $\Delta\nu$ (in Hertz). See text for the stereochemical assignment of the diastereomers **2A** and **2B**.

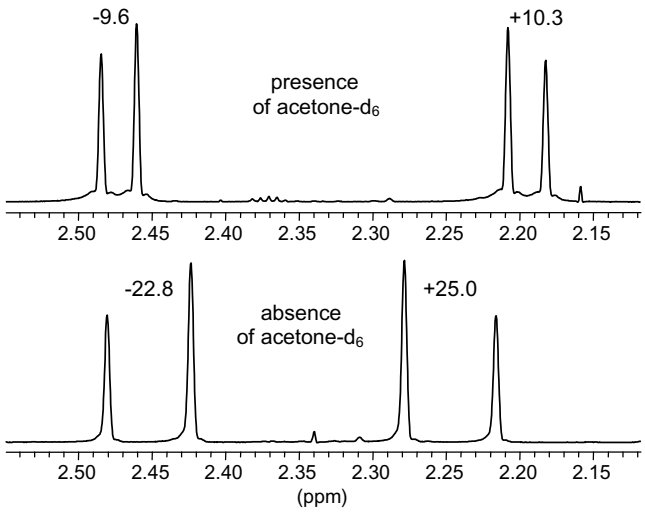


Figure 5. Signals of H-9′ (left) and H-7′ (right) of **1**, recorded at 400 MHz with an equimolar amount of **Rh*** in the presence (top) and absence (bottom) of acetone-d_6. The numbers on top of the signals are dispersions $\Delta\nu$ (in Hertz).

By analogy to the complexation shifts, the signal dispersions of the dichloroamides **3** and **4** differ from those of the monochloro analogues in that they are much less significant although there are still signals available for chirality recognition (Tables 3 and 4). This proves again that the dichloroamides donors are even weaker than the monochloro analogues. The reason for this divergent behaviour is unclear. The dipole character of the amide carbonyl group itself should not be changed significantly by the introduction of a second chlorine at the α-position. Hence, steric repulsion between the $CHCl_2$ group and the approaching **Rh*** may be responsible. Anyway, such a subtle sensitivity difference of the donor ability of the two carbonyl groups is surprising and reflects a remarkable selectivity of the soft acid **Rh*** auxiliary towards multifunctional hard-base ligands. This is reminiscent of the behaviour of xanthines in analogous experiments.[10] **Rh*** seems to be superior in this respect to the classical chiral lanthanide shift reagents (CLSR),[9] which—as hard acids—are not as selective. Currently, we are further investigating this phenomenon.

3. Conclusion

The compounds **1**–**4** provide interesting stereochemical features allowing an assignment of absolute configurations in mixtures of diastereomers **2** and **4**, with respect to their NMR properties and ground state enthalpies. We found that donors, even as weak as an amide or ester groups, can still be effective enough for chirality recognition although the formation of adducts with **Rh*** may be so weak that practically no complexation shifts can be observed. The presence or absence of acetone-d_6, used for enhancing the solubility of **Rh***, may play a decisive role for such ligands. A clear competition between the two carbonyl groups was observed, which can be manipulated by introducing a second chlorine atom. This may be interpreted as a reflection of a significant selectivity of the **Rh*** auxiliary.

4. Experimental

4.1. General

The syntheses of **Rh***,[7] **1**[4,17] and **3**[4] have been described before. All compounds **1**–**4** were synthesized starting from either (*R*)- or (*S*)-methyl lactate (chiral pool). For example, (*S*)-methyl lactate was mesylated and then treated—after isolation—with the appropriate aniline to give the (2*R*)-alanine derivative. Once isolated, it was treated with the respective acyl chloride using anhydrous K_2CO_3 as acid scavenger and THF as solvent. All products were isolated and purified by means of silica gel column chromatography using toluene–ethyl acetate (5:1) as elution solvent. The identification of the products was performed via ^{1}H NMR and GC–MS. The purities of the compounds were obtained by GC analysis using a HP-1 column.

Enantiomeric purities were checked using a chiral HPLC Nucleosil Chiral 3 column with 95% hexane (with 0.05% trifluoroacetic acid) and 5% isopropanol as solvent system. The above mentioned procedure, starting from the (*R*)-isomer of the methyl lactate, yielded the corresponding (*S*)-metalaxyl isomers and analogues.

Compounds **2** and **4** formed diastereomeric mixtures, which could not be resolved by HPLC methods. In order to get information about the interconversion rate (rotation about the chirality axis), we performed high-temperature ^{1}H and ^{13}C NMR experiments with **2** dissolved in deuterated dibromoethane. Some ^{1}H and ^{13}C signals showed line broadening on raising the temperature up to 400 K; in particular, the ^{13}C signals of C-5 and C-6′ show coalescence at 380–390 K. This results in a barrier of ca. 70 kJ/mol proving that the life-times of the individual diastereomers are shorter than 1 s at room temperature and, thereby, too short for preparative separation.

4.2. Preparation of *N*-(chloroacetyl)-*N*-(2,6-dimethylphenyl)alanine methyl ester 1

Yield: 77% (*S*), 68% (*R*); mp 80 °C. IR (ATR) cm^{-1}: $\tilde{\nu}$ = 2951, 1745 (C=O ester), 1672 (C=O amide), 1449, 1373, 1352, 1249, 1197, 1175, 1124, 779. LS-ESI-MS: *m*/*z* = 286.1/284.1 (25/73) $[M+H]^+$, 254.1/252.1 (28/78) $[M-OCH_3]^+$, 226.1/224.1 (37/100) $[M-COOCH_3]^+$, 148.1 (10) $[M-COOCH_3-COCH_2Cl+H]^+$; HR-ESI-MS: 284.1066, calculated for $C_{14}H_{18}{}^{35}ClNO_3$ 284.1053. (*R*): $[\alpha]_D^{20} = -45.9 \pm 1$ (*c* 0.038, $CHCl_3$), (*S*): $[\alpha]_D^{20} = +45.1 \pm 1$ (*c* 0.05, $CHCl_3$).

4.3. Preparation of *N*-(chloroacetyl)-*N*-(2,4-dimethylphenyl)alanine methyl ester (2); mixture of diastereomers

Yield: 76% (*S*), 68% (*R*); viscous oil. IR (ATR) cm^{-1}: $\tilde{\nu}$ = 2950, 1743 (C=O ester), 1668 (C=O amide), 1500, 1376, 1233, 1202, 1104, 787, 737. LS-ESI-MS:

m/z = 286.1/284.1 (28/81) $[M+H]^+$, 254.1/252.1 (24/72) $[M-OCH_3]^+$, 226.1/224.1 (37/100) $[M-COOCH_3]^+$, 148.1 (14) $[M-COOCH_3-COCH_2Cl+H]^+$; HR-ESI-MS: 284.1043, calculated for $C_{14}H_{18}{}^{35}ClNO_3$ 284.1053.

4.4. Preparation of *N*-(dichloroacetyl)-*N*-(2,6-dimethylphenyl)alanine methyl ester 3

Yield: 80% (*S*), 76% (*R*); mp 137–139 °C. IR (ATR) cm^{-1}: $\tilde{\nu}$ = 2960, 1750 (C=O ester), 1676 (C=O amide), 1376, 1350, 1268, 1195, 788, 723, 700, 666. LS-ESI-MS: *m/z* = 322.1/320.1/318.2 (9/53/82) $[M+H]^+$, 290.0/288.0/286.0 (10/56/90) $[M-OCH_3]^+$, 262.0/260.0/258.0 (12/64/100) $[M-COOCH_3]^+$, 222.1/224.1 (4/1) $[M-COOCH_3-HCl]^+$, 148.1 (3) $[M-COOCH_3-COCH_2Cl+H]^+$; HR-ESI-MS: 318.0674, calculated for $C_{14}H_{17}{}^{35}Cl_2NO_3$ 318.0664. (*R*): $[\alpha]_D^{20} = -20.4 \pm 1$ (*c* 0.051, $CHCl_3$), (*S*): $[\alpha]_D^{20} = +19.7 \pm 1$ (*c* 0.05, $CHCl_3$).

4.5. Preparation of *N*-(dichloroacetyl)-*N*-(2,4-dimethylphenyl)alanine methyl ester 4; mixture of diastereomers

Yield: 79% (*S*), 69% (*R*); viscous oil. IR (ATR) cm^{-1}: $\tilde{\nu}$ = 2951, 1746 (C=O ester), 1685 (C=O amide), 1499, 1453, 1378, 1325, 1204, 1103, 806, 671. LS-ESI-MS: *m/z* = 322.1/320.1/318.2 (11/54/82) $[M+H]^+$, 290.0/288.0/286.0 (9/51/81) $[M-OCH_3]^+$, 262.0/260.0/258.0 (12/65/100) $[M-COOCH_3]^+$, 222.1/224.1 (3/4) $[M-COOCH_3-HCl]^+$, 148.1 (2) $[M-COOCH_3-COCH_2Cl+H]^+$; HR-ESI-MS: 318.0674, calculated for $C_{14}H_{17}{}^{35}Cl_2NO_3$ 318.0664.

4.6. NMR spectroscopy

Most room-temperature ^1H (400.1 MHz) and ^{13}C (100.6 MHz) were performed on a Bruker Avance DPX-400 spectrometer. Some spectra were recorded at 500.1 MHz (^1H) and 125.6 MHz (^{13}C) on a Bruker Avance DRX-500 spectrometer. Chemical shift standards were internal tetramethylsilane ($\delta = 0$) for ^1H and ^{13}C. Signal assignments were assisted by DEPT, COSY, HMQC, HMBC, NOESY and ROESY (standard Bruker software).

1D and 2D NOESY as well as ROESY experiments were recorded at 500 MHz using standard Bruker microprograms. Mixing times were 300 ms in the selective 1D und 2D NOESY and 250 ms in the 2D ROESY experiments. There was no significant difference in the spectral information of NOESY as compared to ROESY applications.

Variable-temperature ^1H (500.1 MHz) and ^{13}C NMR (125.6 MHz) spectra were recorded in the presence of **Rh*** on a Bruker Avance DRX-500 spectrometer. Temperatures were read from the instrument panel; no further measures for more precise temperature determinations were taken.

Mixtures with molar ratios of (2*R*)/(2*S*) = 3:2 for **1** and 2:1 for **2**–**4** were prepared for the NMR experiments in the presence of **Rh*** so that the enantiomers could be discerned easily from each other by their relative signal intensities. In the standard dirhodium experiment, one drop of acetone-d_6 was added to each NMR sample before measurement in order to increase the solubility of **Rh***.[14] Thereby, 48.6 mg (42 μmol) of **Rh***, an equimolar amount of the ligands **1**–**4** and ca. 4 μl acetone-d_6 (ca. 53 μmol corresponding to 1–1.5 mol equiv relative to **Rh***) were dissolved in 0.7 ml $CDCl_3$. In the absence of acetone-d_6, however, only 16.2 mg of **Rh*** (ca. 14 μmolar) could be dissolved in 0.7 ml $CDCl_3$.

Table 5. Crystallographic parameters of **1**

Diffractometer	IPDS, Fa. Stoe, Darmstadt, Germany
Temperature	300(2) K
Irradiation	Mo K_α, 0.71073 Å
θ_{min}, θ_{max}	2.20°, 24.27°
Index range	$-9 \leqslant h \leqslant +9$; $-20 \leqslant k \leqslant +20$; $-21 \leqslant l \leqslant +21$
Reflections collected unique	15,889/4167 [R_{int} = 0.1346]
R indices	R_1 = 0.0845, wR_2 = 0.1566
Empirical formula	$C_{14}H_{18}ClNO_3$
Formula weight	283.74
Crystal system	Orthorhombic
Space group	$P2_12_12_1$ (no. 19)
Unit cell dimensions	*a* = 8.919(1) Å *b* = 17.957(2) Å *c* = 18.509(3) Å
Volume	2964.4(7) $Å^3$
Z	8
Calculated density D_x	1.272 g/cm^3
Absorption coefficient μ (Mo K_α)	0.261 mm^{-1}
Crystal size	0.7 × 0.35 × 0.26 mm
Absolute structure parameter	0.0(2)
Largest diff. peak and hole	0.302 and −0.276 e $Å^{-3}$

4.7. X-ray structure determination of 1

For data see Table 5. There are two molecules in the asymmetric unit, which differ mainly in the N–C-4–C-5–Cl torsion angle: 169° and −145°. Atomic distances, bond angles and torsion angles can be requested from the corresponding author as supplementary material. CCDC 261197 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, fax (+44) 1223 336 033, e-mail deposit@ccdc.cam.ac.uk. An X-ray diffraction study of a related structure—Cl in **1** is replaced by C_6H_5—has been published by Bart et al.[13]

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