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INDIRECT ELECTROCHEMICAL α-METHOXYLATION OF N-ACYL AND N-CARBOALKOXY α-AMINO ACID ESTERS AND APPLICATION AS CATIONIC GLYCINE EQUIVALENTS

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Abstract: Indirect electrochemical methoxylation of N-acyl and N-carboalkoxy α-amino acid esters in α-position to nitrogen is possible, if chloride is used as mediator. The course of the reaction depends upon the protecting group as well as upon the amino acid side-chain. Increased electron withdrawing effects of the protecting group are accelerating the reaction. On the other hand aliphatic side-chains are diminishing the reactivity. High chloride ion concentrations improve the current yields surprisingly strong.

1. INTRODUCTION

The oxidation in α-position to the nitrogen atom in protected α-amino acids and dipeptides is of increasing synthetic interest because the products are electrophilic amino acid equivalents and therefore potential amidoalkylation reagents[1]. The electrochemical methodology, in our hands, has been proven to be especially effective and simple for the α-oxidation of these compounds. Direct anodic oxidation of N-acyl and N-carboalkoxy amino acid esters does not work because of the electron withdrawing effect of the ester function. However, indirect electrochemical oxidation using chloride ions as catalyst is effective[2,3].

2. INDIRECT ELECTROCHEMICAL OXIDATION OF N-ACYLAMINO ACID ESTERS WITH SODIUM CHLORIDE AS REDOX-CATALYST

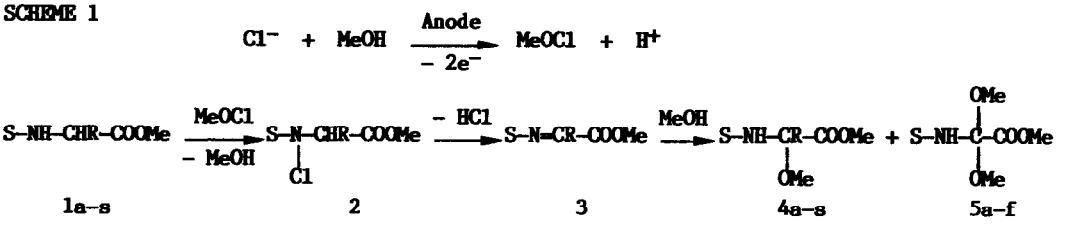
The chloride ion mediated α-methoxylation of protected amino acid esters presumably occurs according to **Scheme 1**. The intermediate formation of methyl hypochlorite is supported by the fact, that these types of reactions may also be performed by application of stoichiometric amounts of t-butyl hypochlorite[4]. For larger scale preparations the electrochemical procedure

has great advantages because of the in-situ generation and regeneration of the reagent and the ease of the operation.

It has been reported by Shono that α-branched amino acid esters which were N-protected as methyl carbamates can be α-methoxylated in methanol at Pt anodes in presence of 0.5 equivalents of NaCl after consumption of 10 F/mol in 83-91% material yield. In case of phenylglycine even 31 F/mol were necessary[2]. The glycine derivative could not be selectively monomethoxylated under these conditions. Instead the dimethoxylation product was obtained in 95% yield[1].

We are presenting the results of our studies of the influence of the N-protecting group, the amino acid side-chain, and the reaction conditions on the course of the reaction. Thereby we are demonstrating that it is possible to methoxylate N-protected amino acid esters in α-position in a very effective way using not more than 3 F/mol.

SCHEME 1



S = PhCO: **a**: R = H; **h**: R = Me; **n**: R = Ph;
S = o-Cl-PhCO: **b**: R = H; **i**: R = Me; **o**: R = Ph;
S = p-Cl-PhCO: **c**: R = H; **j**: R = Me; **p**: R = Ph;
S = p-MeO-PhCO: **d**: R = H; **k**: R = Me; **q**: R = Ph;
S = m-NO_2-PhCO: **e**: R = H; **l**: R = Me; **r**: R = Ph;
S = p-NO_2-PhCO: **f**: R = H; **m**: R = Me; **s**: R = Ph;
S = p-Me-Ph-SO_2: **g**: R = H;

2.1 Influence of Chloride Ion Concentration

To study the influence of the chloride ion concentration on the effectivity and selectivity of the methoxylation of N-benzoyl glycine methyl ester (**1a**) the reaction was performed in an undivided cell equipped with a graphite foil anode and platinum wire cathode using an electrolyte of 100 mL 0.1 M $LiClO_4$/MeOH in presence of different amounts of NaCl. The elctrolyses were run under constant current conditions until the consumption of 3 F/mol of charge. The results for two different concentrations of **1a** are shown in **Fig. 1.**

We could show that in presence of 400-700 mg NaCl in 100 mL electrolyte already after consumption of 3 F/mol over 90% turnover of the protected amino acid ester **1a** could be obtained yielding mono- (**4a**, 66-68%) and dimethoxylated (**5a**, 10-19%) product in a ratio between 4:1 and 6:1. For compounds **1b** and **1c** the ratio of mono- (**4b**, **4c**) to dimethoxylated (**5b**, **5c**) products is between 4:1 and 5:1. N-acyl phenylglycine methyl ester (**4n-s**) could be methoxylated in up to 98% yield after consumption of 3 F/mol. Obviously, high chloride ion concentrations diminish the competing methanol oxidation. Application of LiCl instead of NaCl

is also possible, however the use of KBr or LiBr did not lead to any reaction of **1a**.

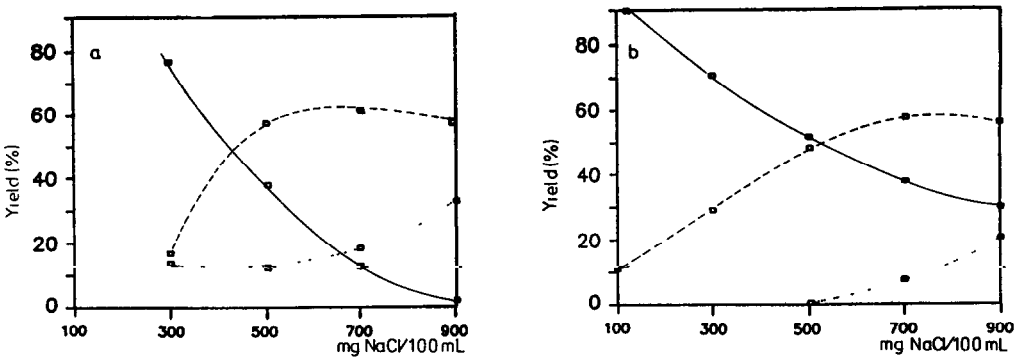


Figure 1. Influence of the chloride ion concentration in 100 ml electrolyte on the yield of mono-(**4a**, broken line) and dimethoxylation product (**5a**, dotted line) during indirect electrochemical oxidation of N-benzoyl glycine methyl ester (**1a**, solid line). The yield was determined always after consumption of 3 F/mol (current density = 7 mA/cm^2).
a: 2 mmol of **1a** as starting material;
b: 4 mmol of **1a** as starting material.

2.2 Influence of N-Protecting Group and Amino Acid Side-Chain

The results of the indirect electrochemical methoxylation of differently protected glycine, alanine, and phenylglycine methyl esters under standard conditions are given in **Table 1.**

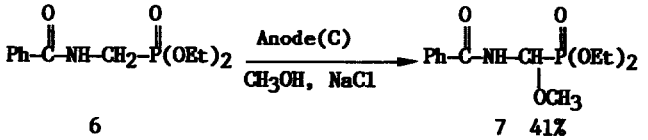
Table 1. Results of the chloride mediated electrochemical methoxylation of N-acyl amino acid esters **1** to monomethoxylation product **4**[a]

Compound R = H	Product (% Yield)	Compound R = CH_3	Product (% Yield)	Compound R = Ph	Product (% Yield)
1a	**4a**, **5a** (68) (19)	**1h**	**4h** (82)	**1n**	**4n** (88)
1b	**4b**, **5b** (78) (19)	**1i**	**4i** (82)	**1o**	**4o** (>98)
1c	**4c**, **5c** (74) (21)	**1j**	**4j** (82)	**1p**	**4p** (79)
1d	**4d**, (64)	**1k**	**4k** (53)	**1q**	**4q** (71)
1e	**4e**, **5e** (63) (33)	**1l**	**4l** (88)	**1r**	**4r** (>98)
1f	**4f**, **5f** (70) (9)	**1m**	**4m** (>98)	**1s**	**4s** (93)
1g	**4g** (quant.)[b]				

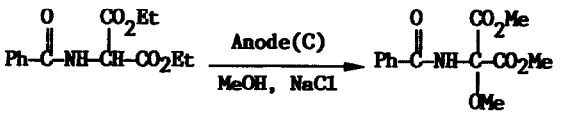
[a] Undivided cell; anode material: graphite foil; cathode material: platinum wire; electrolyte: 100 ml MeOH/ 0.1 M $LiClO_4$/700 mg NaCl; yields determined after 3 F/mol by HPLC; 450 mA = 7 mA/cm^2; [b] partially hydrolyzed during chromatographic separation.

HPLC control of the reaction shows that phenylglycine derivatives react fastest, followed by the glycine derivative, while alanine compounds are slowest. With amino acid derivatives of valine or leucine the reaction rate is further diminished. Generally, the reaction rate was

increased with increasing electron withdrawing effect of the N-protecting group. N-acylamino methylphosphonates **6** are slower, N-acylamino malonates **8** are faster reacting than the corresponding N-acylamino acid esters.



6 **7** **41%**



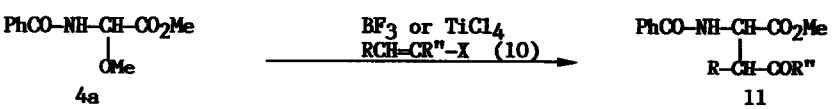
8 **9** **65%**

All these observations can best be interpreted assuming the HCl elimination out of the N-chloro amino acid intermediate under formation of the iminoester to be the rate determining step. E2 reactions are favoured by all groups which are increasing the acidity of the hydrogen to be eliminated. The rate increase by electron withdrawing functions within the protecting group is also paralleled by E2 reactions. Thus the E2 elimination of HBr from ring substituted ß-bromoethyl benzene derivatives follow the appropriate Hammett correlation[5]. The tosylamide protected glycine derivative is so reactive that it is totally transformed after consumption of only 2 F/mol. The product, however, is unstable so that it is partially hydrolyzed during chromatographic separation.

3. APPLICATION OF α-METHOXY-N-BENZOYL GLYCINE METHYLESTER (4a) AS AMIDOALKYLATION REAGENT

α-Methoxylated amino acid esters are useful stable amidoalkylation reagents. Thus **4a** can undergo nucleophilic substitution of the methoxy group by aromatic compounds, CH-acids, olefins, thiols, or phosphite[6,7,8]. We studied the introduction of other carbon nucleophiles under catalysis of Lewis acids. We found that also enamines(**10a**), silyl enol ethers(**10b**), and enol acetates(**10c**) can be introduced (**Scheme 2**) using either $TiCl_4$ or BF_3 as catalysts. Other C-nucleophiles are currently under study.

SCHEME 2



4a **11** (R,R"= $-(CH_2)_4-$)

10a: R,R"= $-(CH_2)_4-$; X = morpholine
10b: R,R"= $-(CH_2)_4-$; X = $OSi(CH_3)_3$
10c: R,R"= $-(CH_2)_4-$; X = $O-CO-CH_3$

If the reaction of **4a** with morpholino cyclohexene (**10a**) was performed with $TiCl_4$ as Lewis acid in CH_2Cl_2 the result was dependent on the ratio of **4a**:$TiCl_4$:**10a** (**Table 2**). It is shown

that best results are obtained, if the concentrations of $TiCl_4$ and the enamine are slightly more than twice that of the α-methoxy amino acid ester. If the $TiCl_4$ concentration is further increased, the yield decreases. The same is true for a further increase of the enamine concentration, however to a lower extent. The reaction is performed in such a way that a mixture of **4a** and **10a** in CH_2Cl_2 is slowly dropped to a solution of the Lewis acid in CH_2Cl_2 at - 55°C. Then the mixture was stirred for three hours under rising of the temperature to + 4°C. The diastereomeric excess for the anti diastereoisomer of **11** was determined by ^1H NMR spectroscopy giving values of 69 - 76% de.

Table 2. Reaction of **4a** with enamine **10a** under variation of the concentration ratios

ratio of **4a** : $TiCl_4$: **10a**	yield of **11** (%)	ratio of **4a** : $TiCl_4$: **10a**	yield of **11** (%)
1 : 1 : 1.2	52	1 : 0.5 : 1.2	38
1 : 1.5 : 1.7	73	1 : 1 : 1.2	52
1 : 2 : 2	78	1 : 2 : 1.2	60
1 : 2 : 2.4	82	1 : 3 : 1.2	47
1 : 2.3 : 2.7	90	1 : 1 : 2	75
		1 : 1 : 3	71
		1 : 1 : 4	70

If the same reaction was performed with $BF_3 \cdot OEt_2$ instead of $TiCl_4$ a somewhat higher concentration of Lewis acid was helpful. With a ratio of **4a** : BF_3 : **10a** of 1 : 4 : 2.4 the yield of **11** was 78%. The diastereomeric excess of the anti form increased to 86% de. The high diastereomeric excess for the anti-diastereoisomer may be explained by a Diels-Alder like transition state as proposed by Steglich[9].

If **4a** was reacted with cyclohexenyl acetate (**10c**), $TiCl_4$ was not effective at all. However $BF_3 \cdot OEt_2$ catalyzed (**4a**:BF_3:**10c** = 1:3:1) the reaction giving **11** in 50% yield with 25 - 31% de in favour of the anti product. As **10c** is not as reactive as **10a** the reaction had to take place at temperatures rising from - 20° to 0°C during one hour followed by 2 hours at room temperature. The low reactivity is also responsible for the lower yields.

If the 1-trimethylsilyloxy cyclohexene (**10b**) is used as nucleophile, $TiCl_4$ again is a good catalyst. Best results are obtained with a ratio of **4a** : $TiCl_4$: **10b** of 1 : 1-2 : 4-6 at a temperature starting from -55° C rising to +7° C after 3 h. **11** is obtained in 71% yield. The diastereomeric excess is 35-38% de. However, surprisingly the **syn** diastereoisomer is favoured. This must be explained by an acyclic transition state as it was proposed for the reaction of carbonyl compounds with allyl tin reagents in presence of Lewis acids[10].

EXPERIMENTAL

All compounds are identified by microanalysis or high resolution mass spectrometry, ^1H NMR-, ^{13}C NMR-, IR-, and mass spectrometry. M.p.s. were determined with a Reichert hot-stage microscope and are uncorrected. IR spectra were obtained using a Pye Unicam SP-1100 unit, ^1H NMR spectra were measured with Varian EM-360 and Bruker WH-90, ^{13}C NMR spectra were recorded on Bruker WH-90, and ^{31}P NMR spectra on Varian CFT 20 instruments. (solutions in deuteriochloroform, tetramethylsilane as internal standard, if not indicated otherwise). Mass spectra were obtained using A.E.I. Kratos MS-50 and MS-30 spectrometers. Liquid chromatography was performed on silica gel 63-100 mesh (Merck) or 36-62 mesh (Woelm). For HPLC separations a Waters UK6 injection system was combined with Waters LC-spectrophotometer, model 481, Waters high pressure pump. model 590, Hewlett Packard integrator, model 3390 A, Gilson fraction collector, model 201, and Knauer Vertex columns 16 mm x 45 cm; 32 mm x 25 cm; 4 mm x 25 cm filled with LiChrosorb Si60 (7 um; Merck). For GC analyses a Fractovap 4100 (Carlo Erba) together with an integrator 3390 A (Hewlett Packard) unit was used in connection with a packed glas column (1.7 mm x 200 cm; 12% SE 30 on Chromosorb W). All solvents are purified by distillation. Dichloromethane and ethyl acetate were dried over P_2O_5 and then distilled.

Cyclohexanone derivatives **10a,b,c** were prepared according to standard procedures.
N-acyl-amino acid methyl esters (**1a-s**) were prepared according to standard procedures via the amino acid methyl ester hydrochlorides: to a solution of 10 mmol amino acid in 25 ml methanol 20 mmol thionyl chloride is slowly added in such a way that 40 °C are not exceeded. After stirring for 6 h at r.t. methanol and unreacted thionyl chloride is removed by distillation. The residue is dissolved in chloroform, the chloroform evaporated, the residue washed with ether, and then the amino acid methyl ester hydrochloride recrystallized from ethanol. This product (11 mmol) is dissolved in 20 mL chloroform and after addition of 30 mmol triethylamine the acid chloride of the protecting group (10 mmol) is added dropwise while cooling on an ice bath. After stirring for 2 h at r.t. and addition of 200 ml chloroform the solution is extracted with 40 ml acetic acid (5%) and 40 mL water. After drying over Na_2SO_4 purification is performed by flash chromatography (SiO_2 36-62 mesh; ethyl acetate/cyclohexane or ethyl acetate/n-heptane). Compounds **1a**[11], **1c**[12], **1d**[13], **1e**[13a], **1f**[14], **1g**[15], **1h**[16], **1i**[17], **1l**[18], **1m**[19], **1n**[16,20], **1p**[12], **1q**[21] are known. Compounds **1b, 1j, 1k, 1o, 1r, 1s** could easily be identified by analysis of the spectroscopic data and comparison with those of the known compounds.

Preparative Electrolyses (General Procedure)

A stabilized current source working in galvanostatic (constant current) mode (NTN 700M-200; FuG, Rosenheim) was used in combination with a digital coulometer for measuring the charge consumption. Undivided beaker-type glass cells with cooling mantle (150 mL, 300 mL) equipped with a Pt wire cathode and a graphite foil cylinder (Sigraflex^R, Sigri Elektrographit, Meitingen) of 59 cm^2 were applied as anode.
The electrolyte was 0.1 M $LiClO_4$ in methanol (100 - 300 mL according to cell volume) containing 400 to 700 mg of NaCl in 100 mL electrolyte (700 mg being the optimum value). No base (NaOMe) was added. The temperature of the electrolyte was between 11 and 15 °C. For large scale electrolyses the temperature was held at 0° C. Between 4 and 60 mmol of substrate were electrolyzed with cell voltages of 7 to 9 V until the consumption of 3 to 4 F/mol.

For work-up the solvent was evaporated under reduced pressure at 40 °C. The residue was treated with 60 mL water(in the case of large scale experiments with 300 mL electrolyte and 50-60 mmol starting material 200 mL water were added) and the aqueous phase three times extracted with 100 mL $CHCl_3$ (200 mL for large scale experiments). After drying over Na_2SO_4 the $CHCl_3$ is evaporated and the products separated by flash chromatography (SiO_2; ethyl acetate/cyclohexane or ethyl acetate/n-heptane). In many cases, especially if the starting material was almost totally consumed, chromatography was not necessary. In those cases the crude products were only recrystallized from ethyl acetate or ethyl acetate/cyclohexane, as side-products were usually not observed or only in very small amounts. This is also necessary, if the products are easily hydrolyzed on SiO_2 like in the case of **4g**, **4l**, and **4m**. The isolated yields in the latter case are almost identical with those determined by analytical HPLC while after chromatographic separation the yields are between 3 and 15 % lower. For example in a large scale experiment starting from 56 mmol **1a** the monomethoxylated product **4a** was isolated after flash chromatography in 63% yield.

To study the influence of the N-protecting group and the amino acid side-chain on the anodic methoxylation it was necessary to work under standardized reaction and analytical conditions. Therefore the electrolyses were performed in a 150 mL undivided beaker-type glass cell with 100 mL electrolyte (0.1 M $LiClO_4$/MeOH) in presence of 700 mg NaCl and 4 mmol substrate at 13 - 15 °C until the consumption of 3 F/mol. The work-up was identical to that described above. The analysis took place by analytical HPLC using a Vertex^R (Knauer) column (D= 4 mm x 25 cm; LiChrosorb Si 60, 7um). As eluent a mixture of ethyl acetate and n-heptane was used in ratios of 1:9, 2:8, and 3:9.

Spectroscopic Data

Spectroscopic data of compound **4a** compared well with reported values[22].

Methyl 2-benzoylamino-2,2-dimethoxy acetate (α,α-dimethoxy-N-benzoyl-glycine methyl ester) (**5a**). m.p. 75-76 °C (Found: M^+-CH_3OH, 221.0692. $C_{11}H_{11}NO_4$ requires M, 221.0685; Found: $M^+-CO_2CH_3$, 194.0842. $C_{10}H_{12}NO_3$ requires M, 194.0814); IR(KBr): 3330, 3050, 2950, 2840, 1755, 1665, 1515, 1485, 1310, 1145, 1120, 1065, 1010, 935, 775, 735, 710, 690, 610 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 3.61 (s,6H, $-C(OCH_3)_2-$), 3.91 (s,3H,$COOCH_3$),6.88 (s,1H,NH), 7.38-7.80 (m,5H,arom.H) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 49.81 (2C, $-C(OCH_3)_2$), 53.08 (CO_2CH_3), 101.12 (-NH-C(OMe)$_2$), 127.27 (2C, arom.C), 128.69 (2C, arom.C), 132.38 (arom.C), 132.51 (arom.C-CONH), 165.92 (2C, CONH, CO_2Me) ppm.

Methyl 2-(2-chlorobenzoyl)amino-2-methoxy acetate (α-methoxy-N-(2-chlorobenzoyl)-glycine methyl ester) (**4b**). m.p. 95 °C (Found: C, 51.31; H, 4.74; N, 5.40. $C_{11}H_{12}ClNO_4$ requires C, 51.27; H, 4.69; N, 5.44); IR (KBr): 3270, 2940, 2840, 1765, 1660, 1535, 1440, 1340, 1230, 1200, 1115, 1065, 925, 750, 640 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 3.58 (s,3H,$CH(OCH_3)$), 3.84 (s,3H,CO_2CH_3), 5.76 (d,8Hz,1H,CH), 7.20 (d,8Hz,1H,NH), 7.24-7.80 (m,4H,arom.H) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 53.05 (OCH_3), 56.93 (CO_2CH_3), 78.65 (-CH-), 127.21 (arom.CH), 130.31 (arom.CH), 130.51 (arom.CH), 130.93 (arom.C), 132.03 (arom.CH), 133.94 (arom.CCl), 166.86 (CONH), 168.18 (CO_2Me) ppm; m/z = 242 ($M^+ - CH_3$, 0.8%), 227(0.8), 226(0.4), 198(43), 139-(100), 111(21), 75(20).

Methyl 2-(2-chlorobenzoyl)amino-2,2-dimethoxy acetate (α,α-dimethoxy-N-(2-chlorobenzoyl)glycine methyl ester) (**5b**). m.p. 135 °C (Found: $M^+-CO_2CH_3$, 228.0417. $C_{10}H_{11}ClNO_3$ requires M, 228.0425); IR (KBr): 3340, 3000, 2940, 2840, 1750, 1680, 1590, 1470, 1430, 1310, 1130, 1065, 785, 760, 610 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 3.34 (s,6H,2xOCH_3), 3.85 (s,3H,CO_2CH_3), 7.04 (s,1H,NH), 7.28-7.83 (m,4H,arom.H) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 50.11 (2xOCH_3), 53.21 (CO_2CH_3), 101.08 (NH-C-), 127.30 (arom.CH), 130.44 (arom.CH), 130.83 (2C,arom.CH,arom.C), 132.19 (arom.CH), 133.16 (arom.CCl), 164.88 (CONH), 165.69 (CO_2Me) ppm.

Methyl 2-(4-chlorobenzoyl)amino-2-methoxy acetate (α-methoxy-N-(4-chlorobenzoyl)glycine methyl ester) (**4c**). m.p. 119 °C (Found: C, 51.42; H, 4.69; N, 5.44. $C_{11}H_{12}ClNO_4$ requires C, 51.27; H, 4.69; N, 5.44. Found: M^++H, 258.0536. $C_{11}H_{13}ClNO_4$ requires M, 258.0530. Found: $M^+-CO_2CH_3$, 198.0326. $C_9H_9ClNO_2$ requires 198.0320); IR (KBr): 3380, 2960, 2835, 1750, 1665, 1590, 1510, 1480, 1320, 1230, 1100, 1010, 910, 840, 790, 760, 670 cm^{-1}; ^1H NMR ($CDCL_3$), 90 MHz): 3.51 (s,3H,OCH_3), 3.84 (s,3H,CO_2CH_3), 5.60 (d,8Hz,1h,CH), 7.17 (d,8Hz,NH), 7.47 (d,7.5Hz, 2H,arom.H,AA'BB'), 7.91 (d,7.5Hz,2H,arom.H,AA'BB') ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 53.11 (OCH_3), 57.00 (CO_2CH_3), 78.82 (NH-CH-), 128.86 (2C,arom.CH), 129.05 (2C,arom.CH), 131.51 (arom.C), 138.76 (arom.CCl), 166.60 (CO_2Me), 168.67 (CONH) ppm; m/z = 258 (M^++1, 0.01%), 242 (0.2), 226 (0.2), 198 (36), 139 (100), 111 (25), 75 (15).

Methyl 2-(4-chlorobenzoyl)amino-2,2-dimethoxy acetate (α,α-dimethoxy-N-(4-chlorobenzoyl)glycine methyl ester) (**5c**). m.p. 118-119 °C (Found: $M^+-CO_2CH_3$, 228.0424. $C_{10}H_{11}ClNO_3$ requires 228.0425); IR (KBr): 3360, 3080, 2950, 2840, 1745, 1660, 1510, 1480, 1430, 1310, 1140, 1110, 1070, 1010, 935, 855, 770, 730, 620 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 3.29 (s,6H,2xOCH_3), 3.81 (s,3H,CO_2CH_3), 6.80 (s,1H,NH), 7.40 (d,9Hz,2H,arom.H,AA'BB'), 7.74 (d,9Hz,2H,arom.H,AA'BB') ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 49.88 (2C,2xOCH_3), 53.18 (CO_2CH_3), 101.18 (-NH-C-). 128.76 (2C,arom.CH), 129.76 (2C,arom.CH), 130.93(arom.C), 138.76 (arom.CCl), 164.95 (CONH), 165.89 (CO_2Me) ppm.

Methyl 2-(4-methoxybenzoyl)amino-2-methoxy acetate (α-methoxy-N-(4-methoxybenzoyl)glycine methyl ester) (**4d**). oil (Found: $M^+-CO_2CH_3$, 194.0821. $C_{10}H_{12}NO_3$ requires 194.0814); IR (KBr): 3320, 2950, 2840, 1765, 1650, 1530, 1505, 1340, 1260, 1235, 1150, 1105, 1020, 930, 845, 770, 665, 635 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 3.48 (s,3H,OCH_3), 3.80 (s,3H,ArOCH_3), 3.82 (s,3H,-CO_2CH_3), 5.73 (d,9Hz,1H,CH), 6.91 (d,9Hz,2H,arom.H,AA'BB'), 7.07 (d,9Hz,1H,NH), 7.79 (d,9Hz,-2H,arom.H,AA'BB') ppm.

Methyl 2-(3-nitrobenzoyl)amino-2-methoxy acetate (α-methoxy-N-(3-nitrobenzoyl)glycine methyl ester) (**4e**). m.p. 122 °C (Found: M⁺+H, 269.0780. $C_{11}H_{13}N_2O_6$ requires 269.0770. Found: M⁺-CO_2CH_3, 209.0547. $C_9H_9N_2O_4$ requires 209.0560); IR (KBr): 335, 2935, 2840, 1745, 1675, 1520, 1355, 1230, 1100, 1060, 1015, 920, 830, 815, 780, 710, 685, 660 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 3.49 (s,3H,OCH_3), 3.80 (s,3H,CO_2CH_3), 5.71 (d,9Hz,1H,CH), 7.31 (d,9Hz,1H,NH), 7.60-8.73 (m,4H,arom.H) ppm.

Methyl 2-(4-nitrobenzoyl)amino-2-methoxy acetate (α-methoxy-N-(4-nitrobenzoyl)glycine methyl ester) (**4f**). m.p. 147 °C (Found: M⁺+H, 269.0757. $C_{11}H_{13}N_2O_6$ requires 269.0770); IR (KBr): 3365, 2955, 2835, 1750, 1670, 1520, 1480, 1325, 1230, 1100, 1065, 1010, 910, 865, 835, 785, 715, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 3.47 (s,3H,OCH_3), 3.80 (s,3H,CO_2CH_3), 5.69 (d,9Hz,-1H,CH), 7.27 (d,9Hz,1H,NH), 8.00 (d,8Hz,2H,arom.H,AA'BB'), 8.36 (d,8Hz,2H,arom.H,AA'BB') ppm.

Methyl 2-(4-toluenesulphonyl)amino-2-methoxy acetate (α-methoxy-N-(4-toluenesulphonyl)-glycine methyl ester) (**4g**). oil (Found: M⁺-CH_3OH, 241.0409. $C_{10}H_{11}NO_4S$ requires 241.0406; Found: M⁺-CO_2CH_3, 214.0534. $C_9H_{12}NO_3S$ requires 214.0535); IR (KBr): 3260, 2950, 2830, 1745, 1595, 1440, 1430, 1335, 1300, 1160, 1090, 1065, 880, 810, 660 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 2.42 (s,3H,$ArCH_3$), 2.87 (s,3H,OCH_3), 3.71 (s,3H,CO_2CH_3), 5.04 (d,9Hz,1H,CH), 5.80 (d,9Hz,-1H,NH), 7.31 (d,8Hz,2H,arom.H,AA'BB'), 7.78 (d,8Hz,2H,arom.H,AA'BB') ppm.

Methyl 2-benzoylamino-2-methoxy propionate (α-methoxy-N-benzoyl-alanine methyl ester) (**4h**). m.p. 129-130 °C (Found: M⁺+H, 238.1069. $C_{12}H_{16}NO_4$ requires 238.1075. Found: M⁺-CO_2CH_3, 178.0869. $C_{10}H_{12}NO_2$ requires 178.0865); IR (KBr): 3310, 2950, 2840, 2360, 2338, 1760, 1650, 1530, 1490, 1465, 1315, 1140, 1050, 980, 900, 870, 720, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 1.64 (s,3H,CH_3), 3.07 (s,3H,OCH_3), 3.62 (s,3H,CO_2CH_3), 7.00 (s,1H,NH), 7.13-7.71 (m,5H,-arom.H) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 23.21 (CH_3), 51.79 (OCH_3), 53.24 ($CO_2\underline{C}H_3$), 85.42 (NH-C-), 127.14 (2C,arom.CH), 128.73 (2C,arom.CH), 132.06 (arom.CH), 133.87 (arom.C), 166.53 ($\underline{C}O_2Me$), 171.34 (CONH) ppm.

Methyl 2-(2-chlorobenzoyl)amino-2-methoxy propionate (α-methoxy-N-(4-chlorobenzoyl)-alanine methyl ester (**4i**). m.p. 104-105 °C (Found: C,53.13; H,5.19; N,5.24. $C_{12}H_{14}ClNO_4$ requires C,53.05; H,5.19; N,5.16. Found: M⁺+H, 272.0664. $C_{12}H_{15}ClNO_4$ requires 272.0686); IR (KBr): 3280, 2945, 2840, 1745, 1675, 1535, 1430, 1315, 1145, 1050, 860, 755, 630 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 1.90 (s,3H,CH_3), 3.39 (s,3H,OCH_3), 3.88 (s,3H,CO_2CH_3), 7.31 (s,1H,NH), 7.35-7.78 (m,4H,arom.H) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 23.21 (CH_3), 52.01 (OCH_3), 53.21 ($CO_2\underline{C}H_3$), 85.65 (-NH-C-), 127.17 (arom.CH), 130.22 (arom.CH), 130.31 (arom.CH), 130.64 (arom.C), 134.65 (arom.CCl), 165.72 ($\underline{C}O_2Me$), 171.00 (CONH) ppm.

Methyl 2-(4-chlorobenzoyl)amino-2-methoxy propionate (α-methoxy-N-(4-chlorobenzoyl)-alanine methyl ester) (**4j**). m.p. 124 °C (Found: C,53.20; H,5.21; N,4.96. $C_{12}H_{14}ClNO_4$ requires C,53.05; H,5.19; N,5.16. Found: M⁺+H, 272.0694. $C_{12}H_{15}ClNO_4$ requires 272.0686. Found: M⁺-CO_2CH_3, 212.0478. $C_{10}H_{11}ClNO_2$ requires 212.0476); IR (KBr): 3355, 2940, 2825, 1740, 1660, 1590, 1520, 1480, 1430, 1310, 1140, 1055, 1010, 870, 855, 770, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 1.81 (s,3H,CH_3), 3.21 (s,3H,OCH_3), 3.80 (s,3H,CO_2CH_3), 7.17 (s,1H,NH), 7.38 (d,8Hz,-2H,arom.H,AA'BB'), 7.71 (d,8Hz,2H,arom.H,AA'BB') ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 23.08 (CH_3), 51.34 (OCH_3), 53.34 ($CO_2\underline{C}H_3$), 85.58 (-NH-C-), 128.63 (2C,arom.CH), 128.99 (2C,arom.CH), 132.25 (arom.C), 138.40 (arom.CCl), 165.50 ($\underline{C}O_2Me$), 171.39 (CONH) ppm; m/z = 240 (M⁺-OCH_3, 1.5%), 239 (1), 212 (49), 139 (100), 111 (32), 76 (16).

Methyl 2-(4-methoxybenzoyl)amino-2-methoxy propionate (α-methoxy-N-(4-methoxybenzoyl)-alanine methyl ester) (**4k**). oil (Found: M⁺-CH_3OH, 235.0842. $C_{12}H_{13}NO_4$ requires 235.0841. Found: M⁺-CO_2CH_3, 208.0973. $C_{11}H_{14}NO_3$ requires 208.0970); IR (KBr): 3320, 3060, 3000, 2940, 2840, 1740, 1645, 1600, 1520, 1485, 1430, 1370, 1310, 1250, 1180, 1130, 1055, 1015, 980, 870, 815, 760, 620 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 1.91 (s,3H,CH_3), 3.33 (s,3H,OCH_3), 3.89 (s,3H,$ArOCH_3$), 3.91 (s,3H,CO_2CH_3), 7.01 (d,9Hz,2H,arom.H,AA'BB'), 7.15 (s,1H,NH), 7.84 (d,9Hz,2H,arom.H,AA'BB) ppm.

Methyl 2-(3-nitrobenzoyl)amino-2-methoxy propionate (α-methoxy-N-(3-nitrobenzoyl)-alanine methyl ester) (**4l**). m.p. 143-144 °C (Found: M⁺+H, 283.0921. $C_{12}H_{15}N_2O_6$ requires 283.0930); IR (KBr): 3310, 3080, 3000, 2950, 2840, 1740, 1670, 1615, 1530, 1450, 1435, 1378, 1350, 1310, 1285, 1270, 1140, 985, 915, 878, 820, 720, 680, 670, 600 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 1.86 (s,3H,CH_3), 3.26 (s,3H,OCH_3), 3.82 (s,3H,CO_2CH_3), 7.37 (s,1H,NH), 7.50-8.5 (m,4H,arom.H) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 22.88 (CH_3), 51.85 (OCH_3), 53.4 ($CO_2\underline{C}H_3$), 85.7 (-NH-C-), 122.12 (arom.CH), 126.52 (arom.CH), 130.02 (arom.CH), 133.29 (arom.CH), 135.52 (arom.C), 148.22 (arom.CNO_2), 164.23 ($\underline{C}O_2CH_3$), 171.09 (CONH) ppm; m/z = 283 (M⁺+H,0.04%), 252 (4), 251 (7), 250 (3), 224 (20), 223 (100), 193 (11), 149 (12), 134 (15), 104 (60),92 (10), 76 (52), 75 (57), 50 (13), 43 (18), 42 16).

Methyl 2-(4-nitrobenzoyl)amino-2-methoxy propionate (α-methoxy-N-(4-nitrobenzoyl)-alanine methyl ester) (**4m**). m.p. 161 °C (Found: M^++H, 283.0886. $C_{12}H_{15}N_2O_6$ requires 283.0930); IR (KBr): 3325, 3110, 3000, 2950, 2840, 1765, 1660, 1600, 1530, 1485, 1370, 1345, 1325, 1310, 1275, 1140, 1100, 900, 870, 850, 810, 735, 720, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 1.90 (s,3H,CH_3), 3.28 (s,3H,OCH_3), 3.88 (s,3H,CO_2CH_3), 7.38 (s,1H,NH), 7.98 and 8.24 (AA'BB',4H, arom.H) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 22.65 (CH_3), 50.97 (OCH_3), 52.56 (CO_2CH_3), 84.38 (-NH-C-), 123.13 (2C,arom.CH), 128.76 (2C,arom.CH), 138.89 (arom.C), 149.35 (arom.C-NO_2), 164.75 (CO_2CH_3), 170.55 (CONH) ppm; m/z = 283 (M^++H,0.04%), 252 (5), 251 (8), 250 (5), 224 (25), 223 (100), 218 (9), 149 (11), 134 (10), 120 (12), 104 (38), 92 (9), 76 (20), 75 (32).

Methyl 2-benzoylamino-2-methoxy-2-phenyl acetate (α-methoxy-N-benzoyl-phenylglycine methyl ester) (**4n**). m.p. 115-116 °C (Found: C, 68.08; H, 5.90; N, 4.50. $C_{17}H_{17}NO_4$ requires C, 68.22; H, 5.72; N, 4.68. Found: M^+, 299.1171. $C_{17}H_{17}NO_4$ requires 299.1153); IR (KBr): 3310, 2820, 1940, 1740, 1645, 1510, 1480, 1260, 1180, 1130, 1095, 1065 , 955, 855, 725, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 3.35 (s,3H,OCH_3), 3.69 (s,3H,CO_2CH_3), 7.24 (s,5H,arom.H), 7.98 (s,5H,-arom.H), 7.43 (s,1H,NH) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 51.78 (OCH_3), 53.63 (CO^2CH_3), 87.65 (NH-C-), 125.94 (2C,arom.CH), 127.24 (2C,arom.CH), 128.66 (2C,arom.CH), 128.82 (2C,arom.CH), 128.95 (arom.CH), 132.25 (arom.CH), 133.61 (arom.C-CO-NH), 137.73 (arom.C), 165.85 (CO_2CH_3), 170.51 (CONH) ppm.

Methyl 2-(2-chlorobenzoyl)amino-2-methoxy-2-phenyl acetate (α-methoxy-N-(2-chlorobenzoyl)-phenylglycine methyl ester) (**4o**). m.p. 102-103 °C (Found: C,61.28; H,4.78; N,4.14. $C_{17}H_{16}Cl-NO_4$ requires C,61.18; H,4.83; N,4.20. Found: M^+, 333.0760. $C_{17}H_{16}NO_4$ requires 333.0764); IR (KBr): 3220, 2950, 2830, 1755, 1650, 1515, 1305, 1260, 1105, 1095, 750, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 3.41 (s,3H,OCH_3), 3.70 (s,3H,CO_2CH_3), 7.20-7.81 (m,9H,arom.H), 7.88 (s,1H,-NH) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 51.92 (OCH_3), 53.60 (CO_2CH_3), 87.98 (-NH-C-), 125.98 (2C,arom.CH), 127.34 (arom.CH), 128.67 (2C,arom.CH), 128.99 (arom.CH), 130.44 (arom.CH), 130.67 (arom.C-CO-NH), 130.93 (arom.CH), 132.00 (arom.CH), 134.04 (arom.CCl), 137.37 (arom.C), 164.91 (CO_2CH_3), 170.13 (CONH) ppm.

Methyl 2-(4-chlorobenzoyl)amino-2-methoxy-2-phenyl acetate (α-methoxy-N-(4-chlorobenzoyl)-phenylglycine methyl ester) (**4p**). m.p. 128-129 °C (Found: C, 61.18; H,4.83; N,4.20. $C_{1716}Cl-NO_4$ requires C,61.02; H,4.96; N,3.92. Found: M^+, 333.0758. $C_{17}H_{16}ClNO_4$ requires 333.0764); IR (KBr): 3340, 2940, 2840, 1760, 1650, 1510, 1480, 1270, 1090, 1070, 760, 600 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 3.35 (s,3H,OCH_3), 3.71 (s,3H,CO_2CH_3), 7.31-8.13 (m,10H,arom.H,1 NH) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 51.76 (OCH_3), 53.67 (CO_2CH_3), 87.72 (-NH-C-), 125.85 (2C,arom.CH) 128.66 (4C,arom.CH), 129.02 (3C,arom.CH), 131.95 (arom.C-CO-NH), 137.50 (arom.CCl), 138.53 (arom. C), 164.72 (CO_2CH_3), 170.45 (CONH) ppm.

Methyl 2-(4-methoxybenzoyl)amino-2-methoxy-2-phenyl acetate (α-methoxy-N-(4-methoxybenzoyl)-phenylglycine methyl ester) (**4q**). oil (Found: M^+, 329.1271. $C_{18}H_{19}NO_5$ requires 329.1258); IR (KBr): 3350, 2940, 2840, 1745, 1630, 1605, 1570, 1525, 1495, 1250, 1175, 1030, 850, 760, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 3.42 (s,3H,OCH_3), 3.78 (s,3H,CO_2CH_3), 3.97 (s,3H,Ar-OCH_3), 6.85-7.93 (m,10H, 9 arom.H,1 NH) ppm.

Methyl 2-(3-nitrobenzoyl)amino-2-methoxy-2-phenyl acetate (α-Methoxy-N-(3-nitrobenzoyl)-phenylglycine methyl ester) (**4r**). m.p. 147-148 °C (Found: C,59.16, H,4.64; N,7.92. $C_{17}H_{16}N_2O_6$ requires C,59.30; H,4.68; N,8.14. Found: M^+, 344.1044. $C_{17}H_{16}N_2O_6$ requires 344.1004); IR (KBr): 3370, 2960, 2840, 1750, 1670, 1520s, 1482, 1330, 1235, 1105, 1065, 1012, 835, 785, 717, 685, 690 ppm; ^1H NMR (CD_2Cl_2, 90 MHz): 3.37 (s,3H,OCH_3), 3.72 (s,3H,CO_2CH_3), 6.22-7.70 (m,5H,arom.H), 7.90 (1H,NH), 7.59-8.71 (m,4H,O_2N-Ar-H) ppm.

Methyl 2-(4-nitrobenzoyl)amino-2-methoxy-2-phenyl acetate (α-methoxy-N-(4-nitrobenzoyl)-phenylglycine) (**4s**). m.p. 182 °C (Found: C, 59.78; H, 4.81; N, 7.94. $C_{17}H_{16}N_2O_6$ requires C, 59.30; H, 4.68; N, 8.14. Found: M^+, 344.0984. $C_{17}H_{16}N_2O_6$ requires 344.1004); IR (KBr): 3260, 2940, 2835, 1745, 1655, 1515, 1345, 1295, 1100, 1065, 865, 845, 735, 715 cm^{-1}; ^1H NMR (CD_2Cl_2, 90 MHz): 3.35 (s,3H,OCH_3), 3.71 (s,3H,CO_2CH_3), 6.24-7.71 (m,5H,arom.H), 7.89 (1H, NH), 7.75 (d,9Hz,2H,arom.H,AA'BB'), 8.30 (d,9Hz,2H,AA'BB') ppm.

Diethyl 1-benzoylamino-1-methoxy methylphosphonate (**7**). m.p. 72-73 °C (Found: M^+, 301.1065. $C_{13}H_{20}NO_5P$ requires 301,1074); IR (KBr): 3250, 2820, 1660, 1520, 1490, 1305, 1235, 1055, 1015, 965, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 1.33 (t,3H,7Hz,CH_3), 1.40 (t,3H,7Hz,CH_3), 3.53 (s,3H,OCH_3), 4.18 (q,2H,7Hz,OCH_2-), 4.33 (q,2H,7Hz,OCH_2-), 5.48 (dd,1H,10Hz/8Hz,CH), 6.87-7.18 (m,1H,NH), 7.40-8.00 (m,5H,arom.H) ppm; ^{13}C-NMR ($CDCl_3$, 90MHz): 16.31 (CH_3), 16.54 (CH_3), 57.39 (1C,d,^3J=14.7Hz,OCH_3), 63.38 (1C,d,^2J=6.5Hz,OCH_2), 63.67 (1C,d,^2J=6.6Hz,OCH_2), 76.78 (1C,d,^1J=200.6Hz,CH), 127.40 (arom.CH), 128.73 (arom.CH), 132.35 (arom.CH), 133.13 (arom.C), 167.93 (1C,d,^3J=8.8Hz,CONH) ppm; ^{31}P NMR ($CDCl_3$, H_3PO_4=external standard): +16.26 ppm (s).

Dimethyl 2-benzoylamino-2-methoxy malonate (9). oil (Found: M^++1, 282.0973. $C_{13}H_{16}NO_6$ requires 282.0973; Found: M^+-CO_2CH_3, 222.0755. $C_{11}H_{12}NO_4$ requires 222.0763); IR (NaCl): 3400, 2830, 1770, 1745, 1675, 1500, 1470, 1285, 1225, 1105, 920, 800, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 3.42 (s,3H,OCH_3), 3.91 (s,6H,2 x CO^2CH_3), 7.35-8.02 (m,6H,arom.H and NH) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 52.44 (OCH_3), 53.96 (2 x CO_2CH_3), 84.61 (-NH-C), 127.40 (2C,arom.CH), 128.86 (2C,arom.CH), 132.42 (arom.CH), 132.64 (arom.C), 166.24 (2 x CO_2CH_3), 166.44 (CONH) ppm.

Substitution of the Methoxy Group in **4a** by C-Nucleophiles **10a, 10b, 10c** (General Procedure) The Lewis acid dissolved in 1.5 mL CH_2Cl_2 is placed in a Schlenk flask under argon atmosphere and stirred at the given temperature (see above) for 20 min. Then a solution of **4a** (usually 0.5 mmol)and the nucleophile **10** dissolved in 1 mL CH_2Cl_2 is added dropwise during 5 min. After the given reaction time in which the temperature rose from the starting value (mostly - 55°C) to the end value (mostly about + 7°C) 15 mL water are added. After stirring for 1 h the mixture is extracted twice with 20 mL ethyl acetate. The organic phase is washed with 1 M $NaHCO_3$ solution and water, then dried over Na_2SO_4, and the solvent distilled off. The residue is separated by HPLC (Si60, 7 um, $CHCl_3$/n-heptane).

Physical and spectroscopic data of compound **11** compare well with those reported in the literature[9].

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