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Ring Opening with Kinetic Resolution of Azlactones by Ti-TADDOLates

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Abstract

The kinetic resolution of azlactones by the *Lewis*-acid-mediated transfer of an isopropoxide ligand from the chiral ligand sphere of Ti-TADDOLate is described. The reactions proceed with *in-situ* racemization of the starting material to afford highly enantiomerically enriched *N*-benzoyl-amino acid isopropylesters (er > 95:5 after recrystallization). The absolute configuration of the major enantiomer of *N*-benzoyl-phenylalanine isopropyl ester and its analogs with other aromatic substituents was shown to be (*S*)-(+) when the (*R,R*)-Ti-TADDOLate was employed. Only benzyl-substituted azlactones can be opened enantioselectively by the method described here. © 1998 Elsevier Science Ltd. All rights reserved.

*Keywords: Kinetic resolution; Oxazol-5-(4*H*)-ones; Azlactones; Ti-TADDOLates.*

Introduction

Oxazol-5-(4*H*)-ones, also known as azlactones, are activated cyclic esters easily prepared from *N*-acyl-amino acids by dehydration [1-4]. They are suitable substrates for kinetic resolution with *in-situ* recycling of the substrate (so-called "dynamic kinetic resolution" [5-8] or "asymmetric transformation" [9]), because they react readily with nucleophiles and racemize spontaneously, under very mild conditions, *via* a resonance-stabilized tautomer. This behaviour has been known for long in peptide chemistry, the racemization in peptide couplings of *N*-acyl-amino acids being ascribed to azlactone intermediates [10, 11].
Kinetic resolutions of azlactones (see Scheme 1) with hydrolytic enzymes [12-16] and cyclodextrins [17, 18] were first studied, focussing on the properties of the intermediate catalyst-acyl complex. With new screening methods for enzymes, more powerful systems

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[1] Part of the projected Ph. D. thesis of *K. G.*, ETH Zürich.

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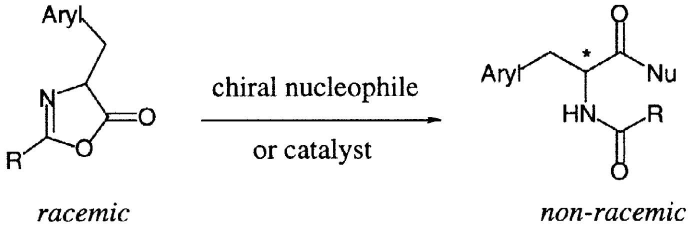
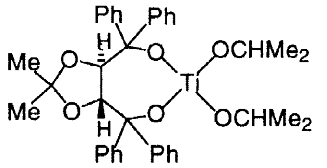
were at hand to develop preparative applications of this method [19-22]. Non-enzymatic variants comprise mainly ring opening reactions of an azlactone with a stoichiometric amount of a chiral nucleophile to give diastereoisomeric products, from which the enantiomerically enriched amino acid derivative is set free after chromatographic separation [23-28]. A catalytic process [29] and a crystallization-induced kinetic resolution of azlactones [30] have been described as well.





1 (Ti-TADDOLate)

Scheme 1. *a) Kinetic resolution with* in-situ *recycling of azlactones. The Ti-TADDOLate **1** is used for enantiomer-differentiating alkoxide transfer in the ring opening of azlactones.*

In model reactions, the effects of the substituents R and Aryl (see Scheme 1) on the rates of racemization and ring opening of azlactones have been investigated [31]. Azlactones from phenylalanine derivatives (see Scheme 1) were shown to exhibit an enhanced rate of racemization, whereas substituent R is more influential with respect to ring opening rates. Thus, judicious choice of the substituents should allow optimal conditions for a dynamic kinetic resolution, for which racemization has to be faster than ring opening. This is, for instance, the case for the azlactone derived from *N*-benzoyl-phenylalanine (Aryl = R = Ph), and, indeed, some of the best examples have been reported for this derivative [20, 21].

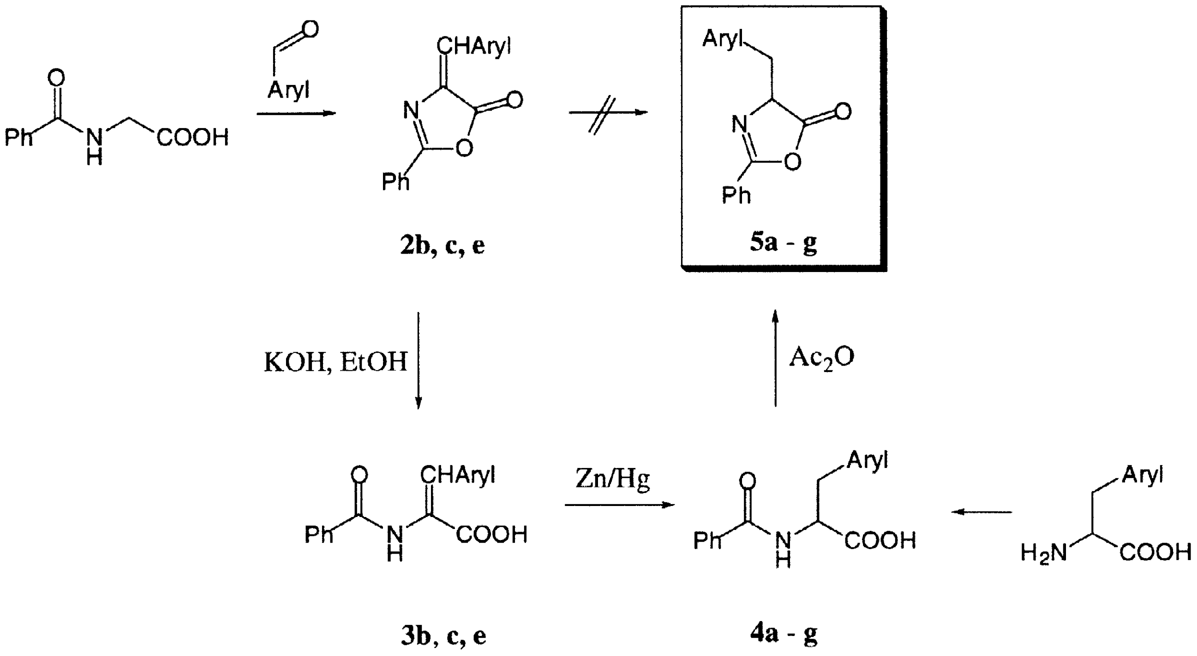
The *Lewis*-acid-mediated transfer of an alkoxide group from the chiral ligand sphere of Ti-TADDOLates to cyclic carboxylic acid derivatives has been described in preceding papers [32-36]. This alkoxide transfer can be realized by two approaches: by "desymmetrization" reactions of *meso*-compounds [32-34] or by kinetic resolutions of racemic substrates [35, 36]. A first TADDOLate-mediated ring opening of an azlactone (Aryl = R = Ph in Scheme 1) yielded, after a single recrystallization, the resulting isopropylester in highly enantioenriched form (er 98:2, major enantiomer (*S*) with (*R*,*R*)-TADDOLate) [36].

In this paper we describe the investigation of substituent effects and the extension of the previously described methodology to various other azlactones, affording highly enriched *N*-protected amino acid esters (er > 95:5 after recrystallization).

Preparative Results

1. Preparation of the Substrates

Based on our previous work on the ring opening of azlactone **5a** [36] we decided to first investigate the analogous reaction of the related azlactones **5b-g** which were easily prepared from the corresponding *N*-benzoylated amino acids **4b-g** by dehydration with Ac_2O [37] (see Scheme 2). Hydrogenation of the benzylidene azlactones **2** (using Pd/C [38, 39], $PdCl_2$ [40], PtO_2 (*cf.* [41]), or HI/P_{red} [42]) afforded the corresponding oxazolones **5** in only moderate yields [43]. For amino acids which are not commercially available we therefore took the route *via* the corresponding cinnamic acid derivatives **3**, which could be readily and cleanly transformed to the *N*-benzoylated amino acids **4** [44].

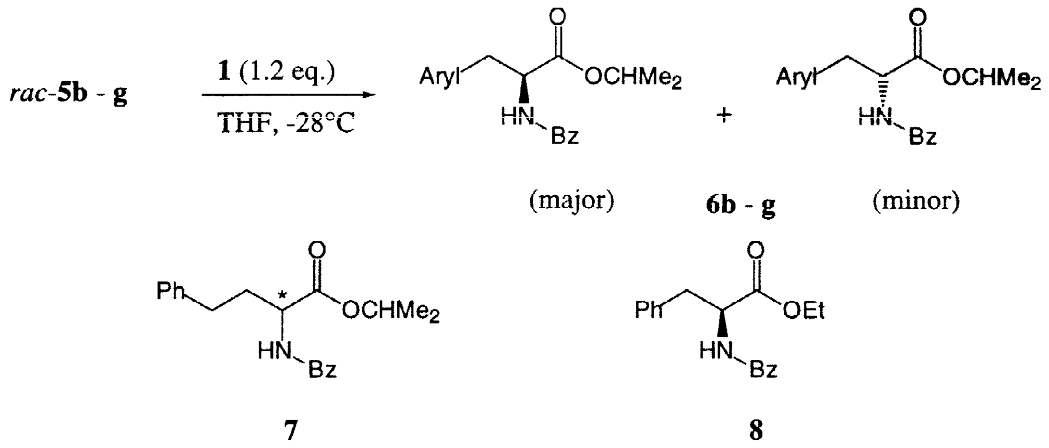


	a	b	c	d	e	f	g
Aryl	Ph	4-Me-Ph	4-MeO-Ph	4-Cl-Ph	1-Naphthyl	2-Thienyl	4-NO_2-Ph

Scheme 2. Preparation of azlactones 5a - g.

2. Enantioselective Ring opening of Azlactones

The ring opening of azlactones **5b-g** (see Scheme 3) was carried out on a 1 mmolar scale with 1.2 equivalents of (*R,R*)-TADDOLate **1** in THF at -28°C (storage in a deep freezer for several days, as described previously [36]).



*Scheme 3. Ring opening reactions of azlactones **5** to isopropylesters **6** with diisopropoxy-Ti-TADDOLate (cf. Table 1, Bz = COPh). Specification of **b**-**g** as in Scheme 2. Product **7** was obtained by TADDOLate-mediated ring opening of a homophenylalanine-derived azlactone, product **8** by ring opening of **5a** with diethoxy-Ti-TADDOLate.*

Table 1

*Conversion of Azlactones **5** to Enantioenriched Phenylalanine Derivatives **6**.* - Standard conditions: 1.2 equiv. of Ti-TADDOLate **1** were used. Conversion was monitored by ^{1}H-NMR, 75 % conversion was generally reached within 5 to 10 days, 100 % within up to 20 days. Enantiomer ratios were determined by HPLC analysis of the product esters. Recrystallizations from diisopropyl ether.

Entry	Azlactone	Enantiomer Ratio of **6b**-**g** (er)	Yield of **6b**-**g** (%)	Enantiomer Ratio of **6b**-**g** after Recrystallization	Yield of **6b**-**g** after Recrystallization (%)
1	**5b**	80:20	60	99:1	19
2	**5c**	77:23	65	95:5	31
3	**5d**	82:18	48	97:3	9
4	**5e**	77:23	67	96:4	9
5	**5f**	86:14	74	> 99:1[a)]	15
6	**5g**	80:20	74	95:5[b)]	16

[a)] Obtained from the mother liquor; [b)] Recrystallized from ethanol.

The results are shown in Table 1. Azlactones **5b**-**g** are ring-opened with selectivities ranging from 77:23 to 84:16 to give isopropylesters **6b**-**g** in 48-74% yield. By a single recrystallization the enantiomer ratios could be raised to > 95:5 (entries 1-6). Neither structural nor electronic effects of the aromatic moiety seem to play a crucial role in the degree of selectivity. Thus, for the azlactones derived from amino acids with a benzylic side chain, this method seems to be generally applicable.

The method does not work with azlactones with non-benzylic side chains. A homophenylalanine-derived azlactone was opened with a somewhat lower selectivity (er 68:32), and the isopropyl ester **7** was obtained, after recrystallization, with an er of only 86:14. Preliminary experiments have also been carried out with azlactones bearing aliphatic side chains, which showed no enantiomer differentiation at all. It is known that the ratio of ring opening *vs.* racemization rate is not optimal for the kinetic resolution of azlactones with non-benzylic side chains, but we have not determined whether this unfavorable ratio or poor enantiomer differentiation by the titanate is the reason for the lower selectivity in these cases.

Figure 1 shows the X-ray structure of azlactone **5f**. The observed folding of the thienyl aromatic moiety over the azlactone ring is a characteristic feature of azlactone structures with benzylic side chains [45-49]. Such folding has also been reported for hydantoins [50] and for diketopiperazines [51] of phenylalanine derivatives and of peptides, and it was proposed that the conformation is stabilized by intramolecular dipole-dipole interactions. The importance of conformational effects on racemization rates of azlactones with benzylic side chains has been discussed extensively [31].

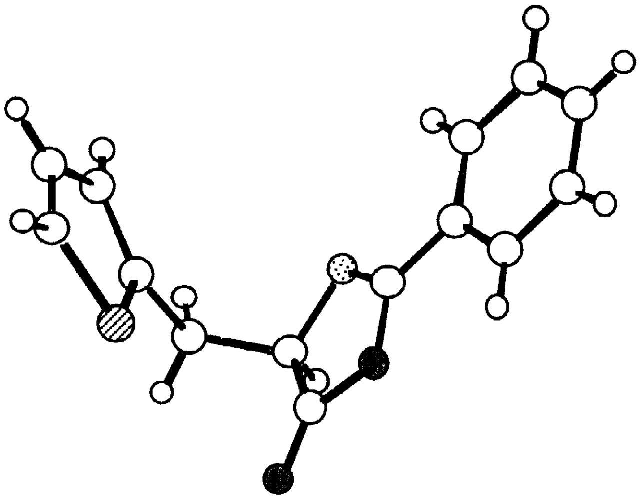


Figure 1. *MacMoMo representation of the X-ray structure of azlactone **5f**[2] (the heterocyclic ring is disordered with respect to a 180° rotation around the C^2(Thienyl)-CH_2-bond, only one of the two conformers is shown here). Structure determination by* V. Gramlich, *Laboratorium für Kristallographie, ETH Zürich.*

Azlactones from phenylglycines are known to equilibrate with their mesoionic forms in polar solvents [52, 53], so that they are not suitable substrates for our investigations, and as expected, experiments to open such azlactones (derived from *N*-benzoyl- or *N*-trifluoroacetyl-phenylglycine) with tetraisopropyltitanate failed.

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[2] The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 IEW. Any request should be accompanied by the full literature citation for this communication.

We were also interested in the ring opening of azlactones derived from α,α-disubstituted amino acids, which cannot racemize *in situ* but which can be suitable substrates for a so-called "simple" kinetic resolution [27, 28]. However, in a preliminary experiment with tetraisopropyltitanate, it was shown that even at room temperature, the reaction was too slow to be of synthetic utility (70% conversion after 14 days for the 4-methyl derivative of **5a**). With an azlactone derived from *N*-pivaloyl- instead of *N*-benzoyl-phenylalanine (variation of the amino protecting group), a decrease of the reaction rate was observed: after 14 days at –28°C, the TADDOLate-mediated ring opening had reached a conversion of less than 5%. To study the effect of the variation of the nucleophile, diethoxy- and di-*tert*-butoxy-Ti-TADDOLate instead of the diisopropoxy compound **1** were tested in the ring opening of azlactone **5a**. For the former, the reaction was complete after 10 days at –28°C and product **8** was isolated in 75% yield, however, with an er of only 60:40. In the latter case, essentially no conversion was obtained after 14 days at –28°C. Similar effects of different nucleophiles have been observed in the ring opening of *meso*-anhydrides by Ti-TADDOLates [33].

The (*S*)-configuration of the major enantiomer of **6**, formed in the ring opening of azlactones **5**, as shown in Scheme 3, was assigned in the following way: (i) for the parent compound **6a**, derived from phenylalanine, an optical comparison with an authentic material had been carried out [36]; (ii) for the thienyl-substituted product **6f**, we were able to assign (*S*)-configuration by anomalous dispersion (see Figure 2).

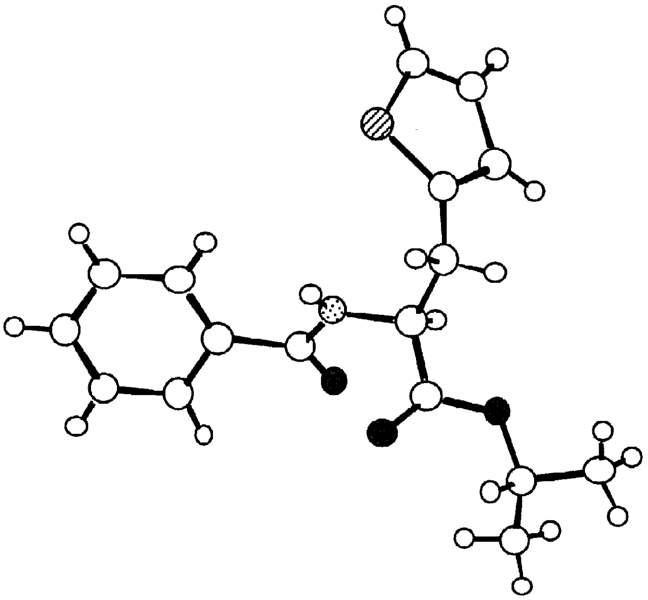
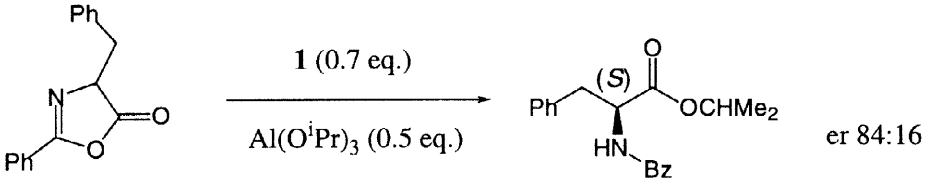


Figure 2. *MacMoMo representation of the X-ray structure of isopropylester (S)-**6f**, confirming its absolute configuration (anomalous diffraction). Structure determination by* W. B. Schweizer, *Laboratorium für Organische Chemie, ETH Zürich.*

For all other compounds **6** shown in Scheme 3 and Table 1, the (*S*)-configuration is assigned by analogy, based on the characteristic positive sign of the optical rotation, and based on the elution behaviour in HPL chromatography using a chiral stationary phase (the major isomer is always eluted first, see experimental section).

Although the TADDOL could be recovered nearly quantitatively after hydrolysis and chromatography, a substoichiometric use of the Ti-TADDOLate in these reactions is desirable. One possible approach is the use of a stoichiometric amount of an achiral alkoxide source (generally free $Ti(O^iPr)_4$ [54-56] or $Al(O^iPr)_3$ [33]) in combination with a small amount of TADDOLate. By the so-called "cleansing effect" [57], the TADDOLate is recycled and the product is set free, in some reactions with even better selectivities than in the reaction with stoichiometric amounts of TADDOLate [54-56] .

With azlactone **5a**, the use of 0.7 equivalents of **1** together with 0.5 equivalents of $Al(O^iPr)_3$ resulted in a lowering of reaction rate, but in no loss of selectivity, as compared to the reaction conducted with a stoichiometric amount of **1** (see Scheme 4). Smaller amounts of TADDOLate (0.5 or 0.25 equiv.) in combination with larger amounts of $Al(O^iPr)_3$ (0.7 or 0.95 equiv.) resulted in a dramatic decrease of the reaction rate (66 *vs.* *ca.* 5 % conversion after 40 d).



5a **6a**

***Scheme 4**: Ring opening of azlactone **5a** with a substoichiometric amount of Ti-TADDOLate **1**.*

Table 2

*Substoichiometric Use of Ti-TADDOLate **1** in the Ring opening of **5a** with an Excess of* $Al(O^iPr)_3$. - 0.7 equiv. of Ti-TADDOLate **1** were used in addition to 0.5 equiv. of $Al(O^iPr)_3$ which was added together with the substrate.

Entry	Enantiomer ratio of **6a**	time (d)	conversion
1	86:14	7	58
2	84:16	14	81
3	84:16	21	100

As shown in Table 2, the selectivity of the ring opening is not a function of conversion, which means that the *in-situ* racemization of the substrate is still faster than the reaction. With $Ti(O^iPr)_4$ instead of $Al(O^iPr)_3$ this is not the case: after 74% conversion an er of 78:22 is obtained, after 86% this ratio is 64:36, and after complete conversion it is only 60:40.

Experimental

General Remarks

1. Abbreviations: CC (column chromatography), FC (flash chromatography), HV (high vacuum, 0.01-0.1 Torr), R_t (retention time in min), tlc (thin layer chromatography).

2. Reagents and Equipment: All reactions were carried out under an Ar or N_2 atmosphere in oven- or flame-dried glassware. Solvents used for reactions and crystallizations were purchased from *Fluka* (puriss.). $Ti(O^iPr)_4$ (Hüls) was distilled under an Ar atmosphere; dry THF and Et_2O were freshly distilled from K or Na under an Ar atmosphere. Solvents used for extraction and flash chromatography were distilled as follows: AcOEt, CH_2Cl_2 and toluene from Sikkon, Et_2O from $KOH/FeSO_4$. Solvents used for HPLC were purchased from *Riedel-de Haën* (Chromosolv).

Tlc separations were run on *Merck* silica gel 60-F_{254} analytical plates; CC was performed on *Merck* silica gel 60 (0.063-0.200 mm); FC was performed on *Fluka* silica gel 60 (0.040-0.063 mm), pressure 0.2-0.4 bar. Melting points were determined on a *Büchi-510* apparatus and are uncorrected. Optical rotations were measured with a *Perkin-Elmer 241* polarimeter at room temperature (10 cm, 1 ml cell). HPLC: *Knauer* HPLC system (pump type *64*, integration system Eurochrom 2000, UV-detector (variable wavelength monitor)); column DNBPG, 4.6 x 250 mm, 5 μm (*Baker*), λ = 254 nm, flow 1 ml/min. NMR spectra were recorded with TMS (δ = 0) as internal standard on *Varian-Gemini 200* (200 MHz (^1H), 50 MHz (^{13}C)), on *Varian-Gemini 300* or *Bruker AC 300* (300 MHz (^1H), 75 MHz (^{13}C)), or on *Bruker AC 400* (400 MHz (^1H), 100 MHz (^{13}C)) spectrometers. Chemical shifts are given in ppm. IR spectra: *Perkin-Elmer-1600 FT-IR* infrared spectrophotometer. Mass Spectra: *Hitachi Perkin-Elmer RMU-6M* spectrometer (EI) and *VG-Tribrid* spectrometer (FAB), fragment ions in *m/z* with relative intensities (%) in parentheses. Elemental analyses were performed by the Microanalytical Services of the Laboratorium für Organische Chemie (ETH).

1. Preparation of the Substrates

Benzylidene azlactones **2b**, **c**, **e**, prepared according to standard procedures [58], were hydrolyzed with KOH/EtOH to the cinnamic acid derivatives **3b**, **c**, **e** [59, 60], which were hydrogenated to give the *N*-benzoylated amino acids **4b**, **c**, **e** in analogy to a literature procedure [44]. Addition of THF (ca. 10 vol %) was necessary in the hydrogenation reactions to dissolve the starting material. *N*-benzoylated amino acids **4a**, **d**, **f** and **g** were prepared by benzoylation of the corresponding commercially available amino acids with benzoyl chloride [61]. Azlactones **5a**-**g** were prepared from *N*-benzoylated amino acids by dehydration with acetic anhydride [37]. If not otherwise noted, all products were recrystallized from EtOH.

4-Naphthalen-1-ylmethylene-2-phenyl-4H-oxazol-5-one (**2e**): Yield 71%; mp. 166°C, ([62]: mp. 160°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.04-9.01 (*m*, 1H), 8.31-8.28 (*m*, 1H), 8.21-8.18 (*m*, 2H), 8.11 (*s*, 1H), 7.97-7.88 (*m*, 2H), 7.66-7.50 (*m*, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.59, 163.95, 133.77, 133.60, 133.31, 132.36, 131.94, 131.85, 129.19, 129.05, 128.87, 128.35, 127.36, 126.80, 126.15, 125.66, 125.52, 122.67. MS (EI): *m/z* = 299 (100) [M^+], 166 (3), 139 (2), 105 (52), 77 (8). IR ($CHCl_3$): $\tilde{\nu}$ = 3062w, 1792s, 1648s, 1600w, 1589w, 1573m, 1555w, 1510w, 1491w, 1450w, 1338m, 1325m, 1297m, 1168m, 1112w, 1071w, 1041w, 1020w, 980m, 875m.

2-Benzoylamino-3-p-tolyl-acrylic acid (**3b**): Yield 64%; mp. 227-228°C, ([63]: mp. 221-222°C); ^{1}H NMR (400 MHz, D_6-DMSO): δ = 12.69 (*s*, 1H), 9.88 (*s*, 1H), 7.99-7.98 (*m*, 2H), 7.61-7.43 (*m*, 6H), 7.20-7.18 (*m*, 2H), 2.29 (*s*, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.34, 165.82, 139.09. 133.53, 133.17, 131.64, 130.87, 129.69, 129.08, 128.36, 127.56, 126.44, 20.84. MS (FAB): *m/z* = 563 (6) [M_2H^+], 320 (20), 307 (17), 289 (11), 283 (21), 282 (100) [MH^+], 281 (43) [M^+], 264 (11), 192 (17), 107 (16), 106 (10), 105 (65), 91 (12), 89 (13), 77 (18); IR (KBr): $\tilde{\nu}$ = 3259m, 2962w, 1701s, 1643s, 1604w, 1581w, 1504m, 1480m, 1427m, 1321w, 1292w, 1262m, 1189m, 1154m, 908m, 808m, 798w, 731m, 687m.

2-Benzoylamino-3-(4-methoxy-phenyl)-acrylic acid (**3c**): Yield 75%; mp. 224°C ([64]: mp. 229-230°C); ^{1}H NMR (400 MHz, D_6-DMSO): δ = 12.60 (s, 1H), 9.84 (*s*, 1H), 8.01-7.99 (*m*, 2H), 7.66-7.45 (*m*, 6H), 6.98-6.94 (*m*, 2H), 3.76 (*s*, 3H). ^{13}C NMR (100 MHz, D_6-DMSO): δ = 166.46, 165.82, 160.06, 133.59, 133.30, 131.61, 131.55, 128.36, 127.56, 126.11, 124.90, 114.01, 55.14. MS (FAB): *m/z* = 892 (3) [M_3H^+], 633 (14), 617 (11), 596 (9), 595 (22) [M_2H^+], 336 (32), 320 (19), 307 (19), 298 (100) [MH^+], 297 (70) [M^+], 289 (11), 280 (20), 192 (28), 176 (18), 108 (15), 106 (10), 105 (52), 89 (12), 77 (17); IR (KBr): $\tilde{\nu}$ = 3283m, 2971w, 1694s, 1648s, 1605s, 1574w, 1505m, 1481m, 1433m, 1253s, 1173m, 1117w, 1027m, 914m, 894w, 821m, 690m.

2-Benzoylamino-3-naphthalen-1-yl-acrylic acid (**3e**): Yield 69%, mp. 212-214°C ([65]: mp. 221°C); ^{1}H NMR (400 MHz, CD_3OD): δ = 8.19 (s, 1H), 8.05-7.97 (*m*, 1H), 7.84-7.66 (*m*, 5H), 7.52-7.35 (*m*, 6H); ^{13}C NMR (100 MHz, CD_3OD): δ = 169.94, 168.00, 135.00, 134.85, 133.61, 132.99, 132.66, 132.05, 130.60, 129.64, 129.61, 129.46, 128.64, 127.67, 127.65, 127.13, 126.21, 125.15; MS (FAB): *m/z* = 952 (7) [M_3H^+], 636 (26), 635 (51) [M_2H^+], 471 (11), 460 (13), 346 (12), 319 (29), 318 (100) [MH^+], 317 (44), 307 (30), 289 (12), 105 (19), 77 (7); IR (KBr): $\tilde{\nu}$ = 3228m, 3058m, 1685s, 1646s, 1602m, 1579m, 1513s, 1481s, 1139m, 1340m, 1279s, 1209m, 1151m, 1111w, 948m, 923m, 862w, 795m, 777m, 767m, 714s, 698m, 687m, 620m.

2-Benzoylamino-3-p-tolyl-propionic acid (**4b**): Yield 69%; mp. 177-178°C ([66]: mp. 179.5-180.5°C). For analytical and spectroscopic data see the literature [63].

2-Benzoylamino-3-(4-methoxy-phenyl)-propionic acid (**4c**): Yield 87%; mp. 174-175°C ([67]: mp. 175-176°C). For analytical and spectroscopic data see the literature [63].

2-Benzoylamino-3-naphthalen-1-yl-propionic acid (**4e**): Yield 75%; mp. 203-207°C ([68]: mp. 192-193°C; [69]: mp. 245-246°C). For analytical and spectroscopic data see the literature [63].

4-(4-Methyl-benzyl)-2-phenyl-4H-oxazol-5-one (**5b**): Yield 74%; mp. 75°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95-7.92 (*m*, 2H), 7.58-7.43 (*m*, 3H), 7.18-7.06 (*m*, 4H), 4.69-4.65 (*m*, 1H), 3.37-3.31 (*m*, 1H), 3.19-3.12 (*m*, 1H), 2.28 (*s*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.79, 161.77, 136.84, 132.73, 132.28, 129.51, 129.21, 128.79, 127.98, 125.97, 66.65, 36.85, 20.91. MS (EI): *m/z* = 265 (3) [M^+], 105 (100), 77 (21), 51 (6). IR ($CHCl_3$): $\tilde{\nu}$ = 3008w, 2927w, 1818s, 1654s, 1580w, 1515m, 1496w, 1451m, 1324m, 1306m, 1150w, 1075m, 1048s, 1024m, 965m, 915m, 890m. Anal. calcd. for $C_{17}H_{15}NO_2$ (265.31): C 76.96, H 5.70, N 5.28; found: C 77.02, H 5.84, N 5.27.

4-(4-Methoxy-benzyl)-2-phenyl-oxazol-5-one (**5c**): Yield 85%; mp. 64°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.95-7.90 (*m*, 2H), 7.59-7.41 (*m*, 3H), 7.27-7.16 (*m*, 2H), 6.81-6.76 (*m*, 2H), 4.69-4.63 (*m*, 1H), 3.75 (*s*, 3H), 3.40-3.10 (*m*, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.64, 161.64, 158.71, 132.65, 130.65, 128.71, 127.86, 127.16, 125.82, 113.79, 66.76, 55.14, 36.43; MS (EI): *m/z* = 281 (0.6) [M^+], 121 (100), 105 (6), 77 (11); IR ($CHCl_3$): $\tilde{\nu}$ = 3008w, 2838w, 1817s, 1655s, 1613m, 1581w, 1513s, 1452m, 1325m, 1302 m, 1048s, 890m, 829m; Anal. calcd. for $C_{17}H_{15}NO_3$ (281.31): C 72.58, H 5.37, N 4.98; found: C 72.33, H 5.54, N 4.98.

4-(4-Chloro-benzyl)-2-phenyl-4H-oxazol-5-one (**5d**): Yield 77%; mp. 60-61°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93-7.91 (*m*, 2H), 7.59-7.43 (*m*, 3H), 7.62-7.18 (*m*, 4H), 4.68-4.65 (*m*, 1H), 3.38-3.32 (*m*, 2H), 3.19-3.12 (*m*, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.30, 161.95, 133.69, 133.20, 132.89, 130.97, 128.80, 128.60, 127.90, 125.59, 66.29, 36.53; MS (EI): *m/z* = 285 (5) [M^+], 127 (31), 126 (7), 125 (100), 105 (22), 77 (21), IR ($CHCl_3$): $\tilde{\nu}$ = 3008m, 1818s, 1654s, 1601w, 1580w, 1494s, 1451m, 1410w, 1324m, 1300m, 1150m, 1093m, 1048s, 1024m, 968m, 915w, 890m, 826m. Anal. calcd. for $C_{16}H_{12}NO_2Cl$ (285.73): C 67.26, H 4.23, N 4.90; found: C 67.12, H 4.34, N 4.84.

4-Naphthalen-1-ylmethyl-2-phenyl-4H-oxazol-5-one (**5e**): Yield 92%; mp. 92-93°C; ^{1}H NMR (400 MHz, CDCl3): δ = 8.17-8.15 (*m*, 1H), 7.90-7.76 (*m*, 4H), 7.58-7.40 (*m*, 7H), 4.83-4.80 (*m*, 1H), 3.86-3.50 (*m*, 2H); ^{13}C NMR (100 MHz, CDCl3): δ = 177.78, 161.69, 133.91, 132.70, 131.92, 131.87, 128.84, 128.70, 128.14, 128.02, 127.91, 126.13, 125.80, 125.66, 125.38, 123.77, 66.20, 34.74; MS (EI): *m/z* = 301 (6) [M^+], 142 (12), 141 (100), 105 (6), 77 (5); IR (CHCl3): $\tilde{\nu}$ = 3008w, 1814s, 1654s, 1599w, 1580w, 1512w, 1496w, 1451m, 1323m, 1307m, 1151m, 1076m, 1061m, 1041m, 1029m, 989w, 957w, 919m, 884m; Anal. calcd. for $C_{20}H_{15}NO_2$ (301.34): C 79.72, H 5.02, N 4.65; found: C 79.72, H 5.18, N 4.56.

2-Phenyl-4-thiophen-2-ylmethyl-4H-oxazol-5-one (**5f**): Yield 87% (crude product; after CC 42%, after recrystallization from EtOH 33%); R_f= 0.49 (toluene:AcOEt 98:2); mp. 47°C; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.99-7.94 (*m*, 2H), 7.73-7.43 (*m*, 3H), 7.14-7.11 (*m*, 1H), 6.93-6.87 (*m*, 2H), 4.72-4.67 (*m*, 1H), 3.65-3.55 (*m*, 1H), 3.52-3.42 (*m*, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.24, 162.57, 136.55, 132.93, 128.87, 128.09, 127.25, 126.93, 125.86, 125.28, 66.24, 31.30; MS (EI): *m/z* = 257 (6) [M^+], 105 (26), 98 (11), 97 (100), 77 (25); IR ($CHCl_3$): $\tilde{v}$ = 3007w, 1818s, 1654s, 1580w, 1495w, 1452m, 1324m, 1309m, 1284w, 1155w, 1132w, 1049m, 1022m, 956w, 889m; Anal. calcd. for $C_{14}H_{11}NO_2S$ (257.31): C 65.35, H 4.31, N 5.44; found: C 65.34, H 4.29, N 5.40.

4-(4-Nitro-benzyl)-2-phenyl-4H-oxazol-5-one (**5g**): Yield 69%; mp. 147°C ([70]: mp. 147-148°C); ^1H NMR (200 MHz, $CDCl_3$): δ = 8.17-8.14 (*m*, 2H), 7.96-7.90 (*m*, 2H), 7.62-7.43 (*m*, 4H), 4.76-4.70 (*m*, 1H), 3.54-3.44 (*m*, 1H), 3.33-3.23 (*m*, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.13, 162.34, 147.41, 143.02, 133.19, 130.61, 128.95, 127.98, 125.39, 123.71, 65.77, 36.77; MS (EI): *m/z* = 296 (4)[M^+], 160 (43), 106 (13), 105 (100), 77 (29), 51 (6); IR ($CHCl_3$): $\tilde{v}$ = 3011m, 1816s, 1654s, 1602m, 1580w, 1523s, 1496w, 1452w, 1349s, 1322m, 1298m, 1048m, 918w, 890w, 856w.

2. *Enantioselective Ring opening of Azlactones*

General Procedure for the Ti-TADDOLate Mediated Ring Opening of Azlactones (GP)

$Ti(O^iPr)_4$ (0.350 ml, 1.19 mmol) was added to a solution of the tetraphenyl TADDOL (0.579 g, 1.24 mmol) in Et_2O (10 ml) at room temperature under an Ar atmosphere. The resulting clear solution was stirred for 4 h, the solvent removed under reduced pressure (HV) and the resulting Ti-TADDOLate **1** dried for 1 h. A cooled solution (ca. -30°C) of an azlactone (**5b–g**, 1 mmol) in THF (5 ml) was added to a precooled solution (-30°C) of **1** (1.19 mmol) in THF (20 ml). The resulting homogeneous solution was stirred at that temperature for 15 min. The reaction mixture was then allowed to stand at -28°C (freezer). The reaction was monitored by ^1H NMR spectroscopy. After completion of the reaction, sat. NH_4Cl soln. (5 ml) was added and the resulting colloidal precipitate was filtered off. The precipitate was resuspended in AcOEt and Et_2O (10 ml each), stirred for 5 min and filtered off again. The filtrates were extracted three times with CH_2Cl_2 (20 ml). The combined organic layers were washed with sat. NaCl soln., dried over Na_2SO_4 and evaporated in *vacuo*. The remaining oil was subjected to FC (toluene:AcOEt 95:5 or 98:2), yielding the recovered TADDOL and the product ester **6b–g** as colorless solids. The following analytical and

spectroscopic data refer to racemic (rac) and enantioenriched (en) esters **6**. For other details (reaction time, yields, selectivities, recrystallization conditions) see Table 1.
Diethoxy-Ti-TADDOLate and di-*tert*-butoxy-Ti-TADDOLate were prepared from TADDOL and Ti(OEt)$_4$ or Ti(O^{t}Bu)$_4$ in analogy to GP.
For the substoichiometric use of Ti-TADDOLate, 0.7 equiv. of Ti-TADDOLate **1** were prepared according to GP; 0.5 equiv. of Al(O^{i}Pr)$_3$ were added together with the substrate **5a**, the reaction was conducted according to GP.

2-Benzoylamino-3-p-tolyl-propionic acid isopropyl ester (**6b**): R$_f$ = 0.30 (toluene: AcOEt 95:5); mp. 106-107°C (en); $[\alpha]_D^{RT} = +79.5$ (*c* =1, CHCl$_3$) (of a sample with er 99:1); R$_t$ 11.1 (major), 12.9 (minor) (hexane:^{i}PrOH = 95:5); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.74-7.72 (*m*, 2H), 7.52-7.40 (*m*, 3H), 7.09-7.03 (*m*, 4H), 6.59 (*d*, J = 7.4 Hz, 1H), 5.08-4.98 (*m*, 2H), 3.26-3.15 (*m*, 2H), 2.31 (*s*, 3H), 1.26 (*d*, J = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.20, 166.76, 136.67, 134.15, 132.77, 131.68, 129.38, 129.21, 128.60, 127.01, 69.51, 53.63, 37.47, 21.83, 21.77, 21.07; MS (FAB): *m/z* = 327 (26), 326 (100) [M$^+$], 284 (14), 238 (22), 204 (11), 105 (52); IR (CHCl$_3$): $\tilde{\nu}$ = 3432m, 3005m, 2984m, 2935w, 1728s, 1660s, 1603m, 1581m, 1514s, 1446w, 1376s, 1342m, 1146m, 1106s, 1022w, 918w, 894w, 844w, 822w; Anal. calcd. for $C_{20}H_{23}NO_3$ (325.41): C 73.82, H 7.12, N 4.30; found: C 73.65, H 7.07, N 4.45.

2-Benzoylamino-3-(4-methoxy-phenyl)-propionic acid isopropyl ester (**6c**): R$_f$ = 0.22 (toluene:AcOEt 95:5); mp. 112°C (rac) 108-110°C (en); $[\alpha]_D^{RT} = +41.9$ (*c* =1, CHCl$_3$) (of a sample with er 95:5); R$_t$ 17.8 (major), 19.1 (minor) (hexane:^{i}PrOH = 95:5); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.75-7.72 (*m*, 2H), 7.53-7.40 (*m*, 3H), 7.08-7.05 (*m*, 2H), 6.83-6.80 (*m*, 2H), 6.59 (*d*, J = 7.3 Hz, 1H), 5.10-4.97 (*m*, 2H), 3.77 (*s*, 3H), 3.25-3.14 (*m*, 2H), 1.265 (*d*, J = 6.3 Hz, 6H), 1.264 (*d*, J = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.22, 166.74, 158.73, 134.13, 131.70, 130.51, 128.62, 127.89, 127.00, 113.94, 69.52, 55.23, 53.72, 37.04, 21.83, 21.80; MS (FAB): *m/z* = 683 (14) [M$_2$H$^+$], 343 (33), 342 (86) [MH$^+$], 300 (14), 254 (32), 221 (17), 220 (66), 178 (10), 150 (14), 122 (19), 121 (45), 106 (19), 105 (100), 77 (24); IR (CHCl$_3$): $\tilde{\nu}$ = 3431w, 3008w, 1727s, 1660s, 1612m, 1581m, 1512s, 1485m, 1375m, 1105m, 1036w; Anal. calcd. for $C_{20}H_{23}NO_4$ (341.41): C 70.36, H 6.79, N 4.10; found: C 70.37, H 6.89, N 4.06.

2-Benzoylamino-3-(4-chloro-phenyl)-propionic acid isopropyl ester (**6d**): R$_f$= 0.30 (toluene: AcOEt 95:5); mp. 102-104°C (rac) 128°C (en); $[\alpha]_D^{RT} = +91.5$ (*c* =1.18, CHCl$_3$) (of a sample with er 97:3); R$_t$ 11.1 (major), 13.1 (minor) (hexane:^{i}PrOH = 95:5); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76-7.76 (*m*, 2H), 7.54-7.50 (*m*, 1H), 7.46-7.41 (*m*, 2H), 7.27-7.23 (*m*, 2H), 7.11-7.07 (*m*, 2H), 6.65 (*d*, J = 7.2 Hz, 1H), 5.08-4.98 (*m*, 2H), 3.30-3.16 (*m*, 2H), 1.262 (*d*, J = 6.3 Hz, 3H), 1.258 (*d*, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.95, 166.77, 134.55, 133.92, 133.03, 131.85, 130.86, 128.69, 128.63, 126.98, 69.82, 53.54, 37.30, 21.81, 21.78. MS (FAB): *m/z* = 348 (35), 347 (27), 346 (100) [M^+], 304 (21), 258 (13), 224 (6), 106 (12), 105 (91); IR ($CHCl_3$): $\tilde{\nu}$ = 3430m, 2985m, 2939w, 2879w, 1728s, 1661s, 1602m, 1580m, 1514s, 1486s, 1375s, 1342m, 1105s, 1016m, 917w, 895w, 848w, 820w; Anal. calcd. for $C_{19}H_{20}NO_3Cl$ (345.83): C 65.99, H 5.83, N 4.05; found: C 65.88, H 5.95, N 4.06.

2-Benzoylamino-3-naphthalen-1-yl-propionic acid isopropyl ester (**6e**): R_f = 0.35 (toluene: AcOEt 95:5); mp. 131-132°C (rac); $[\alpha]_D^{RT}$ = +5.9 (*c* = 1, CHCl3) (of a sample with er 99:1); R_t 16.0 (major), 17.3 (minor) (hexane:^{i}PrOH = 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23-8.18 (*m*, 1H), 7.86-7.84 (*m*, 1H), 7.78-7.76 (*m*, 1H), 7.68-7.65 (*m*, 2H), 7.54-7.31 (*m*, 7H), 6.66 (*d*, J = 7.4 Hz, 1H), 5.18-5.16 (*m*, 1H), 4.94 (*sept*, J = 6.3 Hz, 1H) 3.76-3.61 (*m*, 2H), 1.15 (*d*, J = 6.3 Hz, 6H), 1.04 (*d*, J = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.50, 166.96, 133.98, 133.88, 132.55, 132.41, 131.68, 128.77, 128.54, 127.96, 127.69, 127.02, 126.38, 125.76, 125.23, 123.86, 69.55, 53.78, 35.56, 21.70, 21.46; MS (FAB): *m/z* = 723 (11) [M_2H^+], 363 (39), 362 (94) [MH^+], 348 (12), 320 (12), 241 (11), 240 (37), 141 (21), 106 (19), 105 (100), 77 (23); IR ($CHCl_3$): $\tilde{\nu}$ = 3430m, 3008m, 2985m, 1728s, 1659s, 1602w, 1580w, 1514s, 1485s, 1377m, 1105s, 1021w, 917w; Anal. calcd. for $C_{23}H_{23}NO_3$ (341.41): C 76.43, H 6.41, N 3.88; found: C 76.25, H 6.28, N 3.91.

2-Benzoylamino-3-thiophen-2-yl-propionic acid isopropyl ester (**6f**): R_f = 0.23 (toluene: AcOEt 98:2); mp. 104-107°C (en); $[\alpha]_D^{RT}$ = +64.3 (*c* =0.77, $CHCl_3$) (of a sample with er > 99:1); R_t 12.8 (*S*), 13.4 (*R*) (hexane:^{i}PrOH = 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81-7.78 (*m*, 2H), 7.54-7.42 (*m*, 3H), 7.18-7.16 (*m*, 1H), 6.94-6.92 (*m*, 1H), 6.82-6.78 (*m*, 2H), 5.10-5.00 (*m*, 2H), 3.57-3.46 (*m*, 2H), 1.30 (*d*, J = 6.3 Hz, 3H), 1.28 (*d*, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.54, 166.83, 137.28, 134.06, 131.78, 128.64, 127.07, 126.94, 126.93, 124.87, 69.88, 53.38, 32.08, 21.82, 21.81; MS (FAB): *m/z* = 635 (5) [M_2H^+], 319 (22), 318 (100) [M^+], 317 (6), 276 (20), 230 (13), 196 (17), 105 (53), 304 (21), 258 (13), 224 (6), 106 (12), 105 (91); IR ($CHCl_3$): $\tilde{\nu}$ = 3428w, 3014s, 2985m, 2340w, 1731s, 1661s, 1603w, 1581w, 1515s, 1485s, 1436m, 1375s, 1340m, 1105s, 892m; Anal. calcd. for $C_{17}H_{19}NO_3S$ (317.41): C 64.33, H 6.03, N 4.41; found: C 64.42, H 6.06, N 4.38.

2-Benzoylamino-3-(4-nitro-phenyl)-propionic acid isopropyl ester (**6g**): R_f = 0.16 (toluene: AcOEt 95:5); mp. 160°C (rac); $[\alpha]_D^{RT}$ = +63.6 (*c* =1, $CHCl_3$) (of a sample with er 99:1); R_t 24.3 (major), 29.7 (minor) (hexane:^{i}PrOH = 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16-8.13 (*m*, 2H), 7.76-7.73 (*m*, 2H), 7.56-7.51 (*m*, 1H), 7.47-7.42 (*m*, 2H), 7.37-7.33 (*m*, 2H), 6.72 (*d*, J = 7.0 Hz, 1H), 5.12-5.03 (*m*, 2H), 3.46-3.29 (*m*, 2H), 1.268 (*d*, J = 6.3 Hz, 6H), 1.266 (*d*, J = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.64, 166.87, 147.21, 144.02, 133.62, 132.06, 130.42, 128.78, 126.96, 123.63, 70.23, 53.41, 37.88, 21.81, 21.79; MS (FAB): *m/z* = 1069 (1) [M_3H^+], 714 (15), 713 (37) [M_2H^+], 358 (30), 357 (100) [MH^+], 315 (11), 105 (40); IR ($CHCl_3$): $\tilde{\nu}$ = 3427m, 2986w, 1730s, 1662s, 1603m, 1581w, 1523s, 1485m, 1376m, 1347s, 1104m, 895w, 858w; Anal. calcd. for $C_{19}H_{20}N_2O_5$ (356.38): C 64.04, H 5.66, N 7.86; found: C 63.97, H 5.66, N 7.89.

2-Benzoylamino-4-phenyl-butyric acid isopropyl ester (**7**): R_f = 0.35 (toluene: AcOEt 95:5); mp. 103-104°C (en); $[\alpha]_D^{RT}$ = +24.8 (c =1, $CHCl_3$) (of a sample with er 87:13); R_t 13.0 (major), 14.0 (minor) (hexane:iPrOH = 98:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75-7.72 (*m*, 2H), 7.53-7.40 (*m*, 3H), 7.30-7.26 (*m*, 2H), 7.20-7.17 (*m*, 3H), 6.71 (*d*, J = 7.6 Hz, 1H), 5.10 (*sept*, J = 6.3 Hz, 1H), 4.88-4.83 (*m*, 1H), 2.80-2.65 (*m*, 2H), 2.36-2.28 (*m*, 1H), 2.17-2.08 (*m*, 1H), 1.299 (*d*, J = 6.3 Hz, 6H), 1.297 (*d*, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.96, 166.96, 140.97, 134.03, 131.71, 128.58, 128.57, 128.42, 127.04, 126.19, 69.48, 52.71, 34.24, 31.67, 21.81, 21.79; MS (FAB): *m/z* = 651 (9) $[M_2H^+]$, 327 (23), 326 (79) $[MH^+]$, 284 (11), 221 (10), 134 (10), 122 (11), 117 (10), 105 (100), 91 (16), 77 (20); IR ($CHCl_3$): $\tilde{\nu}$ = 3433m, 3008m, 2984m, 1726s, 1662s, 1603w, 1581w, 1514s, 1485m, 1454w, 1376m, 1105s, 908w, 822w; Anal. calcd. for $C_{20}H_{23}NO_3$ (325.41): C 73.82, H 7.12, N 4.30; found: C 73.55, H 7.30, N 4.38.

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