Scope and Limitations of the $TiCl_4$-Mediated Additions of Isocyanides to Aldehydes and Ketones with Formation of α-Hydroxycarboxylic Acid Amides[1)]

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The adducts obtained from $TiCl_4$ and achiral (**8**–**12**) or chiral, nonracemic (**13**–**22**) isocyanides are combined with aldehydes (aromatic or aliphatic) and ketones (acetone, cyclohexanone, acetophenone) to give, after aqueous workup, α-hydroxyamides (**27**–**55**) [Passerini-type reaction]. The transformation is compatible with a variety of functional groups (aromatic and heterocyclic rings, amino, ether, ester, and amido groups, halides, and phosphonate substituents). The yields range from 14 to over 95% (with the lower values in the case of more highly functionalised isocyanides). No diastereoselectivity is observed with chiral isocyanides. If the R groups of the isocyanide (R–NC) form a rather stable cation (*t*-alkyl or benzylic), cyanohydrins may result from the reaction, rather than the *N*-substituted α-hydroxyamides (see Scheme 2).

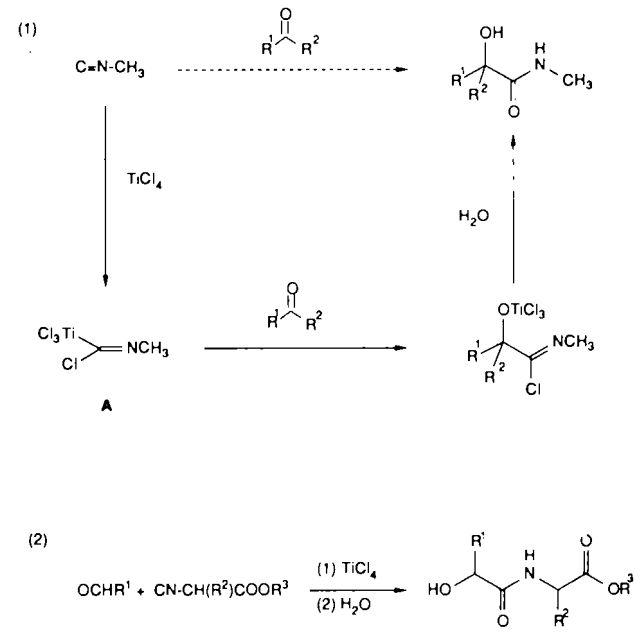
Anwendungsbreite der $TiCl_4$-induzierten Addition von Isocyaniden an Aldehyde und Ketone unter Bildung von α-Hydroxycarbonsäureamiden[1)]

Die Umsetzung der aus achiralen (**8**–**12**) oder chiralen (**13**–**22**) Isocyaniden und $TiCl_4$ gebildeten Addukte mit aliphatischen oder aromatischen Aldehyden oder mit Ketonen (Aceton, Cyclohexanon, Acetophenon) liefert nach wäßriger Aufarbeitung α-Hydroxyamide (**27**–**55**) in einer Passerini-artigen Reaktion. Dies ist mit Substraten durchführbar, welche die verschiedensten funktionellen Gruppen enthalten: aromatische, auch methoxysubstituierte Ringe, Heterocyclen, Amino-, Ether-, Ester- und Amidgruppen, Halogen- und Phosphonatsubstituenten. Die Ausbeuten liegen zwischen 14 und über 95%, wobei die tieferen Werte bei höher funktionalisierten Isocyaniden auftreten. Mit den chiralen Isocyaniden wird keine Diastereoselektivität beobachtet. Bei Derivaten R–NC, deren R-Gruppe relativ stabile Kationen bildet (z. B. *t*-Alkyl-, Benzyl-), kommt es zu einer Cyanhydrine liefernden Konkurrenzreaktion (s. Schema 2).

In 1975 Crociani and his colleagues reported that titanium tetrachloride forms adducts with isocyanides which were unambiguously assigned the C-(trichlorotitanio)formimidoyl structure (**A** in Scheme 1)[6,7)]. Since this is one of the rare cases in which a titanium–carbon bond is formed without intervention of a polar organometallic compound (transmetalation)[8–10)], we decided to investigate the use of such adducts as nucleophilic reagents. In a first paper, we described the additions of methyl isocyanide to aldehydes and ketones to give the *N*-methyl-hydroxyamides shown in Equation (1)[11)]. $TiCl_4$-mediated reactions[12)] of electrophiles other than ketones and aldehydes, such as acetals[13)] and α,β-unsaturated carbonyl compounds[14)], with isocyanides have been known before or were published during our ongoing investigation. We have been mainly interested in extending the scope of the Passerini-type[15,16)] reaction [Equation (1)] with respect to the isocyanide compound[17–21)]. The following questions appeared to be important to us: (i) Which functional groups may be part of the isocyanide structure for the reaction still to take place? (ii) Can isocyanides from α-amino acids be employed, producing fragments of depsipeptides [Equation (2)][22)]? (iii) Are reagents of type **A** diastereoface-selective[23)] in additions to chiral aldehydes? (iv) Do chiral isocyanides show enantioface differentiation in additions to aldehydes and ketones?

The isocyanides for our investigation were purchased or prepared from the corresponding amines. Of the numerous

Scheme 1



methods for this conversion[12)] we chose the formylation with phenyl formate (1-phenylethylamine) or with the mixed anhydride of acetic and formic acid (all other cases), with subsequent dehydration of the formamides using Ugi's methode

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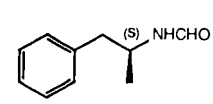
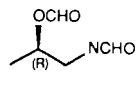
[trichloromethyl chlorocarbonate ("diphosgene")/triethylamine][24]. Of the required formamides the chiral nonracemic representatives **1**–**7** are new.



1



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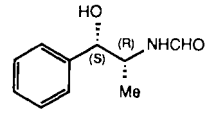

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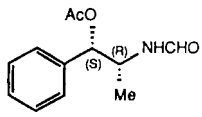

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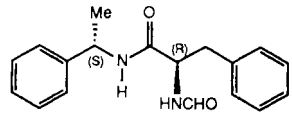

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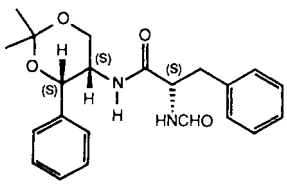

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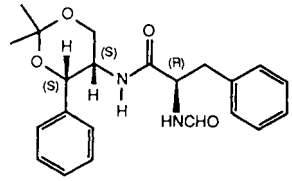
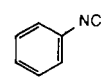


7

The isocyanides used are depicted in the formulae **8**–**24**. For the conversion of the isocyanides **17** and *ent*-**17** from *S*- and *R*-phenylalanine, respectively, the *N*-formyl amino acid esters had to be dehydrated very carefully (−25 °C/*N*-methylmorpholine instead of triethylamine)[24]: in this way we isolated for the first time crystalline (rather than the previously reported oily[24,25]) enantiomerically pure samples of this phenylalanine derivative. The α-isocyano-carboxylic acid amides **22**–**24** posed special problems: while the isocyanoesters **11** and **17** reacted smoothly with *S*-phenylethylamine under TosOH catalysis[26] to give the amides **20** and **21**, respectively, partial or complete epimerisation had occurred at the α-carbonyl position after applying the same procedure to *ent*-**17**! Likewise, diastereoisomeric mixtures were formed when **17** and *ent*-**17** were treated with the (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane in an attempt to prepare **24** and **23**, respectively. Therefore, the amide bond was formed before generating the isocyanide functional group: (*R*)-*N*-formylphenylalanine and (*S*)-phenylethylamine as well as (*R*)- and (*S*)-*N*-formylphenylalanine and the (*S*,*S*)-acetonide of phenylglycinol were condensed (ClCOOEt/*N*-methylmorpholine) to give the corresponding formamidoamides **5**, **6**, and **7**; these were dehydrated to give the isocyanides **22**, **23**, and **24**, respectively (see experimental section). The enantiomerically pure *l*-diastereoisomer **21** was also obtained from the racemic phenylalanine-derived isocyanoester (*rac*-**17**) and enantiomerically pure (*S*)-phenylethylamine in a resolution with in situ recycling: an 8.5:1 mixture of the *l*- (**21**) and *u*-form (**22**) separated after heating the components without solvent for two days at 55 °C – a potentially useful method of preparing (*S*)-phenylalanine derivatives from racemic phenylalanine, with phenylethylamine as a chiral auxiliary! The generality of this procedure and applications with other amino acids are currently being investigated in our laboratory.



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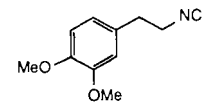

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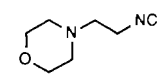

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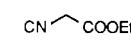

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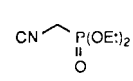

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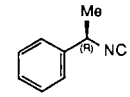

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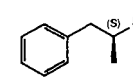

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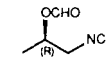

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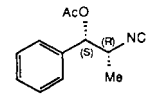

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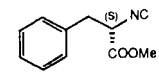

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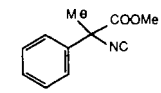
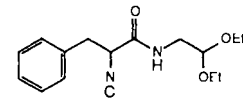
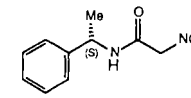


18 *(rac)*



19 *(rac)*



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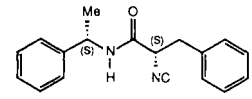

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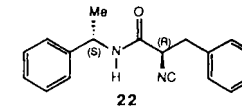

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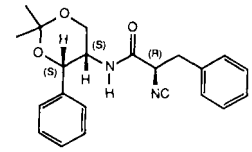

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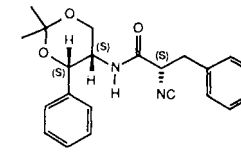
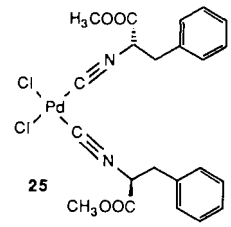


24

The palladium and the platinum complexes **25** and **26** were prepared as derivatives of the isocyanide of phenylalanine[27,28].



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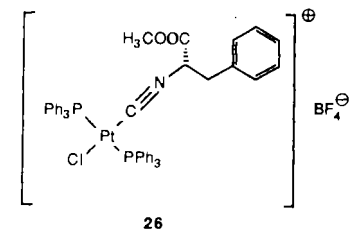
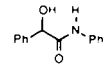
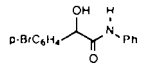
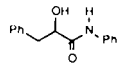
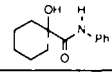
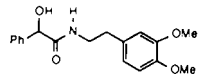
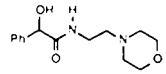
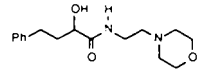
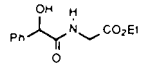
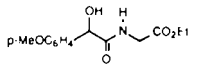


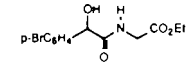
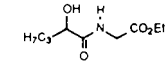
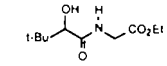
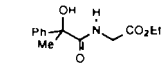
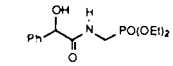
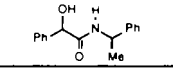
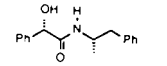
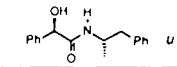
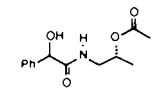
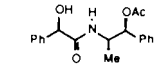
26

Reactions of Isocyanides with Titanium Tetrachloride and Carbonyl Compounds

The isocyanides **8**–**24** were allowed to react first with $TiCl_4$ and then with aldehydes or ketones, as described previously for methyl isocyanide[11]. When equivalent amounts of the isocyanide and the Lewis acid were mixed in dichloromethane at −5 to 0 °C, an insoluble yellow or green-yellow precipitate was formed (presumably an adduct of type **A**,

Table 1. Products from the reactions of isocyanides with aldehydes and ketones. i) The yields from the reactions with isocyanide **8** refer to crude product. – ii) No combustion analyses were obtained for the compounds **41**, **44**, and **51** to **55**, for experimental details please contact the authors. – iii) One diastereoisomer could be isolated in pure form in the cases of **45**, **46**, and **50**, two diastereoisomers in the cases of **42**, **43**, **47**, and **49**

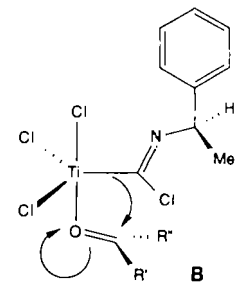
Isocyanide	Aldehyde or Ketone	Product		Yield [%]
8	benzaldehyde		**27**	98
	p-bromobenzaldehyde		**28**	98
	phenylacetaldehyde		**29**	98
	acetone		**30**	88
	cyclohexanone		**31**	59
9	benzaldehyde		**32**	23
10	benzaldehyde		**33**	67
	3-phenylpropanal		**34**	57
11	benzaldehyde		**35**	44
	anisaldehyde		**36**	70

Isocyanide	Aldehyde or Ketone	Product		Yield [%]
11	p-bromobenzaldehyde		**37**	90
	butyraldehyde		**38**	96
	pivalaldehyde		**39**	76
	acetophenone		**40**	81
12	benzaldehyde		**41**	95
13	benzaldehyde		**42**	15
14	benzaldehyde		*l* **43a**	25
			*u* **43b**	22
15	benzaldehyde		**44**	55
16	benzaldehyde		**45**	33

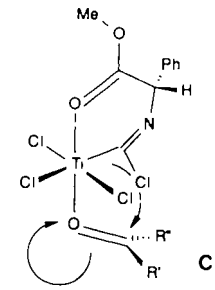
Scheme 1). Subsequent dropwise addition of the carbonyl compound to this suspension at various temperatures usually caused dissolution of the precipitate: within a few minutes a clear yellow to brown solution was obtained. Hydrolytic workup led to the isolation of the crystalline α-hydroxyamides. The results are collected in Table 1.

With achiral (**8**–**12**) and the simple[29] chiral isocyanides (**14**), the yields of hydroxyamides are good to excellent, while additional functional groups in the isocyanides (**15**–**18**, **20**–**22**) cause a decrease of the yields or even prevent the reaction from taking place at all (**23**, **24**)[30].

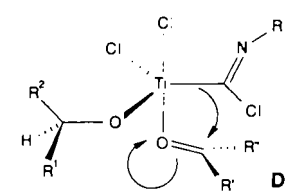
The chiral isocyanides were chosen to test if their $TiCl_4$ adducts show enantioface selectivity in additions to aldehydes. As is evident from the data in Table 1 and in the experimental section, the diastereoisomeric products are formed in ca. 1:1 ratios in all cases. This result might not be too surprising if the reacting species has the *Z* configuration around the CN double bond as depicted in **B**: the stereogenic center is too far away to render the insertion of the aldehyde CO moiety into the TiC bond diastereoselectively. On the other hand, the additional hetero atom in an isocyanide such as the phenylalanine derivative **17** might have caused a geometrical isomerisation to give a chelate bond as shown in **C**, moving the chirality center somewhat closer to the titanium, and thus making the addition diastereoselective.



B



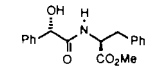
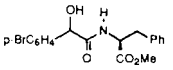
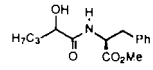
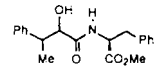
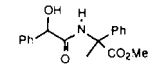
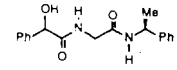
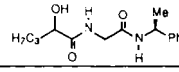
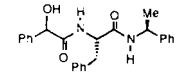
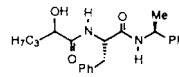
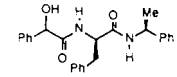
C



D

Finally, we tested whether enantioface differentiation could be observed in the reaction of benzaldehyde and isocyanide **11** in the presence of chiral alkoxy titanates. In

Table 1 (*Continued*)

Isocyanide	Aldehyde or Ketone	Product		Yield [%]
17				
	benzaldehyde		**46**	35
	p-bromobenzaldehyde		**47**	38
	butyraldehyde		**48**	34
	rac-2-phenyl-propanal		**49**	35
rac-**18**	benzaldehyde		**50**	34
20	benzaldehyde		**51**	53
	butyraldehyde		**52**	52
21	benzaldehyde		**53**	31
	butyraldehyde		**54**	16
22	benzaldehyde		**55**	11

this case (**D**) the chirality center would be even closer than in the proposed intermediates **B** and **C**.

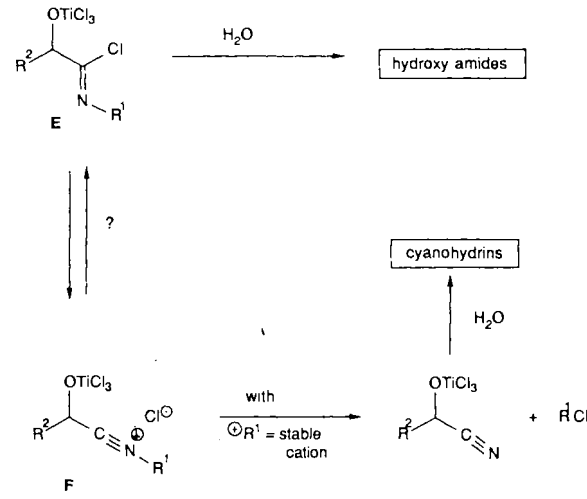
We used (−)-menthoxy-trichloro-titanium and the (+)-diethyl tartrate dichloro complex for this test. While the reaction with titanium tetrachloride was complete after 2 h at 0 - 5 °C, 15 h at room temperature were necessary with the menthoxy derivative. The bidentate ligand prevented a reaction from taking place at all. The product **35** obtained with the menthoxy complex was optically inactive, i.e. a racemic mixture. Thus, all attempts to carry out our modification of the Passerini reaction stereoselectively failed.

In some cases (**42**, **43**, **45**, **46**−**50**, **54**) one or two diastereoisomers could be isolated in pure form by crystallisation and/or flash chromatography. Thus, the enantiomerically pure depsipeptide fragments **46**−**49** and the racemic analogue **50** containing an α-branched amino acid moiety were obtained. With one exception (**46**)[22b], the (relative) configurations of these products were not determined.

In an attempt to find out wether the reaction with a chiral aldehyde is subject to 1,2-induction (Crams's rule)[31−33], we employed *rac*-2-phenylpropanal with the phenylalanine derivative **17** as the isocyanide component: the four possible diastereoisomers of **49** were obtained in equal amounts (by ^{1}H NMR analysis of the crude product).

Analysis of the crude products formed in the reaction of (*R*)-phenylethyl isocyanide (**13**) or *t*-butyl isocyanide with benzaldehyde showed the desired α-hydroxyamides to be present only in low yield. The main product in both cases were the cyanohydrins. In addition we isolated 1-phenylethyl chloride from reaction mixtures involving phenylethyl isocyanide (**13**).

Scheme 2



Similar observations have been made for reactions of isocyanides with acetals[13] (in addition to alkoxy carboxamides, cyanohydrin ethers were formed[13e]) and α,β-unsaturated ketones[14b] in the presence of $TiCl_4$. Obviously, the intermediates of these transformations (**E** in our case, Scheme 2) give rise to cations (see **F**) which can split off the substituent from nitrogen if the resulting cation is tertiary or benzylic, i.e. rather stable. The intermediate **F** is reminiscent of the cation which is thought to be involved in the Beckmann, von Braun, and Ritter reactions[34].

We thank Dr. *E. Zass* for helpful discussions, Dr. *B. Jaun* and Miss *B. Brandenberg* for recording the ^{1}H-NMR spectra. Financial support from the *Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung* (Project No 2.253−0.84) and the *Deutsche Forschungsgemeinschaft* (for W. W.), and from the *Hermann-Schlosser-Stiftung* (for G. A.) is gratefully acknowledged.

Experimental

General: Melting points were determined with a Büchi/Tottoli melting point apparatus and are uncorrected. – TLC: Kieselgel Fertigplatten 60 F_{254} (Merck); visualised with UV or with a solution of 360 ml of 95% EtOH, 18 ml of conc. H_2SO_4, 3 ml of acetic acid, and 9 ml of anisaldehyde. – Fluka Kieselgel 60 (silica, mesh size 0.040−0.063) was used for flash chromatography. – Specific rotations were determined with a Perkin-Elmer 241 polarimeter at room temperature. – IR spectra were recorded using a Perkin-Elmer 297 spectrometer. – ^{1}H-NMR spectra were obtained with either a Varian EM-390 (90 MHz) or a Bruker WM 300 (300 MHz) instrument. ^{13}C-NMR spectra were obtained using a Varian CFT-20 instrument, ^{31}P-NMR spectra with a Bruker HX 90 instrument (90 MHz). All spectra were recorded using TMS as internal standard in $CDCl_3$ as solvent, if not otherwise mentioned. The diastereomeric excess was deduced by NMR analysis of the crude product. – Mass spectra were recorded with a Hitachi-Perkin-Elmer RMV 6 M instrument. – All solvents, except for dichloromethane, were of "purissimum" quality. Dichloromethane was distilled from

P_4O_{10}. (−)-Menthoxytrichloro titanate was obtained according to ref.[8b,35]. – All reactions were carried out in oven-dried glassware under argon.

Preparation of the N-Formamides. – General Procedure 1 (GP 1): Synthesis of the *N*-formamides **1**–**4**. To the amine in 50 ml dichloromethane were added four equivalents of the mixed formic acetic anhydride. When TLC showed the absence of starting material, the reaction mixture was poured into 200 ml of saturated aqueous hydrogen carbonate and extracted with ether. The combined organic layers were dried, the solvent was evaporated, and the residue was distilled or recrystallised.

N-[(S)-1-Methyl-2-phenylethyl]formamide (**1**): According to *GP 1*, 11.5 g (85 mmol) of (*S*)-1-phenyl-2-propaneamine yielded 11.5 g (82%) of **1**. – $[\alpha]_D = -11.4$ ($c = 5.1$ in $CHCl_3$). – ^1H NMR (90 MHz): δ = 1.10 (d, $J = 7$ Hz, 3H, CH_3), 2.73 (t, $J = 7$ Hz, 2H, CH_2), 4.26 (m, 1H, $H-C-CH_3$), 6.56 (br. s, 1H, HN), 7.16 (s, 5H, aromatic H), 7.93 (s, 1H, CHO).

(R)-2-Formamido-1-methylethyl Formate (**2**): According to *GP 1*, 10 g (0.133 mol) of (*R*)-(+)-1-amino-2-propanol yielded 9.5 g (54%) of **2**; b.p. 84 °C/0.4 Torr. – IR ($CHCl_3$): ν = 3310 cm^{-1} (NH), 1718 (C=O), 1680 (C=O), 1650 (amide I), 1520 (amide II). – ^1H NMR (90 MHz): δ = 1.32 (d, $J = 7$ Hz, 3H, CH_3), 3.44 (m, 2H, CH_2), 4.9–5.3 (br. m, 1H, $H-C-CH_3$), 6.90 (br. s, 1H, NH), 8.10 (s, 1H, NCHO), 8.20 (s, 1H, OCHO).

(1S,2R)-2-Formamido-1-phenylpropanol (**3**): From 25 g (0.165 mol) of (1*S*,2*R*)-2-amino-1-phenylpropanol according to *GP 1* was obtained 12.3 g (42%) of **3** as colourless crystals; m.p. 72–73 °C (ether). – $[\alpha]_D = -96$ ($c = 1$ in $CHCl_3$). – IR (KBr): ν = 3350 cm^{-1} (OH), 3220 (NH), 1635 (amide I), 1560, 1535 (amide II). – ^1H NMR: δ = 0.98 (d, $J = 7$ Hz, 3H, CH_3), 3.77 (d, $J = 4$ Hz, 1H, OH), 4.28–4.33 (m, 1H, $H-C-CH_3$), 4.83 (t, $J = 4$ Hz, 1H, $H-COH$), 6.18 (br. d, $J = 6$ Hz, 1H, NH), 7.22–7.36 (m, 5H, aromatic H), 8.04 (d, $J = 1$ Hz, 1H, CHO). – MS: *m/z* (%) = 180 (0.1, $M^+ + 1$), 162 (6.2), 58 (100).

$C_{10}H_{13}NO_2$ (179.2) Calcd. C 67.02 H 7.31 N 7.82
Found C 66.98 H 7.43 N 7.90

(1S,2R)-2-Formamido-1-phenylpropyl Acetate (**4**): To a solution of 8.9 g (50 mmol) of **3** in 40 ml of pyridine was added 5.2 ml of acetic anhydride at 0 °C. After stirring for 70 h at room temperature, 50 ml of dichloromethane was added and the solution washed with five 20-ml portions of saturated aqueous copper(II) sulfate and saturated aqueous sodium chloride. The organic layer was dried (magnesium sulfate), filtered, and the solvent evaporated to give 7.2 g (65%) of **4** as colourless crystals; m.p. 88–91 °C (ether), $[\alpha]_D = -96$ ($c = 1$ in $CHCl_3$). – IR ($CHCl_3$): ν = 3420 cm^{-1} (NH), 1770 (C=O), 1670 (amide I), 1490, 1450. – ^1H NMR (90 MHz): δ = 1.08 (d, $J = 7$ Hz, 3H, CH_3), 2.10 (s, 3H, $COCH_3$), 4.52 (br. m, 1H, $H-C-CH_3$), 5.82 (d, $J = 4$ Hz, 1H, H–C–O), 5.90–6.20 (br. s, 1H, NH), 7.29 (s, 5H, aromatic H), 8.03 (s, 1H, CHO).

$C_{12}H_{15}NO_3$ (221.3) Calcd. C 65.14 H 6.87 N 6.33
Found C 65.09 H 6.82 N 6.30

(1'S,2R)-2-Formamido-3-phenyl-N(1-phenylethyl)propionamide (**5**): (*R*)-*N*-Formylphenylalanine (3.0 g, 15.5 mmol) and 2.2 ml (17.0 mmol) of (*S*)-1-phenylethylamine were coupled according to the procedure described in ref.[36]. White powder, 3.46 g (76%), m.p. 154–155 °C, $[\alpha]_D = -18$ ($c = 1.2$ in CH_2Cl_2). – IR (KBr): ν = 3300 cm^{-1} (NH), 1660, 1640 (C=O, amide I), 1545 (amide II). – ^1H NMR: δ = 1.23 (d, $J = 6.9$ Hz, 3H, CH_3), 2.98 (dd, $J = 13.5$ Hz, $J = 8.8$ Hz, 1H, CH_aH_b), 3.18 (dd, $J = 13.5$ Hz, $J = 5.9$ Hz, 1H, CH_aH_b), 4.65–4.72 (m, 1H, $HCCH_3$), 4.89–4.94 (m, 1H, HCCO), 5.93 (d, $J = 7.2$ Hz, 1H, NH), 6.53 (d, $J = 7.8$ Hz, 1H, NH), 7.10–7.35 (m, 10H, aromatic H), 8.04 (s, 1H, CHO). – MS (70 eV): *m/z* (%) = 296 (4, M^+).

$C_{18}H_{20}N_2O_2$ (296.4) Calcd. C 72.95 H 6.80 N 9.45
Found C 72.85 H 6.90 N 9.32

(2S,4'S,5'S)-N-(2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-2-Formamido-3-phenylpropionamide (**6**): (*S*)-*N*-Formylphenylalanine (1.93 g, 10.0 mmol) and 2.0 ml (11.0 mmol) of (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane gave according ro ref.[36] 3.2 g (84%) of the light yellow crude product. This could be used for the following step. A small sample was recrystallised for the spectroscopic data; m.p. 80–81 °C, $[\alpha]_D = +59.7$ ($c = 1.0$ in CH_2Cl_2). – IR (KBr): ν = 3265 cm^{-1} sh (NH), 1670, 1645 (C=O, amide I), 1539 (amide II). – ^1H NMR: δ = 1.53 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 2.54 (dd, $J = 14.2$ Hz, $J = 6.7$ Hz, 1H, CH_aH_bPh), 2.67 (dd, $J = 14.2$ Hz, $J = 5.7$ Hz, 1H, CH_aH_bPh), 3.82 (dd, $J = 11.9$ Hz, $J = 1.6$ Hz, 1H, $NCHCH_2O$), 4.17–4.26 (m, 2H, CH_2O), 4.67–4.73 (m, 1H, $HNCHCH_2Ph$), 5.21 (d, $J = 1.6$ Hz, 1H, OCHPh), 6.24 (br. d, $J = 6.6$ Hz, 1H, NH), 6.62 (br. d, $J = 8.8$ Hz, NH), 6.72–7.37 (m, 10H, aromatic H), 8.05 (s, 1H, CHO). – ^{13}C NMR ($CDCl_3$): δ = 18.48, 29.47, 37.93, 47.30, 52.22, 64.29, 71.78, 99.55, 125.4, 126.7, 127.7, 128.2, 129.1, 136.9, 138.4, 160.7, 170.1. – MS (70 eV): *m/z* (%) = 382 (0.1, M^+).

$C_{22}H_{26}N_2O_4$ (382.5) Calcd. C 69.09 H 6.85 N 7.32
Found C 69.08 H 7.07 N 7.23

(2R,4'S,5'S)-N-(2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-2-formamido-3-phenylpropionamide (**7**): (*R*)-*N*-Formylphenylalanine (4.56 ml, 22.0 mmol) and 3.87 g (20.0 mmol) of (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane gave 7.34 g (96%) of the crystalline crude product[36], which was recrystallised from ether; m.p. 130.0–130.5 °C, $[\alpha]_D = +74.3$ ($c = 1.1$ in CH_2Cl_2). – IR (KBr): ν = 3260 cm^{-1} br. (NH), 1690, 1670, 1645 (C=O, amide I), 1530 (amide II). – ^1H NMR: δ = 1.47 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.91–2.94 (m, 2H, CH_2Ph), 3.64 (dd, $J = 12.0$ Hz, $J = 1.9$ Hz, 1H, CH_aH_bO), 4.08–4.12 (m, 1H, $HNCHCH_2O$), 4.18 (dd, $J = 12.0$ Hz, $J = 1.9$ Hz, 1H, CH_aH_bO), 4.50–4.57 (m, 1H, $NCHCH_2Ph$), 5.12 (d, $J = 1.8$ Hz, 1H, OCHPh), 5.93 (d, $J = 7.0$ Hz, 1H, NH), 6.29 (d, $J = 9.2$ Hz, 1H, NH), 7.14–7.95 (m, 10H, aromatic H), 8.05 (s, 1H, CHO). – MS (70 eV): *m/z* (%) = 367 (4, $M^+ - 15$).

$C_{22}H_{26}N_2O_4$ (382.5) Calcd. C 69.09 H 6.85 N 7.32
Found C 68.98 H 6.92 N 7.21

Preparation of the Isocyanides: All reactions involving diphosgene were carried out in a three-necked flask equipped with a dry-ice reflux condenser, a dropping funnel, and an argon inlet.

Phenyl isocyanide (**8**) and 2-(3,4-dimethoxyphenyl)ethylisocyanide (**9**) were prepared according to ref.[12c] and ref.[37], respectively. 2-Morpholinoethylisocyanide (**10**), ethyl isocyanoacetate (**11**) and diethyl isocyanomethylphosphonate (**12**) were purchased from Fluka AG (Buchs). (*R*)-1-Phenylethyl isocyanide (**13**) and *ent*-**13** were prepared according to ref.[38]; $[\alpha]_D = +33.2$ (neat, **13**) [ref.[38]: $[\alpha]_D = +35.8$ (neat)] and $[\alpha]_D = -30$ (neat, *ent*-**13**).

General Procedure 2 (GP 2): Dehydration of the *N*-formamides **1**, **2**, and **4**. The *N*-formamide (1 equivalent) was dissolved in dichloromethane and 2.0 to 2.5 equivalents of dry triethylamine were added. The solution was cooled to 0 °C and 0.5 equivalent of diphosgene in dichloromethane was added dropwise. After 1 h, the solution was poured into 50 ml of dist. water and extracted with dichloromethane. The combined organic layers were washed with 7.5% aqueous hydrogen carbonate and dried over activated 4-Å molecular sieves for several hours. Then the solvent was evaporated and the residue distilled under reduced pressure.

(S)-1-Methyl-2-phenylethyl Isocyanide (**14**): Following *GP 2*, 11.5 g (70 mmol) of **1** afforded 5.5 g (53%) of **14**, b.p. 79°C/10^{-3} Torr, $[\alpha]_D$ = +54.6 (neat). – ^{1}H NMR (90 MHz): δ = 1.29 (m, 3H, CH_3), 2.75–2.93 (m, 2H, CH_2), 3.55–3.96 (m, 1H, H–C–CH_3), 7.25 (s, 5H, aromatic H).

(R)-2-Isocyano-1-methylethyl Formate (**15**): From 9.5 g (73 mmol) of **2** following *GP 2* 5 g (61%) of **15** was obtained as a colourless liquid; b.p. 80°C/25 Torr, $[\alpha]_D$ = +39.5 (neat). – ^{1}H NMR (90 MHz): δ = 1.28 (d, *J* = 4 Hz, 3H, CH_3), 3.14–3.52 (m, 2H, CH_2), 5.06–5.11 (br. m, 1H, H–C–O), 7.95 (s, 1H, CHO).

(1S,2R)-2-Isocyano-1-phenylpropyl Acetate (**16**): From 7.1 g (32 mmol) of **4** according to *GP 2* was obtained 5.2 g (80%) of **16** as a pale yellow oil; b.p. 150°C/$8 \cdot 10^{-5}$ Torr, $[\alpha]_D$ = –53.5 (*c* = 1.1 in $CHCl_3$). – IR (film): ν = 2140 cm^{-1} (NC), 1743 (C=O), 1490, 1450. – ^{1}H NMR: δ = 1.31 (d, *J* = 7 Hz, 3H, CH_3), 2.16 (s, 3H, $COCH_3$), 4.04–4.08 (m, 1H, H–C–NC), 5.75 (d, *J* = 4 Hz, 1H, H–C–O), 7.38 (s, 5H, aromatic H).

Methyl (S)-2-Isocyano-3-phenylpropionate (**17**) *and Methyl (R)-2-Isocyano-3-phenylpropionate* (*ent*-**17**): In a 250-ml three-necked flask, equipped with a dry-ice reflux condenser, a dropping funnel, and a rubber septum, 10.0 g (48.3 mmol) of *N*-formyl-(*R*)-phenylalanine methyl ester[24a] {$[\alpha]_D$ = –31.7 (*c* = 1.0 in ethanol)} was dissolved in 60 ml of dichloromethane under an argon atmosphere. The solution was initially cooled to –10°C and 10.4 ml (94 mmol) of *N*-methylmorpholine was added via syringe; then, at a temperature of –30°C, a solution of 2.9 ml (24 mmol) of trichloromethyl chloroformate in 10 ml of dichloromethane was added via dropping funnel at such a rate that the internal temperature did not exceed –30°C. The orange suspension was stirred for 2 h at this temperature and then allowed to warm up slowly to –15°C. Then the mixture was hydrolysed with 40 ml of ice/water and the aqueous layer was extracted three times with dichloromethane (40 ml each). The combined organic layers were washed two times with 7.5% $NaHCO_3$ solution once with water and dried over molecular sieves (4 Å) at –30°C for 10 h. The crude product was purified by flash chromatography on silica gel, employing pentane/ethyl acetate (7:3). The product was obtained as red-orange crystals. Compound *ent*-**17** was prepared in the same way: 7.2 g (79%) of **17** [4.8 g (53%) *ent*-**17**], m.p. 57–58°C (**17**) and m.p. 58–59°C (*ent*-**17**), $[\alpha]_D$ (**17**) = –13.2 (*c* = 1.3 in benzene) {ref.[25b] $[\alpha]_D^{22}$ = –19.4 (*c* = 1.04 in benzene)}, $[\alpha]_D$ (**17**) = –12.0 (*c* = 1.6 in methanol) {ref.[25a] $[\alpha]_D^{22}$ = –10.0 (*c* = 1.0 in methanol)}, $[\alpha]_D$ (*ent*-**17**) = +19.7 (*c* = 1.6 in benzene), $[\alpha]_D$ (*ent*-**17**) = +18.6 (*c* = 1.0 in methanol). – IR (KBr): ν = 2158 cm^{-1} (CNR), 1756 (C=O). – ^{1}H NMR: δ = 3.13 (dd, *J* = 13.8 Hz, *J* = 8.2 Hz, 1H, CH_aH_b), 3.25 (dd, *J* = 13.8 Hz, *J* = 4.9 Hz, 1H, CH_aH_b), 3.79 (s, 3H, CH_3), 4.46 (dd, *J* = 4.9 Hz, *J* = 8.2 Hz, 1H, CH), 7.22–7.38 (m, 5H, aromatic H). – MS (70 eV): *m/z* (%) = 189 (0.2, M^+).

$C_{11}H_{11}NO_2$ (189.2) Calcd. C 69.83 H 5.86 N 7.40
Found C 69.88 H 6.03 N 7.57

Methyl rac-2-Isocyano-2-phenylpropionate (*rac*-**18**): Methyl *rac*-2-benzyl-2-formamidopropionat[39] (1.5 g, 7.3 mmol) in 10 ml of $CHCl_3$, 1.75 ml (14.5 mmol) of pyridine, and 0.33 ml (3.6 mmol) of $POCl_3$ gave according to ref.[39] 0.67 g (49%) of the light-yellow crystalline crude product *rac*-**18**; m.p. <20°C. – IR ($CHCl_3$): ν = 2150 cm^{-1} (CNR), 1750 (C=O). – ^{1}H NMR: δ = 2.03 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 7.33–7.55 (m, 5H, aromatic H). – MS (70 eV): *m/z* (%) = 189 (2.1, M^+).

rac-N-(2,2-Diethoxyethyl)-2-isocyano-3-phenylpropionamide (*rac*-**19**): Compound **17** (0.95 g, 5.0 mmol), 0.73 ml (5.0 mmol) of 1-amino-2-diethoxyethane, and a catalytic amount of *p*-toluenesulfonic acid were stirred for 14 h at 80°C (according to the method described in ref.[26]). The resulting brownish oil was purified by flash chromatography, on silica gel (ether) and recrystallised afterwards from hexane: 0.61 g (42%), m.p. 64.5–65.0°C. – IR (KBr): ν = 3295 cm^{-1} (NH), 2155 (CNR), 1675 (amide I), 1570 (amide II). – ^{1}H NMR: δ = 1.15 (t, *J* = 7.0 Hz, 3H, CH_3), 1.19 (t, *J* = 7.0 Hz, 3H, CH_3), 3.15 (dd, *J* = 13.8 Hz, *J* = 7.5 Hz, 1H, CH_aH_b), 3.30 (dd, *J* = 13.8 Hz, *J* = 4.1 Hz, 1H, CH_aH_b), 3.34–3.72 (m, 6H, CH_2CH_3, $HNCH_2$), 4.35–4.43 (m, 2H, $CHCH_2Ph$, OCHO), 6.48 (br. s, 1H, NH), 7.25–7.37 (m, 5H, aromatic H). – MS (70 eV): *m/z* (%) = 290 (0.1, M^+).

$C_{16}H_{22}N_2O_3$ (290.4) Calcd. C 66.18 H 7.64 N 9.65
Found C 66.21 H 7.78 N 9.59

(1'S)-Isocyano-N-(1'-phenylethyl)acetamide (**20**): According to ref.[26] 23% (ref.[26] 80%) of a twice recrystallised product was isolated; m.p. 121–125°C (ref.[26] 122–123°C), $[\alpha]_D$ = –50.2 (*c* = 1.0 in CH_2Cl_2). – IR (KBr): ν = 3275 cm^{-1} (NH), 2162 (CNR), 1655 (amide I), 1553 (amide II). – ^{1}H NMR: δ = 1.54 (d, *J* = 7.0 Hz, 3H, CH_3), 4.07 (d, *J* = 18.5 Hz, 1H, CH_aH_b), 4.14 (d, *J* = 18.5 Hz, 1H, CH_aH_b), 5.12 (m_c, 1H, CH), 6.63 (br. s, 1H, NH), 7.25–7.38 (m, 5H, aromatic H). – MS (70 eV): *m/z* (%) = 188 (71.3, M^+), 172 (1.2, M^+ – CN), 106 (100, M^+ – 82).

(2S,1'S)-2-Isocyano-3-phenyl-N-(1'-phenylethyl)propionamide (**21**): Compound **17** (2.47 g, 13.0 mmol), 1.65 ml (13.0 mmol) of (*S*)-1-phenylethylamine, and a catalytic amount of *p*-toluenesulfonic acid were mixed and stirred for 14 h at 50°C. The brown solid was washed with several portions of ether (100 ml total). 1.8 g (49%) of a white powder was isolated, m.p. 137–138°C, $[\alpha]_D$ = –36.7 (*c* = 1.3 in $CHCl_3$). – IR (KBr): ν = 3295 cm^{-1} (NH), 2150 (CNR), 1670 (amide I), 1555 (amide II). – ^{1}H NMR: δ = 1.37 (d, *J* = 6.9 Hz, 3H, CH_3), 3.16–3.29 (m, 2H, CH_2), 4.36–4.39 (m, 1H, $CHCH_2Ph$), 5.00–5.10 (m, 1H, $HCCH_3$), 6.37 (br. d, *J* = 6.4 Hz, 1H, NH), 7.20–7.37 (m, 10H, aromatic H). – MS (70 eV): *m/z* (%) = 278 (4, M^+).

(2R,1'S)-2-Isocyano-3-phenyl-N-(1'-phenylethyl)propionamide (**22**): Formamide **5** (3.0 g, 10.0 mmol) in 30 ml of dichloromethane, 2.2 ml (20.0 mmol) of *N*-methylmorpholine, and a solution of 0.6 ml (5.0 mmol) of diphosgene in 20 ml of dichloromethane gave according to the preparation of **17** the crude product, which was washed twice with ether and hexane; 1.9 g (68%), m.p. 126–127.5°C, $[\alpha]_D$ = +12.5 (*c* = 1.3 in CH_2Cl_2). – IR (KBr): ν = 3370 cm^{-1} (NH), 2138 (CNR), 1656 (amide I), 1538 (amide II). – ^{1}H NMR: δ = 1.49 (d, *J* = 6.9 Hz, 3H, CH_3), 3.15–3.22 (m, 2H, CH_2Ph), 4.43–4.47 (dd, *J* = 6.7 Hz, *J* = 4.7 Hz, 1H, CNCH), 5.07 (m_c, 1H, $HCCH_3$), 6.39 (br. m, 1H, NH), 7.10–7.34 (m, 10H, aromatic H). – MS (70 eV): *m/z* (%) = 278 (4.9, M^+), 105 (100, M^+ – 173).

*Resolution with in-situ Recycling of the Isocyanides l-***21** *and u-***21**: A mixture of 2.9 g (15.3 mmol) of *rac*-**17**, 2.0 ml (15.3 mmol) of (*S*)-phenylethylamine, and a catalytic amount of *p*-toluenesulfonic acid was heated without solvent for two days at 55°C. After this time a brown solid was obtained. The ^{1}H-NMR spectra of this crude product showed an 8.5:1 mixture of the *l*-**21** (R_f = 0.47, ethyl acetate/hexane, 1:1) and the *u*-form (**22**) (R_f = 0.44, ethyl acetate/hexane, 1:1).

(2R,4'S,5'S)-N-(2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-2-isocyano-3-phenylpropionamide (**23**): The preparation was carried out in a similar way to the procedure for **17**. From 5.73 g (15.0 mmol) of **7** in 40 ml of dichloromethane, 1.82 ml (16.5 mmol) of *N*-methylmorpholine, and 0.9 ml (7.5 mmol) of diphosgene resulted 3.5 g (64%) of yellow crystals. Recrystallisation from ether gave white

crystals, m.p. 101–102°C, $[\alpha]_D$ = +137.6 (*c* = 0.7 in CH_2Cl_2). – IR ($CHCl_3$): ν = 3430 cm^{-1} (NH), 2140 (CNR), 1685 (C=O, amide I), 1525 (amide II). – ^1H NMR: δ = 1.58 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 2.24–2.32 (dd, *J* = 14.0 Hz, *J* = 10.2 Hz, 1H, CH_aH_bPh), 2.92–2.98 (dd, *J* = 14.0 Hz, *J* = 3.4 Hz, 1H, CH_aH_bPh), 3.88–3.92 (dd, *J* = 12.1 Hz, *J* = 1.8 Hz, 1H, CH_aH_bO), 4.13–4.18 (m, 2H, $CHCH_2Ph$, $NCHCH_2O$), 4.29–4.33 (dd, *J* = 12.1 Hz, *J* = 1.8 Hz, 1H, CH_aH_bO), 5.25 (d, *J* = 2.0 Hz, 1H, HCPhO), 7.07–7.36 (m, 11H, NH, aromatic H). – MS (70 eV): *m/z* (%) = 364 (0.1, M^+).

$C_{22}H_{24}N_2O_3$ (364.4) Calcd. C 72.51 H 6.64 N 7.69
Found C 72.24 H 6.59 N 7.63

(2S,4'S,5'S)-N-(2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-2-isocyano-3-phenylpropionamide (**24**): This compound was synthesised like the isocyanides **17** and **23**. 7.76 g (20.0 mmol) of **6** in 60 ml of dichloromethane, 2.46 ml (22.0 mmol) *N*-methylmorpholine, and 1.2 ml (10.0 mmol) of diphosgene in 30 ml of dichloromethane gave after purification (flash chromatography on silica gel, column diameter 3.0 cm, height 20 cm, ether) 3.8 g (52%) of **24**; light yellow foam, m.p. 44.0–45.2°C, $[\alpha]_D$ = +66.5 (*c* = 3.2 in CH_2Cl_2). – IR (KBr): ν = 3340 cm^{-1} (NH), 2139 (CNR), 1695 br. (amide I), 1525 (amide II). – ^1H NMR: δ = 1.51 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.97 (dd, *J* = 13.9 Hz, *J* = 8.3 Hz, CH_aH_bPh), 3.10 (dd, *J* = 13.9 Hz, *J* = 3.9 Hz, 1H, CH_aH_bPh), 3.71 (dd, *J* = 12.1 Hz, *J* = 1.9 Hz, 1H, CH_aH_bO), 4.03 (dd, *J* = 8.2 Hz, *J* = 4.0 Hz, 1H, $CHCH_2Ph$), 4.06–4.11 (m, 1H, $NCHCH_2O$), 4.24 (dd, *J* = 12.1 Hz, *J* = 1.9 Hz, 1H, CH_aH_bO), 5.19 (d, *J* = 1.9 Hz, 1H, HCPhO), 6.93 (d, *J* = 8.9 Hz, 1H, NH), 7.17–7.36 (m, 10H, aromatic H). – MS (70 eV): *m/z* (%) = 364 (0.1, M^+), 132 (100, M^+ – 232).

cis-Dichlorobis[methyl (S)-2-isocyano-3-phenylpropionate-(isocyano-C)]palladium(II) (**25**): $PdCl_2$ (177 mg, 1.0 mmol) was suspended in 10 ml of dichloromethane and a solution of 383 mg (2.2 mmol) of isocyanide **17** in 2 ml of dichloromethane was added. The brown red suspension was stirred for 24 h at room temperature. The solvent was evaporated from the almost clear orange solution and the crude product was recrystallised three times from a small volume of $CHCl_3$ and ether/pentane (1:2). The solution was kept for 2 d in a refrigerator; yellow crystals, 468 mg (84.5%), m.p. 153.0–154.1°C, $[\alpha]_D$ = –20.8 (*c* = 1.03 CH_2Cl_2). – IR (KBr): ν = 2245, 2263 cm^{-1} (CNR), 1769 (C=O). – ^1H NMR: δ = 3.25–3.38 (m, 4H, CH_2), 3.77 (s, 6H, CH_3), 4.92–4.96 (m, 2H, CH), 7.23–7.38 (m, 10H, aromatic H). – MS (FAB): *m/z* (%) = 520 (17.5, M^+ – ^{35}Cl).

$C_{22}H_{22}Cl_2N_2O_4Pd$ (555.8) Calcd. C 47.55 H 3.99 N 5.04
Found C 46.94 H 4.13 N 4.96

trans-Chloro[methyl (S)-2-isocyano-3-phenylpropionate-(isocyano-C)]bis(triphenylphosphane)platinum(II) Tetrafluoroborate (**26**): Di-μ-chlorotetrakis(triphenylphosphane)diplatinum(II) tetrafluoroborate[40] (842 mg, 0.5 mmol) was suspended in 5 ml of $CHCl_3$, and a solution of 189 mg (1.0 mmol) of **17** in 5 ml of $CHCl_3$ was added slowly. Within a few minutes a clear light yellow solution resulted. After stirring for 2 h at room temperature the solution was concentrated to half of the volume and then mixed with 30 ml of ether. 2 d later white crystals could be isolated; 0.94 g, 91% yield; m.p. 195.5–197.0°C, $[\alpha]_D$ = –17.0 (*c* = 1.06 in $CHCl_3$). – IR ($CHCl_3$): ν = 2218 cm^{-1} (CNR), 1755 (C=O), 1048 (BF_4). – ^1H NMR: δ = 2.21 (dd, *J* = 14.0 Hz, *J* = 8.1 Hz, 1H, CH_aH_b), 2.41 (dd, *J* = 14.0 Hz, *J* = 5.8 Hz, 1H, CH_aH_b), 3.49 (s, 3H, CH_3), 4.19 (m, br, 1H, CH), 7.08–7.63 (m, 35H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 36.6 (s, CH_2), 53.5 (s, OCH_3), 60.7 (s with ^{195}Pt satellites, *J* = 17 Hz, CH), 117.8 (br. s, CN), 126.5–134.5 (aromatic C), 164.1 (s, C=O). ^{31}P NMR ($CHCl_3$/[D_6]acetone): δ = 18.9 with ^{195}Pt satellites, *J* = 2188 Hz). – MS (FAB): *m/z* (%) = 943 (100, M^+ – HBF_4).

General Procedure 3 (GP 3) for the Reaction of Isocyanides with Carbonyl Compounds: To a solution of isocyanide (5.0 mmol) in 20–30 ml of dichloromethane was added at 0°C under argon with stirring 2.75 ml (5.5 mmol) of a solution (*c* = 2 mol/l) of titanium tetrachloride in dichloromethane. The colour of the clear solution changed from yellow to dark brown. After a few minutes a pale yellow precipitate was formed. About 60 min later the mixture was treated with 5.0 mmol of the carbonyl compound whereby the precipitate disappeared within a few minutes. The clear solution was stirred until TLC showed the absence of starting material, then it was hydrolysed, and 20 min later the resulting two layers were separated. The aqueous layer was extracted twice with dichloromethane, and the combined organic layers were washed with saturated $NaHCO_3$ solution, with water, brine, water, and then dried over Na_2SO_4. The unreacted aldehyde could be separated via the hydrogen sulfite adduct. Removal of the solvent afforded crude products which were purified by flash chromatography and/or recrystallised from ether/pentane or the solvent mentioned.

2-(4-Bromophenyl)-2-hydroxyacetanilide (**28**): Following the *GP 3*, 10 mmol of titanium tetrachloride was treated with 1.76 g (9.5 mmol) of 4-bromobenzaldehyde at 0°C; yield 2.86 g (98%); m.p. 132–133°C ($CHCl_3$). – IR (KBr): ν = 3275 cm^{-1} (NH, OH), 1635 (amide I), 1595 (amide II). – ^1H NMR: δ = 3.8 (d, *J* = 4 Hz, 1H, OH), 5.1 (d, *J* = 4 Hz, 1H, HCOH), 7.1–7.6 (m, 10H, aromatic H, NH). – MS (70 eV): *m/z* (%) = 307/305 (M^+, 46, 47), 187/185 (95/100).

$C_{14}H_{12}BrNO_2$ (306.2) Calcd. C 54.92 H 3.95 N 4.57
Found C 55.02 H 4.00 N 4.55

2-Hydroxy-3-phenylpropionanilide (**29**): The reaction of 10 mmol of titanium tetrachloride with 9.5 mmol of 2-phenylacetaldehyde at 0°C following the *GP 3* afforded 2.25 g (98%) of **29**; m.p. 136–136.5°C ($CHCl_3$). – IR (KBr): ν = 3305 cm^{-1} (NH, OH), 1650 (amide I), 1600 (amide II). – ^1H NMR: δ = 2.70 (br. s, 1H, OH), 2.95 (dd, *J* = 14 Hz, *J* = 8 Hz, 1H, CH_2), 3.35 (dd, *J* = 14 Hz, *J* = 6 Hz, 1H, CH_2), 4.40 (m, 1H, H–COH), 7.10–7.60 (m, 10H, aromatic H), 8.30 (br. s, 1H, NH). – MS (70 eV): *m/z* (%) = 241 (M^+, 11), 93 (100).

$C_{15}H_{15}NO_2$ (241.3) Calcd. C 74.67 H 6.27 N 5.80
Found C 74.68 H 6.33 N 5.80

2-Hydroxy-2-methylpropionanilide (**30**): The reaction of 10 mmol of titanium tetrachloride and 0.7 ml (9.5 mmol) of acetone at 0°C following the *GP* 3 yielded 1.49 g (88%) of **30**; m.p. 133–134°C ($CHCl_3$). – IR (KBr): ν = 3275 cm^{-1} (NH, OH), 1655 (amide I), 1605 (amide II). – ^1H NMR: δ = 1.55 (s, 6H, CH_3), 2.85 (s, 1H, OH), 7.05–7.65 (m, 5H, aromatic H), 8.65 (br. s, 1H, NH). – MS (70 eV): *m/z* (%) = 179 (M^+, 26), 59 (100).

$C_{10}H_{13}NO_2$ (179.2) Calcd. C 67.02 H 7.31 N 7.82
Found C 66.93 H 7.40 N 7.81

1-Hydroxycyclohexanecarboxanilide (**31**): From 10 mmol of titanium tetrachloride and 0.93 g (10 mmol) of cyclohexanone at 0°C following the *GP 3* was obtained 1.23 g (59%) of **31**; m.p. 172–173.5°C ($CHCl_3$). – IR (KBr): ν = 3325 cm^{-1} (NH, OH), 1655 (amide I), 1605 (amide II). – ^1H NMR: δ = 1.35–2.05 (m, 10H, cyclohexyl H), 2.40 (s, 1H, OH), 7.06–7.60 (m, 5H, aromatic H), 8.70 (br. s, 1H, NH). – MS (70 eV): *m/z* (%) = 219 (M^+, 21), 93 (100).

$C_{13}H_{17}NO_2$ (219.3) Calcd. C 71.21 H 7.81 N 6.39
Found C 70.97 H 7.75 N 6.55

rac-N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-hydroxy-2-phenylacetamide (**32**): To a solution of 0.488 g (2.55 mmol) of isocyanide **9**[37] in 20 ml of dichloromethane was added dropwise 1.5 ml (3.0 mmol) of titanium tetrachloride (c = 2 mol/l in CH_2Cl_2) at −70°C. The brown solution was stirred for 1 h and then 0.27 ml (2.58 mmol) of benzaldehyde was added via a syringe. The obtained light brownish suspension was stirred at −60°C for 6 h and then warmed to room temperature during 15 h. Then the wine-red solution was hydrolysed and worked up according to the *GP 3*. The oily crude product was purified by flash chromatography (silica gel, diameter 3 cm, height 18 cm, ether/pentane, 7:1): 0.186 g (23.1%) of white crystals m.p. 92.0−93.5°C. − IR (KBr): ν = 3415, 3380 cm^{-1} (OH, NH), 1680 (amide I), 1590 (amide II). − ^1H NMR: δ = 2.67−2.73 (m, 2H, H_2CN), 3.33 (br. s, 1H, OH), 3.44−3.50 (m, 2H, Ph−CH_2), 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.95 (s, 1H, CH), 6.26 (br. s, 1H, NH), 6.55−7.31 (m, 8H, aromatic H). − MS (70 eV): m/z (%) = 315 (6.9, M^+).

$C_{18}H_{21}NO_4$ (315.4) Calcd. C 68.55 H 6.71 N 4.44
Found C 68.48 H 6.81 N 4.56

2-Hydroxy-N-(2-morpholinoethyl)-2-phenylacetamide (**33**): 2-Morpholinoethyl isocyanide (1.4 ml, 10 mmol) was added to a solution of 1.1 ml (10 mmol) of titanium tetrachloride in 40 ml of dichloromethane. The heterogeneous mixture was stirred for 4 h at 0°C, then cooled to −70°C, and 9.5 mmol of benzaldehyde was added. After the reaction mixture was slowly warmed to room temperature and stirred for 24 h at the same temperature, 25 ml 2 N hydrochloric acid was added, and the mixture was stirred for another 2 h at room temperature. Then the layers were separated, and the organic phase was extracted with two 50-ml portions of 2 N hydrochloric acid. The aqueous layer were combined and basefied, filtered through celite, and extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, the solvent was evaporated, and the obtained solid was recrystallised from chloroform to yield 1.68 g (67%) of **33**; m.p. 140.5−142°C. − IR (KBr): ν = 3320 cm^{-1} (NH, OH), 1655 (amide I), 1535 (amide II). − ^1H NMR: δ = 2.30−2.50 [m, 6H, $(CH_2)_3N$], 3.20−3.70 [m, 8H, CH_2−N*H*, O*H*, $(CH_2)_2O$], 5.10 (br. s, 1H, *H*−COH), 6.90 (br. s, 1H, N*H*), 7.30−7.50 (m, 5H, aromatic H). − MS (70 eV): m/z (%) = 264 (M^+, 1), 100 (100).

$C_{14}H_{20}N_2O_3$ (264.3) Calcd. C 63.62 H 7.63 N 10.60
Found C 63.49 H 7.65 N 10.53

2-Hydroxy-N-(2-morpholinoethyl)-4-phenylbutanamide (**34**): Following the procedure for the preparation of **33** and using 1.25 ml (9.5 mmol) of 3-phenylpropanal instead of benzaldehyde, 1.57 g (57%) of **34** was obtained; m.p. 177−179°C (hydrochloride from ethanol). − IR (film): ν = 3420 cm^{-1} (NH, OH), 1670 (amide I), 1525 (amide II). − ^1H NMR: δ = 1.80−2.20 (m, 2H, CH_2−CH_2−Ph), 2.30−2.50 [m, 6H, $(CH_2)_3N$], 2.70−2.80 (m, 2H, CH_2−CH_2−Ph), 3.20−3.50 (m, 2H, CH_2−NH), 3.51−3.80 [m, 4H, $(CH_2)_2O$], 4.00−4.25 (m, 1H, *H*−COH), 5.00 (br. s, 1H, O*H*), 7.20−7.40 (m, 6H, aromatic H, N*H*). − MS (70 eV): m/z (%) = 292 (M − HCl, 0.5), 100 (100).

$C_{16}H_{25}ClN_2O_3$ (328.8, hydrochloride)
Calcd. C 58.44 H 7.66 N 8.52
Found C 58.09 H 7.56 N 8.27

rac-N-[Hydroxy(phenyl)acetyl]glycine Ethyl Ester (**35**): Using 0.54 g (0.51 ml, 5.0 mmol) of benzaldehyde and following the *GP 3*, 0.52 g (44.0%) of **35** resulted after recrystallisation, m.p. 97.0−97.8°C (ether/pentane). − IR (KBr): ν = 3365 cm^{-1} (OH), 3195 (NH), 1730 (C=O), 1650 (amide I), 1530 (amide II). − ^1H NMR (90 MHz): δ = 1.24 (t, J = 7.5 Hz, 3H, CH_3), 3.65 (d, J = 4.5 Hz, 1H, OH), 3.97 (d, J = 6.0 Hz, 2H, HNCH_2), 4.15 (q, J = 7.5 Hz, 2H, CH_2CH$_3$), 5.03 (d, J = 4.5 Hz, 1H, CH), 6.77 (br. m, 1H, NH), 7.23−7.44 (m, 5H, aromatic H). − MS (70 eV): m/z (%) = 237 (5, M^+).

$C_{12}H_{15}NO_4$ (237.3) Calcd. C 60.73 H 6.38 N 5.91
Found C 60.53 H 6.36 N 5.82

rac-N-[Hydroxy(4-methoxyphenyl)acetyl]glycine Ethyl Ester (**36**): Using 0.69 g (0.61 ml, 5.0 mmol) of 4-methoxybenzaldehyde, according to the *GP 3*, 1.21 g (90.0%) of **36** resulted as white crystals, m.p. 78.0−79.4°C (ether/hexane). − IR (KBr): ν = 3365 cm^{-1} (OH), 3200 (NH), 1732 (C=O), 1651 (amide I), 1514 sh (amide II). − ^1H NMR (90 MHz): δ = 1.27 (t, J = 7.5 Hz, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.95 (d, J = 5.0 Hz, 2H, HNCH_2), 4.15 (q, J = 7.5 Hz, 2H, CH_2CH$_3$), 4.97 (s, 1H, CH), 6.75−7.28 (m, 4H, aromatic H). − MS (70 eV): m/z (%) = 267 (10.3, M^+).

$C_{13}H_{17}NO_5$ (267.3) Calcd. C 58.41 H 6.42 N 5.24
Found C 58.17 H 6.35 N 5.33

rac-N-[Hydroxy(4-bromophenyl)acetyl]glycine Ethyl Ester (**37**): Using 0.92 g (5.0 mmol) of 4-bromobenzaldehyde and following the *GP 3*, 0.91 g (70.2%) of **37** resulted as white crystals, m.p. 110.8−111.6°C (ether/pentane). − IR (KBr): ν = 3358 cm^{-1} (OH), 3185 (NH), 1730 (C=O), 1649 (amide I), 1530 (amide II). − ^1H NMR: δ = 1.28 (t, J = 7.4 Hz, 3H, CH_3), 3.97 (d, J = 6.0 Hz, 2H, HNCH_2), 4.17 (q, J = 7.5 Hz, 2H, CH_2CH$_3$), 5.00 (s, 1H, CH), 6.95 (br. m, 1H, NH), 7.20−7.50 (m, 4H, aromatic H). − MS (70 eV): m/z (%) = 315, 317 (5.4, 5.2, M^+).

$C_{12}H_{14}BrNO_4$ (316.2) Calcd. C 45.59 H 4.46 N 4.43
Found C 45.42 H 4.21 N 4.32

rac-N-(2-Hydroxyvaleryl)glycine Ethyl Ester (**38**): From 0.45 ml (0.36 g, 5.0 mmol) of *n*-butyraldehyde, employing a method analogous to the *GP 3*, 0.95 g (96.4%) of white crystals were isolated; m.p. 84.4−85.5°C (ether/hexane). − IR (KBr): ν = 3295, 3245 cm^{-1} (OH, NH), 1749, 1737 (C=O), 1639, 1625 (amide I), 1542 (amide II). − ^1H NMR: δ = 0.95 (t, J = 7.3 Hz, 3H, CH_3), 1.29 (t, J = 7.3 Hz, 3H, CH_3, ester), 1.40−1.87 (m, 4H, CH_2CH_2), 3.04 (br. s, 1H, OH), 3.97−4.13 (m, 2H, HNCH_2), 4.18 (dd, J = 3.8 Hz, J = 7.9 Hz, 1H, CH), 4.21 (q, J = 7.3 Hz, 2H, CH_2, ester), 7.11 (br. s, 1H, NH). − MS (70 eV): m/z (%) = 204 (2.6, M^+).

$C_9H_{17}NO_4$ (203.2) Calcd. C 53.19 H 8.43 N 6.89
Found C 52.98 H 8.43 N 6.75

rac-N-(2-Hydroxy-3,3-dimethylbutyryl)glycine Ethyl Ester (**39**): From 0.55 ml (5.0 mmol) of pivalaldehyde, following the *GP 3*, 0.83 g (76.4%) of white long needles were isolated, m.p. 52.0 to 53.0°C (ether/hexane). − IR (KBr): ν = 3375 cm^{-1} br. (OH, NH), 1730 (C=O), 1652 (amide II); 1552, 1540 sh (amide II). − ^1H NMR: δ = 1.02 [s, 9H, $C(CH_3)_3$], 1.29 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.86 (br. s, 1H, OH), 3.78 (s, 1H, CH), 4.01 (dd, J = 18.2 Hz, J = 5.3 Hz, 1H, CH_aH$_b$), 4.12 (dd, J = 18.2 Hz, J = 5.3 Hz, 1H, CH$_a$H$_b$), 6.73 (br. s, 1H, NH). − MS (70 eV): m/z (%) = 217 (0.2, M^+).

$C_{10}H_{19}NO_4$ (217.3) Calcd. C 55.28 H 8.81 N 6.45
Found C 55.42 H 8.80 N 6.27

rac-N-(2-Hydroxy-2-phenylpropionyl)glycine Ethyl Ester (**40**): Acetophenone (0.58 ml, 5.0 mmol) was injected into the reaction mixture as described in the *GP 3*. This time the precipitate did not dissolve. The greenish yellow suspension was stirred for 17.5 h and then worked up: 1.02 g (81.0%) of white crystals, m.p. 85.8−86.7°C (ether/pentane). − IR (KBr): ν = 3365 cm^{-1} (OH), 3280 br. (NH), 1725 (C=O), 1652 (amide I), 1531 (amide II). − ^1H NMR: δ = 1.24 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.80 (s, 3H, CH_3), 3.89 (dd, J = 18.2 Hz, J = 5.4 Hz, 1H, CH_aH$_b$), 3.99 (dd, J = 18.2 Hz, J = 6.6 Hz, 1H, CH$_a$H$_b$), 4.16 (q, J = 7.1 Hz, 2H, CH_2), 7.16 (br. m,

1H, NH), 7.25–7.58 (m, 5H, aromatic H). – MS (70 eV): *m/z* (%) = 251 (3.0, M^+).

$C_{13}H_{17}NO_4$ (251.3) Calcd. C 62.14 H 6.82 N 5.57
Found C 61.86 H 6.93 N 5.60

(R)- and (S)-N-[(R)-1-Phenylethyl]mandelamide (**42**): The isocyanide **13** (0.66 g, 5.0 mmol) and 0.51 ml (5.0 mmol) of benzaldehyde were treated following the *GP 3* to give the two diastereoisomers, which could be separated by flash chromatography.

42a: Yield 90 mg (7%); R_f = 0.17 (ether/pentane = 4:1); m.p. 88–89.5°C; $[\alpha]_D$ = 0 (*c* = 1 in $CHCl_3$). – ^1H NMR: δ = 1.42 (d, *J* = 7 Hz, 3H, CH_3), 4.16 (d, *J* = 4 Hz, 1H, OH), 4.82 (d, *J* = 6 Hz, 1H, H–COH), 4.97 (p, *J* = 7 Hz, 1H, H–CCH_3), 6.79 (br. d, *J* = 8 Hz, 1H, NH), 7.11–7.30 (m, 10H, aromatic H). – ^{13}C NMR: δ = 171.6, 142.7, 139.6, 128.6, 128.3, 127.3, 126.7, 126.0, 74.12, 48.63, 21.26.

42b: Yield 100 mg (8%); R_f = 0.24 (ether/pentane, 4:1); m.p. 112–112.5°C $[\alpha]_D$ = +3.5 (*c* = 1 in $CHCl_3$). – ^1H NMR: δ = 1.42 (d, *J* = 7 Hz, 3H, CH_3), 3.68 (d, *J* = 4 Hz, 1H, OH), 4.98 (d, *J* = 4 Hz, 1H, H–COH), 5.07 (p, *J* = 7 Hz, 1H, H–CCH_3), 6.45 (br. d, *J* = 2 Hz, 1H, NH), 7.21–7.35 (m, 10H, aromatic H). – ^{13}C NMR: δ = 171.5, 143.8, 139.6, 128.6, 128.4, 127.3, 126.8, 125.9, 73.99, 48.45, 21.85.

$C_{16}H_{17}NO_2$ (255.3) Calcd. C 75.27 H 6.71 N 5.49
Found C 75.00 H 6.62 N 5.63

(R)- and (S)-N-[(1S)-1-methyl-2-phenylethyl]mandelamide (**43a**, **43b**): According to *GP 3*, 0.75 ml (5 mmol) of the isocyanide **14** and 0.51 ml (5 mmol) benzaldehyde afforded the two diastereoisomers, which could be separated by flash chromatography and whose relative configuration was determined by comparison with a sample derived from mandelic acid.

43a (*l*-diastereoisomer): Yield 340 mg (25%); R_f = 0.13 (petroleum ether/ethyl acetate, 3:2); m.p. 83–84°C; $[\alpha]_D$ = –69.8 (*c* = 5 in $CHCl_3$). – ^1H NMR: δ = 1.09 (d, *J* = 6 Hz, 3H, CH_3), 2.72 (d, *J* = 6 Hz, 2H, CH_2), 3.71 (s, 1H, OH), 4.18 (m, 1H, H–CCH_3), 4.88 (s, 1H, H–COH), 6.22 (d, *J* = 6 Hz, 1H, NH), 7.08–7.31 (m, 10H, aromatic H).

$C_{17}H_{19}NO_2$ (269.2) Calcd. C 75.81 H 7.11 N 5.20
Found C 75.63 H 7.27 N 5.09

43b (*u*-diastereoisomer): Yield 300 mg (22%); R_f = 0.22 (petroleum ether/ethyl acetate 3:2), m.p. 119–120°C; $[\alpha]_D$ = +30.2 (*c* = 5.1 in $CHCl_3$). – ^1H NMR: δ = 1.09 (d, *J* = 7 Hz, 3H, CH_3), 2.68 (dd, *J* = 6 Hz, *J* = 6 Hz, 2H, CH_2), 3.80 (d, *J* = 4 Hz, 1H, OH), 4.23–4.28 (m, 1H, H–CCH_3), 4.90 (d, *J* = 4 Hz, 1H, H–COH), 5.78 (d, *J* = 7 Hz, 1H, NH), 6.89–7.37 (m, 10H, aromatic H).

(R)- or (S)-N-[(1R,2S)-2-acetoxy-1-methyl-2-phenylethyl]mandelamide (**45**): The isocyanide **16** (1.03 g, 5 mmol) and 0.51 ml (5 mmol) of benzaldehyde were treated according to *GP 3*. Upon treatment with pentane/ether, one of the diastereoisomers crystallised from the crude product, yield 0.55 g (33%); R_f = 0.13 (petroleum ether/ethyl acetate, 3:2); m.p. 123–123.5°C; $[\alpha]_D$ = –102 (*c* = 1 in $CHCl_3$). – ^1H NMR: δ = 1.04 (d, *J* = 7 Hz, 3H, CH_3), 2.03 (s, 3H, $COCH_3$), 3.50 (br. s, 1H, OH), 4.42–4.50 (m, 1H, H–CCH_3), 4.95 (s, 1H, H–COH), 5.75 (d, *J* = 4 Hz, 1H, H–COAc), 6.35 (br. d, *J* = 8 Hz, 1H, HN), 7.23–7.34 (m, 10H, aromatic H).

$C_{19}H_{21}NO_4$ (327.4) Calcd. C 69.71 H 6.47 N 4.28
Found C 69.56 H 6.62 N 4.29

(R)-N-(Hydroxyphenylacetyl)-(S)-phenylalanine Methyl Ester[22b] (**46**): Isocyanide **17** (0.95 g, 5.0 mmol), 2.75 ml (5.5 mmol) of a solution of titanium tetrachloride in dichloromethane (*c* = 2.0 mol/l), and 0.51 ml (5.0 mmol) of benzaldehyde reacted in accordance to the *GP 3*. After 10 h, the mixture was worked up as described above. The crude product (diastereomeric ratio 1:1), a brownish oil was purified by flash chromatography on silica gel (column diameter 3.0 cm, height 15 cm, ether/pentane 4:1) to yield 0.54 g (34.9%) of the enantiomerically pure **46** (white crystals), m.p. 112–113°C, $[\alpha]_D$ = +84.3 (*c* = 1.0 in $CHCl_3$) {ref.[22a] $[\alpha]_D^{20}$ = +99.2 (*c* = 1.0 in $CHCl_3$)}. – IR (KBr): ν = 3470 cm^{-1} (OH), 3358 (NH), 1733 (C=O), 1655 (amide I), 1505 (amide II). – ^1H NMR: δ = 3.02 (dd, *J* = 13.9 Hz, *J* = 6.4 Hz, 1H, CH_aH_b), 3.14 (dd, *J* = 13.9 Hz, *J* = 5.6 Hz, 1H, CH_aH_b), 3.69 (s, 3H, CH_3), 4.83 (m, 1H, HNCH), 5.00 (s, 1H, HOCH), 6.82 (br. m, 1H, NH), 7.00–7.34 (m, 10H, aromatic H). – MS (70 eV): *m/z* (%) = 313 (17.9, M^+). Further 0.58 g was isolated from the column as a mixture of the two diastereoisomers (diastereomeric ratio 10:1), which could not be separated.

(R)- and (S)-N-[Hydroxy-(4-bromophenyl)acetyl]-(S)-phenylalanine Methyl Ester (**47a**, **47b**): With 0.93 g (5.0 mmol) of *p*-bromobenzaldehyde and 0.95 g (5.0 mmol) of **17**, following the *GP 3*, a brownish crystalline crude product (diastereomeric ratio 1:1) was isolated. Both diastereoisomers could be separated by flash chromatography on silica gel (column diameter 3.0 cm, height 20 cm, ether/*n*-pentane 4:1).

1st diastereomer **47a** (configuration not assigned) (R_f = 0.20), yield 0.34 g (17.5%), m.p. 137.0–138.1°C, $[\alpha]_D$ = +9.4 (*c* = 1.0 in $CHCl_3$). – IR (KBr): ν = 3375 cm^{-1} (OH), 3230 (NH), 1739 C=O), 1645 (amide I), 1529 (amide II). – ^1H NMR: δ = 3.04 (m, 2H, CH_2), 3.64 (d, *J* = 3.8 Hz, 1H, OH), 3.72 (s, 3H, CH_3), 4.86 (m, 1H, HNCH), 4.96 (d, *J* = 3.8 Hz, 1H, HOCH), 6.32 (d, *J* = 8.1 Hz, 1H, NH), 6.78–7.50 (m, 9H, aromatic H). – MS (70 eV): *m/z* (%) = 391, 393 (8.8, 8.7, M^+).

$C_{18}H_{18}BrNO_4$ (392.3) Calcd. C 55.12 H 4.63 N 3.57
Found C 54.99 H 4.80 N 3.48

2nd diastereomer **47b** (configuration not assigned, R_f = 0.27), yield 0.40 g (20.2%), m.p. 125.5–126.5°C, $[\alpha]_D$ = +84.6 (*c* = 1.04 in $CHCl_3$). – ^1H NMR: δ = 3.02 (dd, *J* = 14.0 Hz, *J* = 6.7 Hz, 1H, CH_aH_b), 3.15 (dd, *J* = 14.0 Hz, *J* = 5.6 Hz, 1H, CH_aH_b), 3.40 (br. s, 1H, OH), 3.72 (s, 3H, CH_3), 4.79–4.86 (m, 1H, HNCH), 4.99 (d, *J* = 3.6 Hz, 1H, HOCH), 6.80 (m, 1H, NH), 6.97–7.49 (m, 9H, aromatic H).

$C_{18}H_{18}BrNO_4$ (392.3) Calcd. C 55.12 H 4.63 N 3.57
Found C 55.38 H 4.60 N 3.43

N-[(2R or S)-2-Hydroxyvaleryl]-(S)-phenylalanine Methyl Ester (**48**): Butyraldehyde (0.45 ml, 0.36 g, 5.0 mmol) was injected into the mixture of isocyanide **17** and titanium tetrachloride at –25°C (see GP 3). After stirring for 20 h the reaction was worked up as described above. Flash chromatography of the brown oil (diastereomeric mixture 1:1, R_f = 0.21, 0.24) on silica gel (elution with ether/pentane) gave 0.48 g (34.3%) of one of the diastereoisomers (R_f = 0.21) as white crystals, m.p. 78.6–79.6°C, $[\alpha]_D^{20}$ = +69.9 (*c* = 0.97 in $CHCl_3$). – IR (KBr): ν = 3335, 3210 cm^{-1} br (OH, NH), 1743 (C=O), 1635 (amide I), 1528 (amide II). – ^1H NMR: δ = 0.9 (t, *J* = 7.2 Hz, 3H, H_3CCH_2), 1.35–1.76 (m, 4H, CH_2CH_2), 2.8 (s, br, 1H, OH), 3.08 (dd, *J* = 13.8 Hz, *J* = 6.6 Hz, 1H, CH_aH_b), 3.16 (dd, *J* = 13.8 Hz, *J* = 5.8 Hz, CH_aH_b), 3.71 (s, 3H, OCH_3), 4.06 (m, 1H, HOCH), 4.86 (m, 1H, HNCH), 6.86 (d, *J* = 7.8 Hz, 1H, NH), 7.10–7.31 (m, 5H, aromatic H). – MS (70 eV): *m/z* (%) = 279 (2.0, M^+). – Further 0.34 g could be isolated from the column as a mixture of both diastereoisomers.

$C_{15}H_{21}NO_4$ (279.3) Calcd. C 64.50 H 7.58 N 5.01
Found C 64.31 H 7.77 N 4.93

N-[(2R or S)-2-Hydroxy(3R or S)-3-phenylbutyryl]-(S)-phenylalanine Methyl Ester (**49a**, **49b**): The reaction was carried out in the same way as described for compound **48** with 0.67 ml of *rac*-phenylpropionaldehyde. The crude product was treated with 40 ml ether and the resulting yellow brownish waxy substance was purified on silica gel (flash chromatography, ether/pentane, 4:1). Two of the diastereoisomers (diastereomeric ratio 1:1:1:1) could be separated as white crystals.

1st diastereoisomer **49a** (configuration not assigned) (R_f = 0.4) 335 mg (19.5%), m.p. 125.0–126.1°C, $[\alpha]_D$ = +83.0 (*c* = 0.88 in $CHCl_3$). – IR (KBr): ν = 1730, 1748 (C=O), 1655 (amide I), 1525 (amide II). – ^{1}H NMR: δ = 1.23 (d, *J* = 7.1 Hz, 3H, CH_3), 2.13 (d, *J* = 4.5 Hz, 1H, OH), 3.07 (dd, *J* = 14.0 Hz, *J* = 4.8 Hz, 1H, CH_aH_b), 3.10 (dd, *J* = 14.0 Hz, *J* = 4.2 Hz, 1H, CH_aH_b), 3.37 (qd, *J* = 7.1 Hz, *J* = 3.3 Hz, 1H, *H*–CCH_3), 3.72 (s, 3H, CH_3, ester), 4.18–4.20 (m, 1H, HOC*H*), 4.85–4.92 (m, 1H, HNC*H*), 6.82 (d, *J* = 7.6 Hz, 1H, NH), 7.08–7.36 (m, 10H, aromatic H). – MS (70 eV): *m/z* (%) = 341 (1.2, M^+).

$C_{20}H_{23}NO_4$ (341.4) Calcd. C 70.36 H 6.76 N 4.10
Found C 70.22 H 6.80 N 4.01

2nd diastereoisomer **49b** (configuration not assigned) (R_f = 0.2) 310 mg (16.1%), m.p. 131.2–132.8°C, $[\alpha]_D$ = +17.4 (*c* = 0.93 in $CHCl_3$). – ^{1}H NMR: δ = 1.39 (d, *J* = 7.3 Hz, 3H, CH_3), 2.58 (d, *J* = 5.9 Hz, 1H, OH), 2.74 (dd, *J* = 13.7 Hz, *J* = 5.8 Hz, 1H, CH_aH_b), 2.93 (dd, 13.7 Hz, *J* = 5.6 Hz, 1H, CH_aH_b), 3.37 (qd, *J* = 7.3 Hz, *J* = 4.3 Hz, 1H, *H*CCH_3), 3.66 (s, 3H, CH_3, ester), 4.20 (dd, *J* = 4.2 Hz, *J* = 5.9 Hz, 1H, HOC*H*), 4.77–4.83 (m, 1H, HNC*H*), 6.59 (d, *J* = 8.1 Hz, 1H, NH), 6.67–7.35 (m, 10H, aromatic H). – MS (70 eV): *m/z* (%) = 341 (3.0, M^+).

$C_{20}H_{23}NO_4$ (341.4) Calcd. C 70.36 H 6.76 N 4.10
Found C 69.73 H 6.71 N 3.97

N-[(RS)-Hydroxy(phenyl)acetyl]-(RS)-phenylglycine Methyl Ester (**50**): Methyl *rac*-2-isocyano-2-phenylpropionate *rac*-**18**[39] (0.95 g, 5.0 mmol) was dissolved in 20 ml of dichloromethane and 2.75 ml of a $TiCl_4$ solution (*c* = 2 mol/l in CH_2Cl_2) was added at –10°C. The green solution was stirred at –10°C for 1 h and then 0.53 ml (5.0 mmol) benzaldehyde was injected via syringe. Then the solution was stirred at room temperature for 24 h; workup according to the *GP 3*. One of the diastereoisomers could be separated on silica gel (flash chromatography, ether/pentane, 4:1), 0.53 g (34.1%) yield, m.p. 70.0–71.8°C. – IR (KBr): ν = 3362 cm^{-1} (OH), 3320 br. (NH), 1738 (CO), 1653 (amide I), 1515 br. (amide II). – ^{1}H NMR: δ = 1.99 (s, 3H, CH_3), 3.66 (s, 3H, CH_3, ester), 5.03 (d, *J* = 2.2 Hz, 1H, HOC*H*), 7.20–7.44 (m, 11H, NH, aromatic H). – MS (70 eV): *m/z* (%) = 313 (0.3, M^+).

$C_{18}H_{19}NO_4$ (313.4) Calcd. C 68.99 H 6.11 N 4.47
Found C 68.54 H 6.14 N 4.44

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