Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 2335–2344

TETRAHEDRON: *ASYMMETRY*

Enantiomeric excess determination of α-amino acids by ^{19}F NMR spectroscopy of their *N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C*,*N*)palladium complexes

Fabrice Levrat,[a] Helen Stoeckli-Evans[b] and Norbert Engel[a,*]

[a]*Department of Chemistry, University of Fribourg, CH-1700 Fribourg, rte du Musée 6, Switzerland*
[b]*Institute of Chemistry, University of Neuchâtel, CH-2007 Neuchâtel, av. Bellevaux 51, Switzerland*

Received 29 August 2002; accepted 4 October 2002

Abstract—The synthesis and resolution of the trifluoromethyl-palladacycle, di-μ-chloro-bis(*N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-2-*C*,*N*)palladium(II) are shown. The utility of the complex and its application in the enantiomeric excess determination of α-amino acids by ^{19}F NMR spectroscopy is demonstrated and X-ray diffraction analysis of one of the diastereomeric complexes, *trans*-{[(*R*)-phenylglycinato-*N*,*O*][(*R*)-*N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C*,*N*]-palladium(II)}, is reported. © 2002 Published by Elsevier Science Ltd.

1. Introduction

NMR-based methods of analysis are widely used for the determination of enantiomeric purity of organic compounds.[1] A common method involves conversion of the enantiomers into a mixture of diastereomers by coordinative bond formation with a metal ion bearing an enantiopure auxiliary ligand. Integration of the separated resonance signals of (an) appropriate diastereotopic group(s) then allows the calculation of the enantiomeric composition of the original mixture.

Enantiomeric excess determination of α-amino acids by ^{1}H NMR techniques has already been achieved by derivatization with a palladium complex,[2,3] but in some cases complex ^{1}H NMR spectra were obtained in which overlapping signals hampered reliable signal integration. Diastereomeric shift dispersion was greatly improved by measuring ^{31}P NMR resonances of the corresponding palladium complexes.[4] However, this decreases the spectral sensitivity of the measurement by a factor of 13 due to the lower inherent sensitivity of ^{31}P NMR. In addition, the ^{31}P NMR spectra obtained are complicated by the presence of *cis–trans* isomers giving rise to four signals.

We have chosen the ^{19}F nucleus for NMR-based chiral analysis of amino acids. This decision was based upon the following rationale:

(i) ^{19}F is the only naturally occurring isotope of fluorine,
(ii) the ^{19}F shift range is considerably wider when compared with that for ^{1}H NMR spectra,
(iii) the spectra are simple and independent of the complexity of the amino acid complex,
(iv) the spectroscopic sensitivity of ^{19}F NMR is 83% that of ^{1}H NMR and
(v) multiple fluorine atoms are readily incorporated (for example the CF_3 group) and would additionally increase the sensitivity of the method.

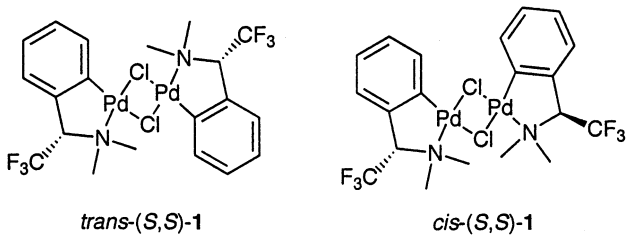
C,*N*-Type cyclopalladated complexes were previously used as organometallic chiral derivatizing agents for enantiomeric purity determination of other functional groups.[5–9] Herein, we report on the synthesis and resolution of a new trifluoromethyl-palladacycle and its application as a chiral coordinative derivatizing agent (CCDA) for enantiomeric excess determination of a series of artificial mixtures of natural α-amino acids using ^{19}F NMR.

2. Results and discussion

Di-μ-chloro-bis((*S*)-*N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-2-*C*,*N*)palladium(II) *cis*/*trans*-(*S*,*S*)-**1** were prepared and used as organometallic coordinative chiral derivatizing agents (CCDA) in a series of α-amino acids (Scheme 1).

* Corresponding author. E-mail: norbert.engel@unifr.ch

0957-4166/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0957-4166(02)00642-0



Scheme 1.

The ligand *N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine **5** was synthesized in a simple three-step sequence starting from commercially available 2,2,2-trifluoroacetophenone **2**. Transformation of **2** into the corresponding oxime **3**,[10,11] and subsequent reduction with lithium aluminum hydride[12] afforded 2,2,2-trifluoro-1-phenylethylamine **4**. Reductive methylation of **4** under Eschweiler–Clarke[13] conditions gave **5** as a colorless oil in an overall yield of 44%. *ortho*-Palladation[14] of **5** with lithium tetrachloropalladate(II) was carried out in methanol at room temperature and afforded dimer **1** as a yellow air-stable powder (Scheme 2). According to the ^{19}F and ^{1}H NMR spectra **1** consists of a mixture of four diastereomers such as racemic-*cis*, racemic-*trans*, *meso*-*cis* and *meso*-*trans*. Unfortunately, the signals are broad and insufficiently resolved to allow reliable assignment and integration.

Dimer **1** was resolved into its constituent enantiomers by flash column chromatography of the (*R*)-phenylglycinate complexes **6** and **7**. Compound **6** was the more polar compound migrating more slowly than **7**. Subsequent treatment of each of the separated complexes with dilute aqueous hydrochloric acid yielded quantitatively both *cis*/*trans*-(*S*,*S*)-**1** and *cis*/*trans*-(*R*,*R*)-**1**. ^{19}F NMR spectra of the phenylglycinate complexes showed that both enantiomers were completely resolved. Line splitting due to *cis*–*trans* isomerism of the complex was not observed (Scheme 3).

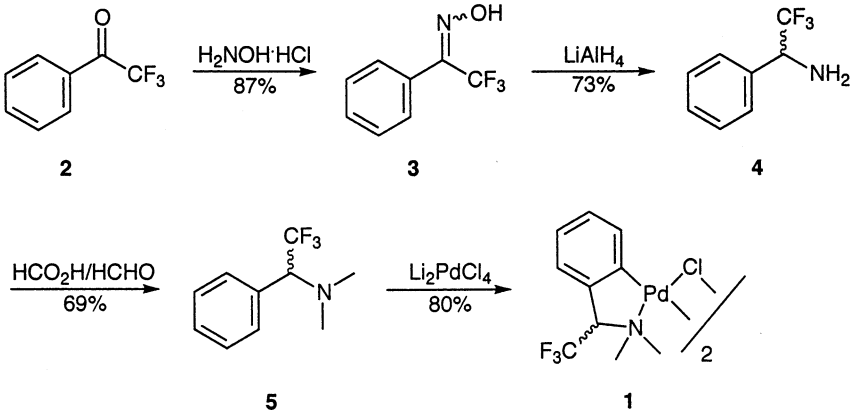
An X-ray structure determination of the less polar (*R*)-phenylglycinate derivative, **7** was carried out in order to elucidate its absolute configuration. A suitable crystal was grown by diffusion of *n*-hexane into an ethyl acetate solution of the complex. In the crystal two independent molecules per asymmetric unit exist together with one water molecule. The crystal belongs to the orthorhombic crystal system. The complex revealed a *trans*-relationship between the two nitrogen donor atoms and an *anti*-relationship between both hydrogen atoms connected to the stereogenic carbon atoms. Considering that the absolute configuration of the amino acid center is known to be *R* [from (*R*)-phenylglycine], the absolute configuration of the second stereogenic center was assigned as *R*. The resulting structure is shown in Fig. 1.

The resolved CCDA dimers were recovered in quantitative yield by treatment of the phenylglycinate derivatives **6** and **7** with diluted hydrochloric acid and extraction into CH_2Cl_2. This manipulation proceeded with complete retention of configuration at the stereogenic centers.

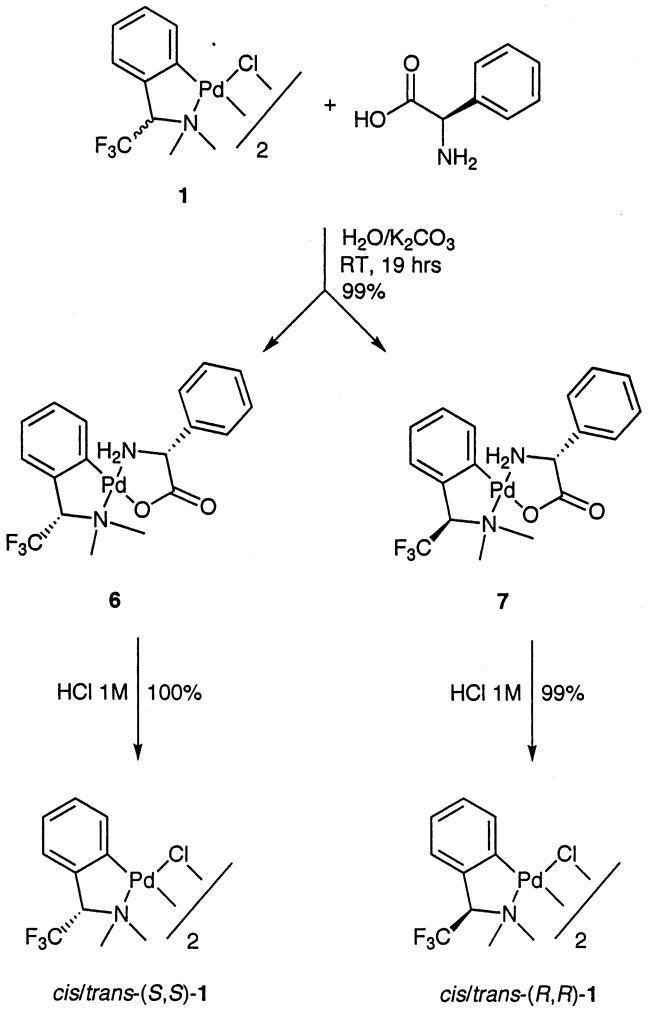
Fig. 2 shows the UV–vis and CD spectra of both *cis*/*trans*-(*S*,*S*)-**1** and *cis*/*trans*-(*R*,*R*)-**1** in CH_2Cl_2 solution, respectively. As expected, both compounds show Cotton effects of opposite signs.

The transformation of α-amino acids into the diastereomers **8** and/or **9** was performed by complexation with *cis*/*trans*-(*S*,*S*)-**1** in water in the presence of potassium carbonate (Scheme 4) according to a method used by Ambach.[15] All amino acid complexes were isolated and characterized by ^{1}H ^{13}C, ^{19}F NMR and FAB mass spectroscopy (see Section 4).

The reaction time for complexation varies depending on the substitution pattern of the α-amino acid. The transformation is complete when the yellow color of the palladate complex disappears. Reaction times of 20 h are generally sufficient for quantitative complexation of an unknown α-amino acid sample; the isolated yields are almost quantitative.



Scheme 2.



Scheme 3.

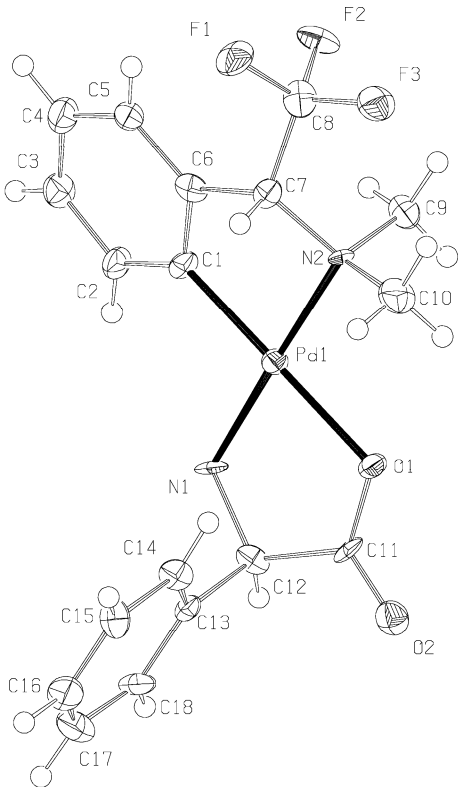
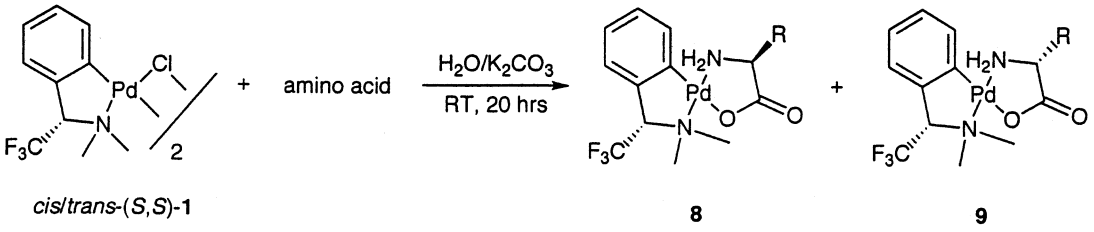


Figure 1. Structure of the (*R*)-phenylglycinate complex, *trans*-{[(*R*)-phenylglycinato-*N*,*O*][(*R*)-*N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C*,*N*]palladium(II)} **7**, determined from X-ray scattering. The atomic coordinates correspond to the absolute configuration in which atoms C-7 (hydrogen above) and C-12 (hydrogen below) have the *R* configuration.

For the determination of the magnitudes of the diastereomeric peak separation ($\Delta\delta$) and to demonstrate the applicability of the method a mixture of amino acid enantiomers of known enantiomeric ratio (weighed with an accuracy of 0.001 mg) was derivatized with the CCDA *cis*/*trans*-(*S*,*S*)-**1**. A small excess of CCDA was used (1%) to ensure that both enantiomers of the amino acid under investigation are complexed. The isolated mixture of diastereomers was dissolved in 0.75 ml dichloromethane-d_2 and analyzed by ^{19}F NMR spectroscopy. The results from the analysis of seven amino acids using this method are shown in Table 1.

All of the amino acids tested show sufficient diastereomeric peak separation, allowing clean integration of the resonance signals. As expected, Each amino acid exhibits two signals, one for each diastereomer.

The two signals were integrated and the ratios were used as a basis for the calculation of enantiomeric purities. The calculated enantiomeric excess takes into account the purity of *cis*/*trans*-(*S*,*S*)-**1** (99% ee) and the purity of the amino acid (99% ee). The determined values do not differ more than 1.8% from the calculated values. As an example, the spectrum of the (*R*)-/(*S*)-phenylglycine complex is shown in Fig. 3.



Scheme 4. The following amino acids were tested: alanine, isoleucine, leucine, phenylalanine, phenylglycine, proline, valine (see Table 1).

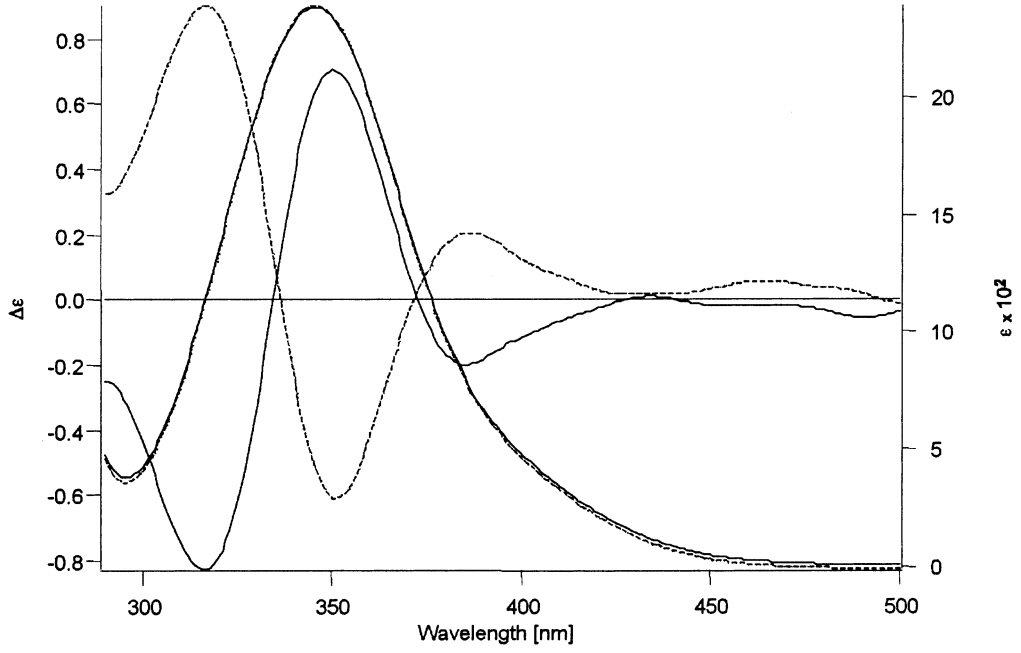


Figure 2. Superimposed UV–vis and CD spectra of the cis–*trans* isomers of (*S*,*S*)-**1** (···) and (*R*,*R*)-**1** (—) in CH_2Cl_2.

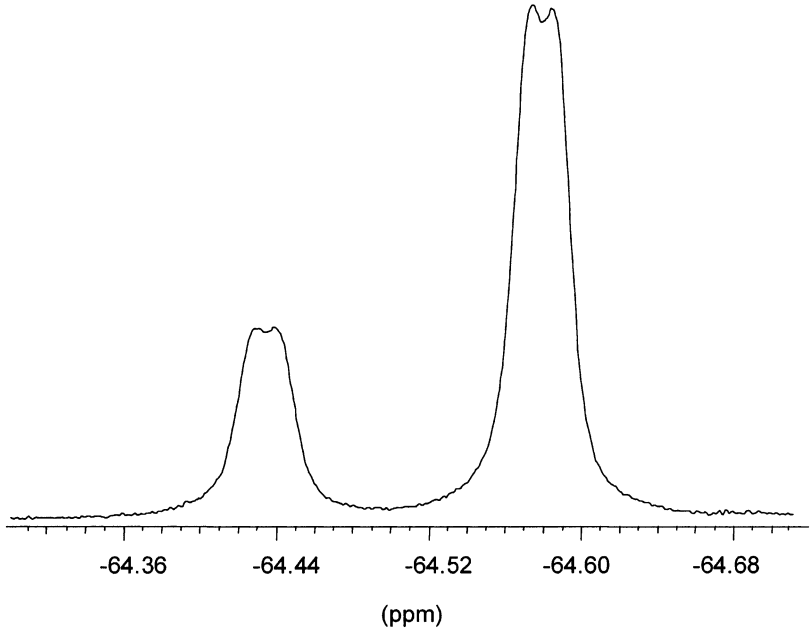


Figure 3. ^{19}F NMR spectrum obtained from an artificial 1/1.6 (*R*)/(*S*)-phenylglycine mixture after complexation with cis/*trans*-(*S*,*S*)-**1**. Lines splitting of the signals are due to ^3J couplings with the neighboring proton. The formation of the corresponding *cis*-diastereomers has not been detected.

In order to prove that no racemization of the CCDA or the amino acidate ligand occurs during derivatization under the conditions used, an (*S*)-phenylglycine chemical probe was subjected to the derivatization method in the presence of deuterated water. In the ^1H NMR spectrum of this (*S*)-phenylglycine derivative only the peaks for the two amino protons showed reduction in their relative integration values, and all other signals showed no diminution relative to the aromatic protons used as internal reference.

3. Conclusion

Di-μ-chloro-bis(*N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-2-*C*,*N*)palladium(II) **1** has been synthesized in four steps and resolved after derivatization with (*R*)-phenylglycine. The relative configuration of the phenylglycinate complex **7** was determined by X-ray diffraction. In this work *cis*/*trans*-(*S*,*S*)-**1** has been used as chiral coordinative agent for the enantiomeric excess determination of seven α-amino acids. The magnitude

Table 1.

Entry	Substrate	Chemical shift (δ, ppm)[a]		Diastereomeric peak separation
		(*R*)	(*S*)	$\lvert\Delta\delta\rvert$
1	Alanine	−64.57	−64.27	0.30
2	Isoleucine	−64.78	−64.55	0.23
3	Leucine	−64.63	−64.42	0.21
4	Phenylalanine	−64.24	−64.45	0.21
5	Phenylglycine	−64.42	−64.57	0.15
6	Proline	−65.33	−63.87	1.46
7	Valine	−64.63	−64.42	0.21

[a] Fluorotrichloromethane was used as internal reference $\delta = 0.00$ ppm

of the diastereomeric peak separation was excellent in all cases, allowing the integration of both resonance signals. The applicability of the method has been validated by measuring the e.e. for mixtures of amino acids of exactly known enantiomeric composition.

4. Experimental

4.1. General remarks

All chemicals are reagent grade; all solvents were distilled before use. Thin-layer chromatography aluminum foils pre-coated with silica gel $60PF_{254+366}$ (0.2 mm) were purchased from Merck, Darmstadt, Germany. Silica gel 60PF (0.04–0.063 mm, 230–400 mesh) and silica gel 60 (0.04–0.063 mm, 230–400 mesh) for column chromatography was purchased from Merck, Darmstadt, Germany and Fluka, Buchs, Switzerland, respectively. UV–vis spectra were recorded on a Perkin–Elmer Lambda 40 spectrometer; λ_{max} ($\log \varepsilon$) in nm. NMR spectra were recorded on a Bruker Avance DPX 360 (^{1}H: 360.13 MHz and ^{13}C: 90.55 MHz) or Bruker Avance DRX 500 (^{1}H: 500.13 MHz, ^{13}C: 125.75 MHz and ^{19}F: 470.50 MHz); chemical shifts (δ) are given in ppm downfield from the Me_4Si peak or downfield from the $CFCl_3$ peak for ^{19}F NMR. Coupling constants (J) are reported in Hz. Mass spectra (MS) were measured on a Vacuum Generators Micromass VG 7070 spectrometer by chemical ionization (CI), electronic ionization (EI) and/or fast atomic bombardment (FAB); all in positive mode. Mass spectra using electrospray ionization technique (positive mode) are recorded on a FT/ICR mass spectrometer Brucker 4.7T BioApex II. CD spectra are obtained with a Jasco J-715 spectropolarimeter, $\Delta\varepsilon$ (at λ_{max}) in l mol^{-1} cm^{-1} are measured at 25°C. A ME22 balance with a BE22 control unit and a BA25 digital display from Mettler–Toledo was used to weigh at the microgram scale.

4.2. Synthesis of the chiral coordinative derivatizing agents, *cis*/*trans*-(*S*,*S*)-1 and *cis*/*trans*-(*R*,*R*)-1

4.2.1. Synthesis of 2,2,2-trifluoro-1-phenylethanone oxime, 3[10,11]. 2,2,2-Trifluoroacetophenone (38.81 g, 223 mmol), hydroxylamine hydrochloride (20.90 g, 301 mmol) and sodium acetate (25.68 g, 313 mmol) were mixed in water (90 ml). Ethanol was added to produce a homogeneous solution. The solution was heated at 80°C for 14 h in an open flask to allow evaporation of ethanol. The solution was cooled to rt. Two layers formed and were separated. The product crystallizing from the lower phase after cooling was washed with cold water and dried to obtain white crystals (36.86 g, 87%); mp 79–81°C, 81–83°C,[10] 75°C,[11] 84–86°C.[12] ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 7.46–7.53 (m, 5H, Ph), 9.13 (br. s., 1H, OH). ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ 117.31–123.86 (q, ^1J(C,F) = 275, CF_3), 125.93 (Ph), 128.59 (Ph), 128.63 (Ph), 130.69 (Ph), 147.38–148.15 (q, ^2J(C,F) = 32, C=N(OH)). MS-EI: m/z 189.15 ([M]$^+$, 100%).

4.2.2. Synthesis of 2,2,2-trifluoro-1-phenylethylamine, 4. To a stirred suspension of lithium aluminum hydride (12.43 g, 328 mmol) in ether (400 ml) was added dropwise 2,2,2-trifluoroacetophenone oxime **3** (38 g, 201 mmol) in ether (400 ml). After stirring for 2 h at rt, saturated sodium sulfate solution (100 ml) was added dropwise to the reaction mixture and stirring was continued for an additional 2 h. Potassium carbonate was added and the mixture was filtered. After evaporation at reduced pressure the residue was distilled in vacuo to give a colorless oil (25.78 g, 73%); bp 32°C (0.2 Torr) (lit.[10] 35°C (0.3 Torr)). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 1.77 (br. s., 2H, NH_2), 4.35–4.41 (q, ^3J(H,F) = 7.5, 1H, CH-CF_3), 7.36–7.40 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ 57.56–58.27 (q, ^2J(C,F) = 29.7, CH-CF_3), 122.29–129.00 (q, ^1J(C,F) = 281, CF_3), 127.77 (Ph), 128.64 (Ph), 128.92 (Ph), 135.42 (Ph). MS-CI (CH_4): m/z 176.50 ([M+H]$^+$, 93%), 159.50 ([M−NH_2]$^+$, 75%), 106.65 ([M−CF_3]$^+$, 100%).

4.2.3. Synthesis *of* *N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine, 5. 2,2,2-Trifluoro-1-phenylethylamine **4** (10 g, 57 mmol) was added to a mixture of formic acid (9.20 g, 200 mmol) and 37% aq. formaldehyde (11.6 g, 143 mmol). After heating for 40 h at 90°C the solution was cooled, mixed with 6 M aq. hydrochloric acid (20 ml) and extracted with ether (3×30 ml). Sodium hydroxide solution (25% aq.) was added until the mixture was alkaline (pH 12), and the mixture was then extracted with ether (3×30 ml). The combined ether extracts were dried over sodium sulfate and evaporated to dryness. The residue was distilled in vacuo

affording a colorless oil (8.00 g, 69%); bp 34°C (0.2 Torr). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 2.33 (q, ^5J(H,F) = 0.9, 6H, N($\underline{CH_3}$)$_2$), 3.91–3.96 (q, ^3J(H,F) = 8.6, 1H, $\underline{CH}$-CF_3), 7.33–7.37 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ 43.13 (N($\underline{CH_3}$)$_2$), 70.46–71.12 (q, ^2J(C,F) = 27, $\underline{CH}$-CF_3), 122.49–129.27 (q, ^1J(C,F) = 284, CF_3), 128. 38 (Ph), 128.58 (Ph), 129.34 (Ph), 132.10 (Ph). MS-EI: m/z 203.30 ([M]$^+$, 14%), 135.60 (30%), 134.60 ([M−CF_3]$^+$, 100%).

4.2.4. Synthesis of di-μ-chloro-bis(*N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-2-*C*,*N*)palladium(II), 1. Lithium tetrachloropalladate(II) (1 g, 3.81 mmol) was dissolved in dry MeOH (40 ml) which was purged with a nitrogen atmosphere. *N*,*N*-Dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine **5** (3.1 g, 15.3 mmol) in MeOH (20 ml) was slowly added. Continuous stirring for 48 h afforded a precipitate, which was filtered to give yellow crystals (1.05 g, 80%); mp 200°C (decomp.). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 2.93–2.97 (m, 6H, N($\underline{CH_3}$)$_2$), 3.11–3.13 (m, 6H, N($\underline{CH_3}$)$_2$), 4.14–4.23 (m, 2H, $\underline{CH}$-CF_3), 6.95–7.05 (m, 6H, Ph), 7.17–7.23 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ 48.66 (N($\underline{CH_3}$)$_2$), 49.06–49.11 (m, N($\underline{CH_3}$)$_2$), 54.28 (m, N($\underline{CH_3}$)$_2$), 54.55 (m, N($\underline{CH_3}$)$_2$), 78.74–79.52 (m, $\underline{CH}$-CF_3), 120.22–126.99 (q, ^1J(C,F) = 284, CF_3), 124.86 (Ph), 124.96 (Ph), 127.01 (Ph), 127.03 (Ph), 133.17 (Ph), 133.20 (Ph), 133.68 (Ph), 133.72 (Ph), 141.63 (Ph), 141.73 (Ph), 143.15 (Ph), 143.27 (Ph). ^{19}F NMR ($CDCl_3$, 470.50 MHz): δ −64.98–64.81 (m). MS-ESI (MeCN): m/z 994.94 ([3/2M−Cl+H]$^+$), 735.02, 693.99 ([M−Cl+MeCN+H]$^+$), 652.96 ([M−Cl+H]$^+$), calcd. average mass for [M−Cl+H]$^+$ 652.94. UV–vis (CH_2Cl_2): 345 (3.40).

4.2.5. Preparation of the diastereomeric (*R*)-phenylgycine complexes 6 and 7: synthesis and separation. (*R*)-Phenylglycine (615 mg, 4.07 mmol) and potassium carbonate (562 mg, 4.07 mmol) were dissolved in water (40 ml). Racemic di-μ-chloro-bis(*N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-2-*C*,*N*)dipalladium(II) **1** (700 mg, 1.02 mmol) was added and the mixture was stirred for 19 h at rt. Water (200 ml) was added and the resulting solution was extracted with CH_2Cl_2 (4×150 ml). The organic layer was dried over sodium sulfate and the solvent was removed at reduced pressure, leaving a mixture of diastereomers as a white solid (922 mg, 99%). The two diastereomers were separated by flash column chromatography (silica gel). Compound **7** was eluted with ethyl acetate/MeOH 15/1; subsequent elution with CH_2Cl_2/MeOH 1/1 yielded **6**. The collected fractions were evaporated to dryness and the diastereomers are isolated by addition of *n*-hexane to a concentrated solution of the complex in CH_2Cl_2. **7** (399 mg, 87%) and **6** (425 mg, 92%) both are obtained as white solids. Diastereomer **6** showed mp 80°C (decomp.). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 2.79–2.81 (m, 1H, $\underline{NH_2}$), 3.02–3.05 (m, 6H, N($\underline{CH_3}$)$_2$), 4.08–4.12 (q, ^2J(H,F) = 7, 1H, $\underline{CH}$-CF_3), 4.67–4.70 (m, 1H, $\underline{NH_2}$), 4.77–4.79 (m, 1H, $\underline{CH}$-Ph(phenylglycine)), 6.64–6.66 (m, 1H, Ph), 6.96–6.99 (m, 1H, Ph), 7.04–7.07 (m, 1H, Ph), 7.11–7.12 (m, 1H, Ph), 7.33–7.40 (m, 3H, Ph(phenylglycine)), 7.82–7.84 (m, 2H, Ph(phenylglycine)). ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ 47.98 (N($\underline{CH_3}$)$_2$), 53.44 (N($\underline{CH_3}$)$_2$), 64.12 ($\underline{CH}$-Ph(phenylglycine)), 78.14–78.78 (q, ^2J(C,F) = 27, $\underline{CH}$-CF_3), 120.41–127.18 (q, ^1J(C,F) = 283, CF_3), 124.84 (Ph), 125.53 (Ph), 127.06 (Ph), 127.36 (Ph(phenylglycine)), 128.75 (Ph(phenylglycine)), 129.18 (Ph(phenylglycine)), 131.85 (Ph), 138.59 ($C_{quat.}$), 142.97 ($C_{quat.}$), 145.18 ($C_{quat.}$), 178.32 (C=O). ^{19}F NMR ($CDCl_3$, 470.50 MHz): δ −64.96. MS-FAB (NOBA): 768.0 ([2M-phenylglycine]$^+$), 458.9 ([M]$^+$), 415.9, 307.9 ([M−phenylglycine]$^+$). Diastereomer **7** showed mp 180°C (decomp.). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 2.70–2.72 (m, 1H, $\underline{NH_2}$), 3.02 (s, 3H, N($\underline{CH_3}$)$_2$), 3.18 (s, 3H, N($\underline{CH_3}$)$_2$), 4.34–4.38 (q, ^3J(H,F) = 7, 1H, $\underline{CH}$-CF_3), 4.59–4.62 (m, 1H, $\underline{NH_2}$), 4.74–4.76 (m, 1H, $\underline{CH}$-Ph), 6.62–6.64 (m, 1H, Ph), 6.96–7.00 (m, 1H, Ph), 7.04–7.07 (m, 1H, Ph), 7.12–7.13 (m, 1H, Ph), 7.32–7.39 (m, 3H, Ph(phenylglycine)), 7.69–7.71 (m, 2H, Ph(phenylglycine)). ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ 47.45 (N($\underline{CH_3}$)$_2$), 53.41 (N($\underline{CH_3}$)$_2$), 63.91 ($\underline{CH}$-Ph(phenylglycine)), 77.87–78.50 (q, ^2J(C,F) = 27, $\underline{CH}$-CF_3), 120.57–127.36 (q, ^1J(C,F) = 285, CF_3), 124.82 (Ph), 125.24 (Ph), 127.05 (Ph), 127.47 (Ph(phenylglycine)), 128.68 (Ph(phenylglycine)), 129.23 (Ph(phenylglycine)), 131.82 (Ph), 139.13 ($C_{quat.}$), 142.90 ($C_{quat.}$), 145.14 ($C_{quat.}$), 178.29 (C=O). ^{19}F NMR ($CDCl_3$, 470.50 MHz): δ −64.45. MS-FAB (NOBA): 767.9 ([2M−phenylglycine]$^+$), 458.9 ([M]$^+$), 413.9; 307.9 ([M−phenylglycine]$^+$).

4.2.6. X-Ray crystal structure analysis of {[(*R*)-phenylglycinato-*N*,*O*][(*R*)-*N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C*,*N*]palladium(II)}, 7. Crystals of **7** are grown by diffusion of *n*-hexane into an ethyl acetate solution of the compound giving pale yellow blocks. Intensity data are collected at 153 K on a Stoe Image Plate Diffraction system using Mo-Kα graphite monochromated radiation. Image plate distance 70 mm, ϕ oscillation scans 0–200°, step $\Delta\phi = 1.0°$, 2θ range 3.27–52.1°, d_{max}–d_{min} = 12.45–0.81 Å. The structure was solved by direct methods using the program SHELXS-97.[16] The refinement and all further calculations were carried out using SHELXL-97.[17] The water H-atoms are located from Fourier difference maps and refined with $U_{eq} = 1.5 \times U_{eq}$(Ow). The remainder of the H-atoms are included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms are refined anisotropically, using weighted full-matrix least-squares on F^2. An empirical absorption correction is applied using DIFABS3; transmission factors $T_{min}/T_{max} = 0.356/0.773$.

Two independent molecules per asymmetric unit exist together with one water molecule. The atomic coordinates correspond to the absolute structure of the molecules in the crystal. Atoms C7, C12 (Molecule A) and atoms C27, C32 (Molecule B) all have *R* configuration. The bond lengths and angles are normal within experimental error.[18]

4.2.7. Synthesis of di-μ-chloro-bis((*S*)-*N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-2-*C*,*N*)palladium(II), *cis*/*trans*-(*S*,*S*)-1. A solution of **6** (404 mg, 0.88 mmol) in CH_2Cl_2 (35 ml) was vigorously shaken with 35 ml

hydrochloric acid 1 M for 30 min. The organic layer is separated, dried over sodium sulfate and evaporated to dryness. The product was obtained as yellow powder (299 mg, 99%) showing an enantiomeric purity of >99% ee (according to the ^{19}F NMR data for the (*R*)-phenylglycinate derivative); mp 200°C (decomp.). ^1H NMR ($CDCl_3$, 500.13 MHz, two sets of signals arrive from *cis–trans* isomers which are present in a relation of 1:0.95): δ 2.92 and 2.96 (2×s, 3H, N($\underline{CH_3}$)$_2$), 3.11 and 3.13 (2×s, 3H, N($\underline{CH_3}$)$_2$), 4.17–4.21 (q, ^3J(H,F) = 6.8, 1H, $\underline{CH}$-CF_3), 6.95–7.05 (m, 3H, Ph), 7.13–7.23 (m, 1H, Ph). ^{13}C NMR ($CDCl_3$, 125.75 MHz, two sets of signals arrive from *cis-trans* isomers): δ 48.64 and 49.01 (N($\underline{CH_3}$)$_2$)), 54.28 and 54.48 (N($\underline{CH_3}$)$_2$)), 78.69–79.54 (2×q, $\underline{CH}$-CF_3), 120.19–126.97 (q, ^1J(C,F) = 284, CF_3), 124.83 (Ph), 124.94 (Ph), 126.97 (Ph), 127.02 (Ph), 133.18 (Ph), 133.65 (Ph), 141.61 (Ph), 141.71 (Ph), 143.13 (Ph), 143.23 (Ph). ^{19}F NMR ($CDCl_3$, 470.50 MHz, two sets of signals arrive from *cis–trans* isomers): δ −64.86, −64.82. UV–vis (CH_2Cl_2): 345 (3.37). CD (CH_2Cl_2): 318 (+0.93), 351 (−0.66), 386 (+0.22). Anal. calcd for $C_{20}H_{22}Cl_2F_6N_2Pd_2$: C, 34.91; H, 3.22; N, 4.07. Found: C, 34.80; H, 3.37; N, 4.12%.

4.2.8. Synthesis of di-μ-chloro-bis((*R*)-*N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-2-*C*,*N*)palladium(II), *cis*/*trans*-(*R*,*R*)-1. A solution of **7** (352 mg, 0.77 mmol) in CH_2Cl_2 (35 ml) was vigorously shaken with aqueous hydrochloric acid (1 M, 35 ml) for 30 min. The organic layer was separated, dried over sodium sulfate and evaporated to dryness. The product was obtained as yellow powder (264 mg, 100%) showing an enantiomeric purity of >99% ee (according to the ^{19}F NMR data for the (*R*)-phenylglycinate derivative); mp 200°C (decomp.). ^1H NMR ($CDCl_3$, 500.13 MHz, two sets of signals are due to *cis–trans* isomers in a relation of 1:0.95): δ 2.92 and 2.97 (2×s, 3H, N($\underline{CH_3}$)$_2$), 3.11 and 3.13 (2×s, 3H, N($\underline{CH_3}$)$_2$), 4.17–4.21 (q, ^3J(H,F) = 6.8, 1H, $\underline{CH}$-CF_3), 6.95–7.05 (m, 3H, Ph), 7.13–7.23 (m, 1H, Ph). ^{13}C NMR ($CDCl_3$, 125.75 MHz, two sets of signals from *cis–trans* isomers): δ 48.66 and 49.03 (N($\underline{CH_3}$)$_2$)), 54.30 and 54.50 (N($\underline{CH_3}$)$_2$)), 78.17–79.55 (2×q, $\underline{CH}$-CF_3), 120.22–127.00 (q, ^1J(C,F) = 284, CF_3), 124.85 (Ph), 124.96 (Ph), 126.99 (Ph), 127.04 (Ph), 133.20 (Ph), 133.68 (Ph), 141.63 (Ph), 141.73 (Ph), 143.14 (Ph), 143.25 (Ph). ^{19}F NMR ($CDCl_3$, 470.50 MHz, two sets of signals from *cis–trans* isomers): δ −64.86, −64.82. UV–vis (CH_2Cl_2): 345 (3.35). CD (CH_2Cl_2): 317 (−0.86), 349 (+0.75), 384 (−0.22). Anal. calcd for $C_{20}H_{22}Cl_2F_6N_2Pd_2$: C, 34.91; H, 3.22; N, 4.07. Found: C, 34.87; H, 3.35; N, 4.03%.

4.3. Procedure for enantiomeric purity determination

The amino acid (0.05 mmol, 1 equiv.) and potassium carbonate (6.91 mg, 0.05 mmol, 1 equiv.) were dissolved in water (2 ml). *cis*/*trans*-(*S*,*S*)-**1** (17.4 mg, 0.02525 mmol, 0.505 equiv.) was added and the mixture was stirred for 20 h at rt. Then, 6 ml water were added and the resulting solution was extracted with CH_2Cl_2 (4×10 ml). The organic layer was dried over sodium sulfate and the solvent was removed at reduced pressure. The products were dissolved in 0.75 ml dichloromethane-d_2, transferred to a NMR tube and measured at rt.

4.4. Synthesis of compounds {[amino acidato-*N*,*O*][(*S*)-*N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C*,*N*]palladium(II)}

4.4.1. General procedure. Amino acid (0.14 mmol) and potassium carbonate (21 mg, 0.14 mmol) were dissolved in 2 ml water. *cis*/*trans*-(*S*,*S*)-**1** (25 mg, 0.036 mmol) was added and the mixture was stirred for 20 h at rt. The reaction mixture was quenched with water (6 ml) and the resulting solution was extracted with CH_2Cl_2 (4×10 ml). The organic layer after drying with sodium sulfate was evaporated under reduced pressure. The resulting oily residue was dissolved in a small amount CH_2Cl_2 which was mixed with *n*-hexane. The resulting suspension was evaporated to dryness, yielding a white powder.

4.4.2. Synthesis of {[(*S*)-alaninato-*N*,*O*][(*S*)-*N*,*N*-dimethyl - (2,2,2 - trifluoro - 1 - phenylethyl)amine - *C*,*N*]-palladium(II)}. The general procedure was followed to afford the desired complex (25 mg, 86%); mp 160°C (decomp.). ^1H NMR ($CDCl_3$, 500.13 MHz): δ 1.59 (d, ^3J(H,H) = 7.1, 3H, CH-$\underline{CH_3}$), 2.96 (s, 3H, N($\underline{CH_3}$)$_2$), 3.00–3.03 (m, 1H, $\underline{NH_2}$), 3.07 (s, 3H, N($\underline{CH_3}$)$_2$), 3.77–3.83 (m, 1H, $\underline{CH}$-CH_3), 4.18–4.24 (m, 2H, $\underline{NH_2}$ and $\underline{CH}$-CF_3), 6.77–6.78 (m, 1H, Ph), 7.01–7.11 (m, 3H, Ph). ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ 46.90 (N($\underline{CH_3}$)$_2$), 52.59 (N($\underline{CH_3}$)$_2$), 55.34 ($\underline{CH}$-CH_3), 77.20–77.84 (q, ^2J(C,F) = 27, $\underline{CH}$-CF_3), 120.06–126.86 (q, ^1J(C,F) = 285, CF_3), 124.28 (Ph), 124.72 (Ph), 126.53 (Ph), 131.68 (Ph), 142.40 (Ph), 144.78 (Ph), 180.31 (C=O). ^{19}F NMR ($CDCl_3$, 470.50 MHz): δ −64.46. MS-FAB (NOBA): *m*/*z* 705.8 ([2M−Ala]$^+$), 396.9 ([M]$^+$), 307.8 ([M−Ala]$^+$).

4.4.3. Synthesis of {[(*S*)-prolinato-*N*,*O*][(*S*)-*N*,*N*-dimethyl - (2,2,2 - trifluoro - 1 - phenylethyl)amine - *C*,*N*]-palladium(II)}. The general procedure was followed to afford the desired complex (29 mg, 94%); mp 118°C (decomp.). ^1H NMR (CD_2Cl_2, 500.13 MHz): δ 1.66–1.74 (m, 1H, CH_2(NH)-$\underline{CH_2}$-CH_2-$CH(CO_2)$), 1.87–1.94 (m, 1H, CH_2(NH)-$\underline{CH_2}$-CH_2-$CH(CO_2)$), 2.08–2.23 (m, 2H, CH_2(NH)-CH_2-$\underline{CH_2}$-$CH(CO_2)$), 2.89–2.90 (m, 3H, N($\underline{CH_3}$)$_2$), 3.11 (s, 3H, N($\underline{CH_3}$)$_2$), 3.20–3.27 (m, 1H, $\underline{CH_2}$(NH)-CH_2-CH_2-$CH(CO_2)$), 3.34–3.40 (m, 1H, $\underline{CH_2}$(NH)-CH_2-CH_2-$CH(CO_2)$), 4.04–4.09 (m, 1H, CH_2(NH)-CH_2-CH_2-$\underline{CH}(CO_2)$), 4.38–4.43 (m, 2H, $\underline{CH}$-CF_3) and NH), 6.97–7.01 (m, 1H, Ph), 7.03–7.08 (m, 2H, Ph), 7.11–7.14 (m, 1H, Ph). ^{13}C NMR (CD_2Cl_2, 125.75 MHz): δ 25.44 (CH_2(NH)-$\underline{CH_2}$-CH_2-$CH(CO_2)$), 30.23 (CH_2(NH)-CH_2-$\underline{CH_2}$-$CH(CO_2)$), 47.42 (N($\underline{CH_3}$)$_2$), 53.08 ($\underline{CH_2}$(NH)-CH_2-CH_2-$CH(CO_2)$), 53.13 (N($\underline{CH_3}$)$_2$), 66.08 (CH_2(NH)-CH_2-CH_2-$\underline{CH}(CO_2)$), 77.77–78.40 (q, ^2J(C,F) = 26, $\underline{CH}$-CF_3), 121.18–127.99 (q, ^1J(C,F) = 285, CF_3), 124.70 (Ph), 125.18 (Ph), 127.11 (Ph), 133.24 (Ph), 143.29 (Ph), 147.08 (Ph), 180.32 (C=O). ^{19}F NMR (CD_2Cl_2, 470.50 MHz): δ −63.87. MS-FAB (NOBA): *m*/*z* 731.2 ([2M−Pro]$^+$), 422.1 ([M]$^+$), 378.1, 307.0 ([M−Pro]$^+$).

4.4.4. Synthesis of {[(*S*)-valinato-*N,O*][(*S*)-*N,N*-dimethyl - (2,2,2 - trifluoro - 1 - phenylethyl)amine - *C,N*]-palladium(II)}. The general procedure was followed to afford the desired complex (30 mg, 97%); mp 90°C (decomp.). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 1.11–1.15 (m, 6H, CH-CH($\underline{CH_3}$)$_2$), 2.43–2.51 (m, 2H, CH-$\underline{CH}$(CH_3)$_2$ and $\underline{NH_2}$), 2.98 (d, ^4J(H,H) = 1.6, N($\underline{CH_3}$)$_2$), 3.09 (s, 3H, N($\underline{CH_3}$)$_2$), 3.50–3.53 (m, 1H, CH-$\underline{CH}$(CH_3)$_2$), 3.83–3.86 (m, 1H, $\underline{NH_2}$), 4.25–4.30 (q, ^3J(H,F) = 7, $\underline{CH}$-CF_3), 6.71–6.75 (m, 1H, Ph), 7.05–7.09 (m, 2H, Ph), 7.12–7.15 (m, 1H, Ph). ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ 17.72 (CH-CH($\underline{CH_3}$)$_2$), 19.85 (CH-CH($\underline{CH_3}$)$_2$), 31.71 (CH-$\underline{CH}$(CH_3)$_2$), 47.87 (N($\underline{CH_3}$)$_2$), 53.73 (N($\underline{CH_3}$)$_2$), 65.59 (CH-$\underline{CH}$(CH_3)$_2$), 78.32–78.96 (q, ^2J(C,F) = 26.7, $\underline{CH}$-CF_3)), 120.86–127.65 (q, ^1J(C,F) = 284, CF_3), 125.14 (Ph), 125.69 (Ph), 127.46 (Ph), 132.10 (Ph), 143.31 (Ph), 145.86 (Ph), 179.59 (C=O). ^{19}F NMR ($CDCl_3$, 470.50 MHz): δ −64.61. MS-FAB (NOBA): m/z 733.9 ([2M−Val]$^+$), 425.0 ([M]$^+$), 378.9, 307.9 ([M−Val]$^+$).

4.4.5. Synthesis of {[(*S*)-phenylalaninato-*N,O*][(*S*)-*N,N*-dimethyl - (2,2,2 - trifluoro - 1 - phenylethyl)amine - *C,N*]-palladium(II)}. The general procedure was followed to afford the desired complex (31 mg, 91%); mp 180°C (decomp.). ^{1}H NMR (CD_2Cl_2, 500.13 MHz): δ 2.86–2.88 (m, 1H, $\underline{NH_2}$), 2.92 (d, ^4J(H,H) = 1.8, 3H, N($\underline{CH_3}$)$_2$), 2.99 (s, 3H, N($\underline{CH_3}$)$_2$), 3.20–3.25 (m, 1H, CH-$\underline{CH_2}$-Ph), 3.38–3.41 (m, 1H, CH-$\underline{CH_2}$-Ph), 3.72–3.75 (m, 1H, $\underline{NH_2}$), 3.81–3.86 (m, 1H, $\underline{CH}$-CH_2-Ph)), 4.17–4.21 (q, ^3J(H,F) = 7, $\underline{CH}$-CF_3), 6.56–6.58 (m, 1H, Ph), 6.95–6.99 (m, 1H, Ph), 7.03–7.06 (m, 1H, Ph), 7.10–7.11 (m, 1H, Ph), 7.27–7.34 (m, 5H, Ph(Phe)). ^{13}C NMR (CD_2Cl_2, 125.75 MHz): δ 40.68 (CH-$\underline{CH_2}$-Ph), 47.82 (N($\underline{CH_3}$)$_2$), 53.54 (N($\underline{CH_3}$)$_2$), 61.34 ($\underline{CH}$-CH_2-Ph), 78.22–78.85 (q, ^2J(C,F) = 26.7, $\underline{CH}$-CF_3), 120.88–127.41 (q, ^1J(C,F) = 284, CF_3), 124.86 (Ph), 125.67 (Ph), 127.13 (Ph), 127.63 (Ph(Phe)), 129.42 (Ph(Phe)), 129.88 (Ph(Phe)), 132.20 (Ph), 137.27 ($C_{quat.}$), 143.40 ($C_{quat.}$), 145.81 ($C_{quat.}$), 178.81 (C=O). ^{19}F NMR (CD_2Cl_2, 470.50 MHz): δ −64.60. MS-FAB (NOBA): m/z 781.9 ([2M−Phe]$^+$), 472.9 ([M]$^+$), 307.9 ([M−Phe]$^+$).

4.4.6. Synthesis of {[(*S*)-leucinato-*N,O*][(*S*)-*N,N*-dimethyl - (2,2,2 - trifluoro - 1 - phenylethyl)amine - *C,N*]-palladium(II)}. The general procedure was followed to afford the desired complex (27 mg, 84%); mp 112°C (decomp.). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 0.97–0.98 (d, ^3J(H,H) = 6.4, 3H, CH-CH_2-CH($\underline{CH_3}$)$_2$), 1.01–1.02 (d, ^3J(H,H) = 6.4, 3H, CH-CH_2-CH($\underline{CH_3}$)$_2$), 1.68–1.74 (m, 1H, CH-$\underline{CH_2}$-CH(CH_3)$_2$), 1.76–1.83 (m, 1H, CH-CH_2-$\underline{CH}$(CH_3)$_2$), 1.99–2.04 (m, 1H, CH-$\underline{CH_2}$-CH(CH_3)$_2$), 2.52–2.53 (m, 1H, $\underline{NH_2}$), 2.98 (s, 3H, N($\underline{CH_3}$)$_2$), 3.10 (s, 3H, N($\underline{CH_3}$)$_2$), 3.65–3.69 (m, 1H, $\underline{CH}$-CH_2-CH(CH_3)$_2$), 3.95 (m, 1H, $\underline{NH_2}$), 4.26–4.31 (q, ^3J(H,F) = 7, $\underline{CH}$-CF_3), 6.68–6.70 (m, 1H, Ph), 7.04–7.13 (m, 3H, Ph). ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ 21.96 (CH-CH_2-CH($\underline{CH_3}$)$_2$), 23.58 (CH-CH_2-CH($\underline{CH_3}$)$_2$), 25.18 (CH-CH_2-$\underline{CH}$(CH_3)$_2$), 44.33 (CH-$\underline{CH_2}$-CH(CH_3)$_2$), 47.83 (N($\underline{CH_3}$)$_2$), 53.60 (N($\underline{CH_3}$)$_2$), 58.79 ($\underline{CH}$-CH_2-CH(CH_3)$_2$), 78.23–78.87 (q, ^2J(C,F) = 26, $\underline{CH}$-CF_3), 120.90–127.69 (q, ^1J(C,F) = 285, CF_3), 125.17 (Ph), 125.67 (Ph), 127.45 (Ph), 132.16 (Ph), 143.31 (Ph), 145.73 (Ph), 180.76 (C=O). ^{19}F NMR ($CDCl_3$, 470.50 MHz): δ −64.51. MS-FAB (NOBA): m/z 745.1 ([2M−Leu]$^+$), 439.1 ([M]$^+$), 396.1, 308.0 ([M−Leu]$^+$).

4.4.7. Synthesis of {[(*S*)-isoleucinato-*N,O*][(*S*)-*N,N*-dimethyl - (2,2,2 - trifluoro - 1 - phenylethyl)amine - *C,N*]-palladium(II)}. The general procedure was followed to afford the desired complex (29 mg, 91%); mp 85°C (decomp.). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 0.96–0.99 (t, ^3J(H,H) = 7.3, 3H, CH-CH(CH_3)-CH_2-$\underline{CH_3}$), 1.14–1.16 (d, ^3J(H,H) = 6.9, 3H, CH-CH($\underline{CH_3}$)-CH_2-CH_3), 1.32–1.41 (m, 1H, CH-CH(CH_3)-$\underline{CH_2}$-CH_3), 1.66–1.74 (m, 1H, CH-CH(CH_3)-$\underline{CH_2}$-CH_3), 2.10–2.17 (m, 1H, CH-$\underline{CH}$(CH_3)-CH_2-CH_3), 2.44–2.46 (m, 1H, $\underline{NH_2}$), 2.98 (s, 3H, N($\underline{CH_3}$)$_2$), 3.10 (s, 3H, N($\underline{CH_3}$)$_2$), 3.57–3.60 (m, 1H, $\underline{CH}$-CH(CH_3)-CH_2-CH_3), 3.87–3.91 (m, 1H, $\underline{NH_2}$), 4.27–4.31 (q, ^3J(H,F) = 7.1, 1H, $\underline{CH}$-CF_3), 6.70–6.73 (m, 1H, Ph), 7.04–7.12 (m, 3H, Ph). ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ 12.32 (CH-CH(CH_3)-CH_2-$\underline{CH_3}$), 16.47 (CH-CH($\underline{CH_3}$)-CH_2-CH_3), 25.02 (CH-CH(CH_3)-$\underline{CH_2}$-CH_3), 38.67 (CH-$\underline{CH}$(CH_3)-CH_2-CH_3), 47.83 (N($\underline{CH_3}$)$_2$), 53.71 (N($\underline{CH_3}$)$_2$), 65.01 ($\underline{CH}$-CH(CH_3)-CH_2-CH_3), 78.29–78.93 (q, ^2J(C,F) = 27, $\underline{CH}$-CF_3), 120.88–127.68 (q, ^1J(C,F) = 285, CF_3), 125.12 (Ph), 125.64 (Ph), 127.44 (Ph), 132.09 (Ph), 143.31 (Ph), 145.94 (Ph), 179.59 (C=O). ^{19}F NMR ($CDCl_3$, 470.50 MHz): δ −64.56. MS-FAB (NOBA): m/z 746.4 ([2M−Ile]$^+$), 439.2 ([M]$^+$), 396.2, 308.1 ([M−Ile]$^+$).

4.4.8. Synthesis of {[(*S*)-phenylglycinato-*N,O*][(*S*)-*N,N*-dimethyl - (2,2,2 - trifluoro - 1 - phenylethyl)amine - *C,N*]-palladium(II)}. (*S*)-Phenylglycine (13 mg, 0.09 mmol) and potassium carbonate (13 mg, 0.09 mmol) were dissolved in 2 ml water. **1a** (15 mg, 0.02 mmol) was added and the mixture was stirred for 20 h at rt. The yield after work-up (see general procedure) was 20 mg, 100% with mp 180°C (decomp.). ^{1}H NMR ($CDCl_3$, 360.13 MHz): δ 2.69–2.71 (m, 1H, $\underline{NH_2}$), 3.01 (s, 3H, N($\underline{CH_3}$)$_2$), 3.17 (s, 3H, N($\underline{CH_3}$)$_2$), 4.34–4.40 (q, ^3J(H,F) = 7.1, 1H, $\underline{CH}$-CF_3), 4.73–4.81 (m, 2H, $\underline{NH_2}$ and $\underline{CH}$-Ph(Phegly)), 6.63–6.65 (m, 1H, Ph), 6.95–6.99 (m, 1H, Ph), 7.03–7.07 (m, 1H, Ph), 7.11–7.13 (m, 1H, Ph), 7.30–7.39 (m, 3H, Ph(Phegly)), 7.69–7.70 (m, 2H, Ph(Phegly)). ^{13}C NMR ($CDCl_3$, 90.55 MHz): δ 47.78 (N($\underline{CH_3}$)$_2$), 53.75 (N($\underline{CH_3}$)$_2$), 64.29 ($\underline{CH}$-Ph(Phegly)), 78.06–78.94 (q, ^2J(C,F) = 27, $\underline{CH}$-CF_3), 119.65–129.09 (q, ^1J(C,F) = 285, CF_3), 125.16 (Ph), 125.54 (Ph), 127.42 (Ph), 127.88 (Ph(Phegly)), 129.02 (Ph(Phegly)), 129.57 (Ph(Phegly)), 132.32 (Ph), 139.52 ($C_{quat.}$), 143.24 ($C_{quat.}$), 145.54 ($C_{quat.}$), 178.91 (C=O). ^{19}F NMR ($CDCl_3$, 470.50 MHz): δ −64.38. MS-FAB (NOBA): m/z 768.2 ([2M−Phegly]$^+$), 459.1 ([M]$^+$), 416.1, 308.0 ([M−Phegly]$^+$).

4.4.9. Synthesis of {[(*R*)-alaninato-*N,O*][(*S*)-*N,N*-dimethyl - (2,2,2 - trifluoro - 1 - phenylethyl)amine - *C,N*]-palladium(II)}. (*R*)-Alanine (10 mg, 0.12 mmol) and potassium carbonate (16 mg, 0.12 mmol) were dissolved in water (2 ml) *cis*/*trans*-(*S,S*)-**1** (20 mg, 0.03 mmol) was added and the mixture was stirred for 9 h at rt. The yield after work-up (see general procedure) was

22 mg, 96% with mp 160°C (decomp.). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 1.62–1.64 (d, ^3J(H,H) = 7.0, 3H, CH-$\underline{CH_3}$), 2.96 (d, ^4J(H,H) = 1.3, 3H, N($\underline{CH_3}$)$_2$), 3.01–3.04 (m, 4H, N($\underline{CH_3}$)$_2$ and $\underline{NH_2}$), 3.76–3.82 (m, 1H, $\underline{CH}$-CH_3), 4.11–4.15 (q, ^3J(H,F) = 7.0, $\underline{CH}$-CF_3), 4.36–4.39 (m, 1H, $\underline{NH_2}$), 6.80–6.82 (m, 1H, Ph), 7.01–7.10 (m, 3H, Ph).^{13}C NMR ($CDCl_3$, 125.75 MHz): δ 47.88 (N($\underline{CH_3}$)$_2$), 53.50 (N($\underline{CH_3}$)$_2$), 56.35 ($\underline{CH}$-CH_3), 78.15–78.79 (q, ^2J(C,F) = 27, $\underline{CH}$-CF_3), 120.83–127.63 (q, ^1J(C,F) = 285, CF_3), 125.11 (Ph), 125.65 (Ph), 127.37 (Ph), 132.62 (Ph), 143.25 (Ph), 145.59 (Ph), 181.42 (C=O). ^{19}F NMR ($CDCl_3$, 470.50 MHz): δ −64.61. MS-FAB (NOBA): m/z 703.8 ([2M−Ala]$^+$), 396.9 ([M]$^+$), 306.9 ([M−Ala]$^+$).

4.4.10. Synthesis of {[(*R*)-prolinato-*N,O*][(*S*)-*N,N*-dimethyl - (2,2,2 - trifluoro - 1 - phenylethyl)amine - *C,N*]-palladium(II)}. (*R*)-Proline (13 mg, 0.12 mmol,) and potassium carbonate (16 mg, 0.12 mmol) were dissolved in water (2 ml). *cis*/*trans*-(*S,S*)-**1** (20 mg, 0.03 mmol) was added and the mixture was stirred for 9 h at rt. The yield after work-up (see general procedure) was 24 mg, 96%, with mp of 180°C (decomp.). ^{1}H NMR (CD_2Cl_2, 500.13 MHz): δ 1.68–1.74 (m, 1H, CH_2(NH)-$\underline{CH_2}$-CH_2-$CH(CO_2)$), 1.92–1.99 (m, 1H, CH_2(NH)-$\underline{CH_2}$-CH_2-$CH(CO_2)$), 2.15–2.20 (m, 2H, CH_2(NH)-CH_2-CH_2-$CH(CO_2)$), 2.91 (s, 3H. N($\underline{CH_3}$)$_2$), 2.93–2.94 (m, 3H, N($\underline{CH_3}$)$_2$), 3.21–3.34 (m, 2H, $\underline{CH_2}$(NH)-CH_2-CH_2-$CH(CO_2)$), 4.01–4.08 (m, 2H, CH_2(NH)-CH_2-CH_2-$\underline{CH}(CO_2)$ and $\underline{CH}$-CF_3), 4.34–4.38 (m, 1H, NH), 6.98–7.01 (m, 1H, Ph), 7.03–7.06 (m, 2H, Ph), 7.10–7.12 (m, 1H, Ph). ^{13}C NMR (CD_2Cl_2, 125.75 MHz): δ 25.79 (CH_2(NH)-$\underline{CH_2}$-CH_2-$CH(CO_2)$), 30.56 (CH_2(NH)-CH_2-$\underline{CH_2}$-$CH(CO_2)$), 48.31 (N($\underline{CH_3}$)$_2$), 53.59 ($\underline{CH_2}$(NH)-CH_2-CH_2-$CH(CO_2)$), 53.91 (N($\underline{CH_3}$)$_2$), 65.93 (CH_2(NH)-CH_2-CH_2-$\underline{CH}(CO_2)$), 78.83–79.47 (q, ^2J(C,F) = 27, $\underline{CH}$-CF_3), 120.75–127.50 (q, ^1J(C,F) = 283, CF_3), 124.61 (Ph), 125.87 (Ph), 127.27 (Ph), 133.19 (Ph), 143.41 (Ph), 147.79 (Ph), 180.76 (C=O). ^{19}F NMR (CD_2Cl_2, 470.50 MHz): δ −67.26. MS-FAB (NOBA): m/z 843.8 ([2M]$^+$), 731.8 ([2M−Pro]$^+$), 422.9 ([M]$^+$), 376.9, 306.9 ([M−Pro]$^+$).

4.4.11. Synthesis of {[(*R*)-valinato-*N,O*][(*S*)-*N,N*-dimethyl - (2,2,2 - trifluoro - 1 - phenylethyl)amine - *C,N*]-palladium(II)}. (*R*)-Valine (14 mg, 0.12 mmol) and potassium carbonate (16 mg, 0.12 mmol) were dissolved in 2 ml water. *cis*/*trans*-(*S,S*)-**1** (20 mg, 0.03 mmol) was added and the mixture was stirred for 20 h at rt. The yield after work-up (see general procedure) was 22 mg, 89% with mp of 125°C (decomp.). ^{1}H NMR ($CDCl_3$, 500.13 MHz): δ 1.18–1.19 (d, ^3J(H,H) = 6.9, 3H, CH-CH($\underline{CH_3}$)$_2$), 1.21–1.22 (d, ^3J(H,H) = 7.0, 3H, CH-CH($\underline{CH_3}$)$_2$), 2.45–2.51 (m, 1H, CH-$\underline{CH}$(CH_3)$_2$), 2.57–2.59 (m, 1H, $\underline{NH_2}$), 2.96 (d, ^4J(H,H) = 1.5, 3H, N($\underline{CH_3}$)$_2$), 3.01 (s, 3H, N($\underline{CH_3}$)$_2$), 3.53–3.55 (m, 1H, $\underline{CH}$-CH(CH_3)$_2$), 3.99–4.03 (q, ^3J(H,F) = 7, $\underline{CH}$-CF_3), 4.32–4.36 (m, 1H, $\underline{NH_2}$), 6.76–6.81 (m, 1H, Ph), 7.03–7.11 (m, 3H, Ph). ^{13}C NMR ($CDCl_3$, 125.75 MHz): δ 18.13 (CH-CH($\underline{CH_3}$)$_2$), 19.92 (CH-CH($\underline{CH_3}$)$_2$), 31.87 (CH-$\underline{CH}$(CH_3)$_2$), 47.96 (N($\underline{CH_3}$)$_2$), 53.36 (N($\underline{CH_3}$)$_2$), 65.75 ($\underline{CH}$-CH(CH_3)$_2$), 77.91–78.54 (q, ^2J(C,F) = 26, $\underline{CH}$-CF_3), 120.83–127.62 (q, ^1J(C,F) = 284, CF_3), 125.23 (Ph), 125.69 (Ph), 127.38 (Ph), 132.13 (Ph), 143.36 (Ph), 145.67 (Ph), 179.78 (C=O). ^{19}F NMR ($CDCl_3$, 470.50 MHz): δ −64.57. MS-FAB (NOBA): m/z 734.0 ([2M−Val]$^+$), 425.0 ([M]$^+$), 382.0, 307.0 ([M−Val]$^+$).

4.4.12. Synthesis of {[(*R*)-phenylalaninato-*N,O*][(*S*)-*N,N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C,N*]-palladium(II)}. (*R*)-Phenylalanine (14 mg, 0.09 mmol,) and potassium carbonate (13 mg, 0.09 mmol) were dissolved in 2 ml water. *cis*/*trans*-(*S,S*)-**1** (15 mg, 0.02 mmol) was added and the mixture was stirred for 24 h at rt. The yield after work-up (see general procedure) was 20 mg, 97% with mp 125°C (decomp.). ^{1}H NMR (CD_2Cl_2, 360.13 MHz): δ 2.67–2.69 (m, 1H, $\underline{NH_2}$), 2.90 (s, 3H, N($\underline{CH_3}$)$_2$), 2.94 (s, 3H, N($\underline{CH_3}$)$_2$), 3.26–3.33 (m, 1H, CH-$\underline{CH_2}$-Ph), 3.42–3.47 (m, 1H, CH-$\underline{CH_2}$-Ph), 3.75–3.81 (m, 1H, $\underline{CH}$-CH_2-Ph), 3.94–4.00 (q, ^3J(H,F) = 7, $\underline{CH}$-CF_3), 4.29–4.33 (m, 1H, $\underline{NH_2}$), 6.59–6.61 (m, 1H, Ph), 6.96–7.00 (m, 1H, Ph), 7.04–7.10 (m, 2H, Ph), 7.25–7.34 (m, 5H, Ph(Phe)). ^{13}C NMR (CD_2Cl_2, 90.55 MHz): δ 41.28 (CH-$\underline{CH_2}$-Ph), 47.97 (N($\underline{CH_3}$)$_2$), 53.37 (N($\underline{CH_3}$)$_2$), 62.22 ($\underline{CH}$-CH_2-Ph), 77.76–78.63 (q, ^2J(C,F) = 26, $\underline{CH}$-CF_3), 120.12–129.57 (q, ^1J(C,F) = 285, CF_3), 125.51 (Ph), 125.86–125.89 (q, ^4J(C,F) = 2.7, Ph), 127.58 (Ph), 128.16 (Ph(Phe)), 129.90 (Ph(Phe)), 130.19 (Ph(Phe)), 132.87 (Ph), 137.51 ($C_{quat.}$), 143.83 ($C_{quat.}$), 145.88 ($C_{quat.}$), 179.58 (C=O). ^{19}F NMR (CD_2Cl_2, 470.50 MHz): δ −64.01. MS-FAB (NOBA): m/z 782.0 ([2M−Phe]$^+$), 473.0 ([M]$^+$), 429.0, 308.0 ([M−Phe]$^+$).

4.4.13. Synthesis of {[(*R*)-leucinato-*N,O*][(*S*)-*N,N*-dimethyl - (2,2,2 - trifluoro - 1 - phenylethyl)amine - *C,N*]-palladium(II)}. (*R*)-Leucine (11 mg, 0.09 mmol) and potassium carbonate (13 mg, 0.09 mmol) were dissolved in 2 ml water. *cis*/*trans*-(*S,S*)-**1** (15 mg, 0.02 mmol) was added and the mixture was stirred for 20 h at rt. The yield after work-up (see general procedure) was 19 mg, 100% with mp 170°C (decomp.). ^{1}H NMR ($CDCl_3$, 360.13 MHz): δ 0.96–0.98 (d, ^3J(H,H) = 6.8, 3H, CH-CH_2-CH($\underline{CH_3}$)$_2$), 1.01–1.02 (d, ^3J(H,H) = 6.4, 3H, CH-CH_2-CH($\underline{CH_3}$)$_2$), 1.74–1.92 (m, 2H,, CH-$\underline{CH_2}$-$CH(CH_3)_2$), 2.01–2.08 (m, 1H,, CH-$\underline{CH_2}$-$CH(CH_3)_2$), 2.65–2.67 (m, 1H, $\underline{NH_2}$), 2.97 (s, 3H, N($\underline{CH_3}$)$_2$), 3.05 (s, 3H, N($\underline{CH_3}$)$_2$), 3.68–3.73 (m, 1H, $\underline{CH}$-CH_2-$CH(CH_3)_2$), 4.07–4.13 (q, ^3J(H,F) = 7, 1H, $\underline{CH}$-CF_3), 4.20–4.24 (m, 1H, $\underline{NH_2}$), 6.73–6.75 (m, 1H, Ph), 7.01–7.12 (m, 3H, Ph). ^{13}C NMR ($CDCl_3$, 90.55 MHz): δ 22.09 (CH-CH_2-CH($\underline{CH_3}$)$_2$), 23.58 (CH-CH_2-CH($\underline{CH_3}$)$_2$), 25.29 (CH-CH_2-$\underline{CH}$(CH_3)$_2$), 44.20 (CH-$\underline{CH_2}$-$CH(CH_3)_2$), 47.97 (N($\underline{CH_3}$)$_2$), 53.54 (N($\underline{CH_3}$)$_2$), 59.05 ($\underline{CH}$-CH_2-$CH(CH_3)_2$), 78.01–78.96 (q, ^2J(C,F) = 26, $\underline{CH}$-CF_3), 119.49–128.94 (q, ^1J(C,F) = 285, CF_3), 125.21 (Ph), 125.76 (Ph), 127.40 (Ph), 132.23 (Ph), 143.34 (Ph), 145.57 (Ph), 181.00 (C=O). ^{19}F NMR ($CDCl_3$, 470.50 MHz): δ −64.70. MS-FAB (NOBA): m/z 748.0 ([2M−Leu]$^+$), 439.0 ([M]$^+$), 394.0, 307.9 ([M−Leu]$^+$).

4.4.14. Synthesis of {[(*R*)-isoleucinato-*N,O*][(*S*)-*N,N*-dimethyl - (2,2,2 - trifluoro - 1 - phenylethyl)amine - *C,N*]-palladium(II)}. (*R*)-Isoleucine (11 mg, 0.09 mmol,) and potassium carbonate (13 mg, 0.09 mmol) were dissolved in 2 ml water. *cis*/*trans*-(*S,S*)-**1** (15 mg, 0.02 mmol) was

added and the mixture was stirred for 24 h at rt. The yield after work-up (see general procedure) was 18 mg, 95% with mp 143°C (decomp.). ^{1}H NMR ($CDCl_3$, 360.13 MHz): δ 0.95–1.00 (t, ^3J(H,H) = 7, 3H, CH-CH(CH_3)-CH_2-$\underline{CH_3}$), 1.18–1.20 (d, ^3J(H,H) = 7.3, 3H, CH-CH($\underline{CH_3}$)-CH_2-CH_3), 1.43–1.54 (m, 1H, CH-CH(CH_3)-$\underline{CH_2}$-CH_3), 1.75–1.86 (m, 1H, CH-CH(CH_3)-$\underline{CH_2}$-CH_3), 2.13–2.20 (m, 1H, CH-$\underline{CH}$(CH_3)-CH_2-CH_3), 2.54–2.56 (m, 1H, $\underline{NH_2}$), 2.98 (s, 3H, N($\underline{CH_3}$)$_2$), 3.01 (s, 3H, N($\underline{CH_3}$)$_2$), 3.60–3.65 (m, 1H, $\underline{CH}$-CH(CH_3)-CH_2-CH_3), 3.99–4.04 (31 (q, ^3J(H,F) = 7, 1H, $\underline{CH}$(CF_3)), 4.21–4.26 (m, 1H, $\underline{NH_2}$), 6.76–6.78 (m, 1H, Ph), 7.02–7.11 (m, 3H, Ph). ^{13}C NMR ($CDCl_3$, 90.55 MHz): δ 11.89 (CH-CH(CH_3)-CH_2-$\underline{CH_3}$), 16.13 (CH-CH($\underline{CH_3}$)-CH_2-CH_3), 24.86 (CH-CH(CH_3)-$\underline{CH_2}$-CH_3), 38.35 (CH-$\underline{CH}$(CH_3)-CH_2-CH_3), 47.63 (N($\underline{CH_3}$)$_2$), 53.05 (N($\underline{CH_3}$)$_2$), 64.72 ($\underline{CH}$-CH(CH_3)-CH_2-CH_3), 77.64–78.28 (q, ^2J(C,F) = 27, $\underline{CH}$(CF_3)), 120.41–127.20 (q, ^1J(C,F) = 285, CF_3), 124.79 (Ph), 125.33 (Ph), 126.97 (Ph), 131.70 (Ph), 142.97 (Ph), 145.37 (Ph), 179.40 (C=O). ^{19}F NMR ($CDCl_3$, 470.50 MHz): δ −64.67. MS-FAB (NOBA): m/z 747.9 ([2M−Ile]$^+$), 439.0 ([M]$^+$), 396.0, 307.9 ([M−Ile]$^+$).

4.4.15. Synthesis of {[(*R*)-phenylglycinato-*N*,*O*][(*S*)-*N*,*N*-dimethyl-(2,2,2-trifluoro-1-phenylethyl)amine-*C*,*N*]-palladium(II)}. See Section 4.2.5.

Acknowledgements

We thank F. Nydegger for measuring mass spectra and F. Fehr for measurements of the nuclear magnetic resonance spectra.

References

1. Parker, D. *Chem. Rev.* **1991**, *91*, 1441–1457.
2. Staubach, B.; Buddrus, J. *Angew. Chem.* **1996**, *35*, 1344–1346.
3. Böhm, A.; Hauck, T.; Beck, W. *Z. Naturforsch.* **1999**, *54b*, 1360–1362.
4. Dunina, V. V.; Gorunova, O. N.; Livantsov, M. V.; Grishin, Y. K. *Tetrahedron: Asymmetry* **2000**, *11*, 2907–2916.
5. Chooi, S. Y. M.; Leung, P.-H.; Lim, C. C.; Mok, K. F.; Quek, G. H.; Sim, K. Y.; Tan, M. K. *Tetrahedron: Asymmetry* **1992**, *3*, 529–532.
6. Kyba, E. P.; Rines, S. P. *J. Org. Chem.* **1982**, *47*, 4800–4801.
7. Albert, J.; Granell, J.; Muller, G.; Sainz, D.; Font-Bardia, M.; Solans, X. *Tetrahedron: Asymmetry* **1995**, *6*, 325–328.
8. Dunina, V. V.; Kuzmina, L. G.; Kazakova, M. Y.; Grishin, Y. K.; Veits, Y. A.; Kazakova, E. I. *Tetrahedron: Asymmetry* **1997**, *8*, 2537–2545.
9. Lim, C.-C.; Leung, P.-H.; Sim, K. Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1883–1886.
10. Wang, Y.; Mosher, H. S. *Tetrahedron Lett.* **1991**, *32*, 987–990.
11. Lustig, E. *J. Phys. Chem.* **1961**, *65*, 491.
12. Shepard, R. A.; Wentworth, S. E. *J. Org. Chem.* **1967**, *32*, 3197–3199.
13. Clarke, H. T.; Gillespie, H. B.; Weisshaus, S. Z. *J. Am. Chem. Soc.* **1933**, *55*, 4571–4587.
14. Cope, A. C.; Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, *1*, 909–913.
15. Ambach, E.; Beck, W. *Chem. Ber.* **1985**, *118*, 2722–2737.
16. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.
17. Sheldrick, G. M. SHELXL-97, Universität Göttingen, Göttingen, Germany, 1999.
18. CCDC 184776 contains the supplementary crystallographic data for **7**. These data can be obtained free of charge from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk.