Supplementary Material (ESI) for Dalton Transactions

Sonogashira and "Click" reactions for the *N*-terminal and side chain functionalization of peptides with $[Mn(tpm)(CO)_3]^+$-based CO releasing molecules (tpm = tris(pyrazolyl)methane)

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Supporting Information

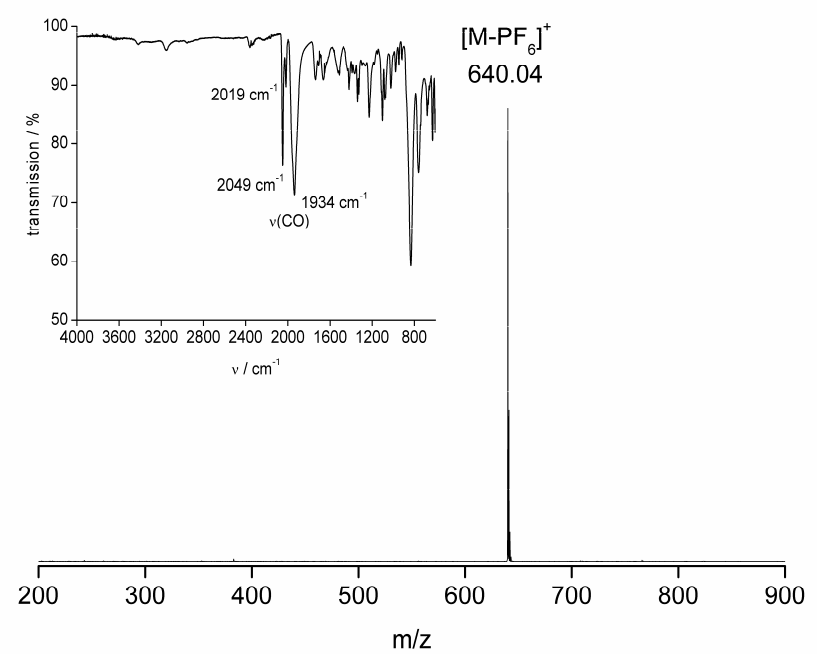


Figure S1. ESI^+ mass spectrum and (inset) ATR-IR spectrum of $[Mn(CO)_3(tpm\text{-}L2)]PF_6$ (**11**).

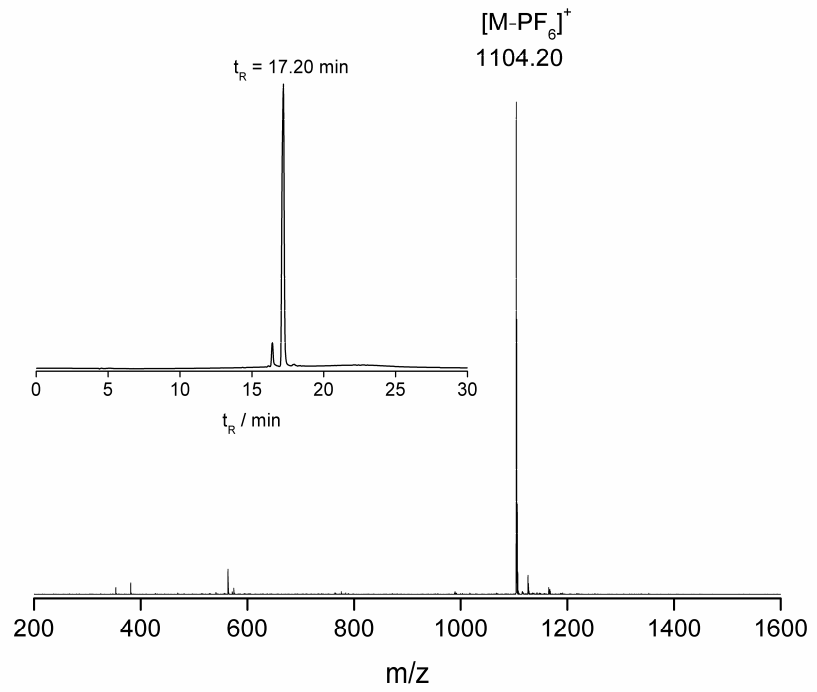


Figure S2. ESI^+ mass spectrum and (inset) analytical HPLC chromatogramm (254 nm) of peptide conjugate **21**.

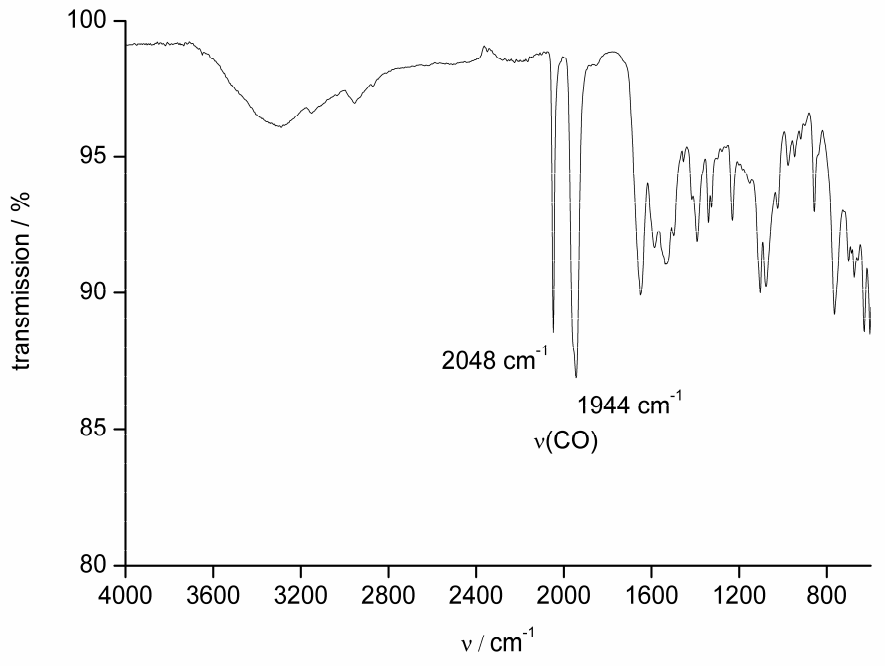


Figure S3. ATR-IR spectrum of peptide conjugate **21**.

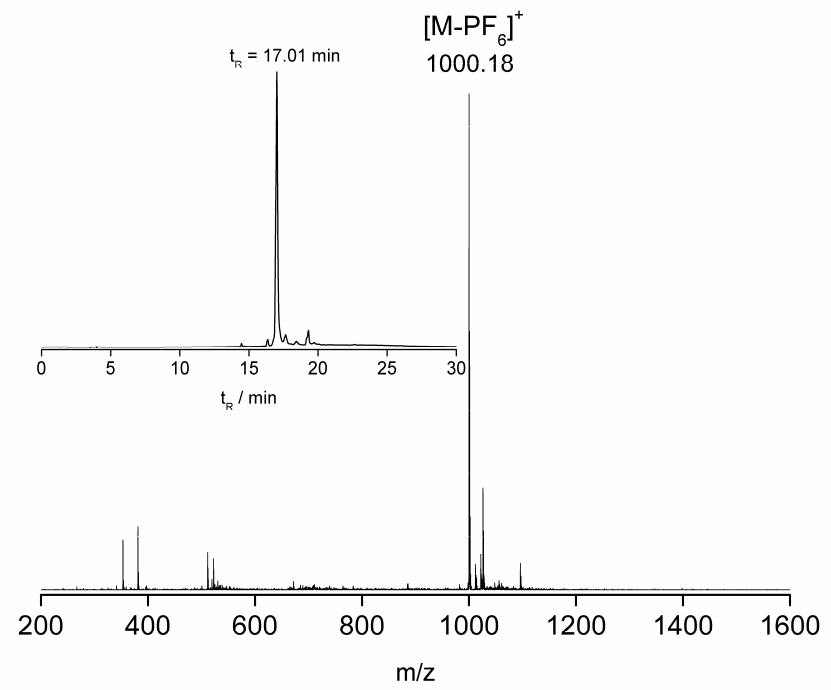


Figure S4. ESI^+ mass spectrum and (inset) analytical HPLC chromatogramm (254 nm) of peptide conjugate **22**.

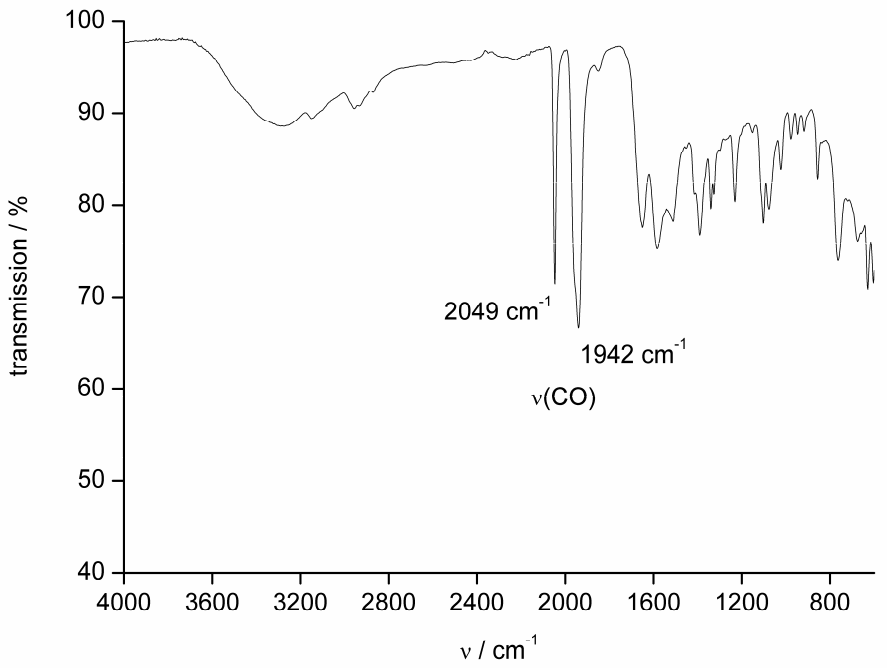
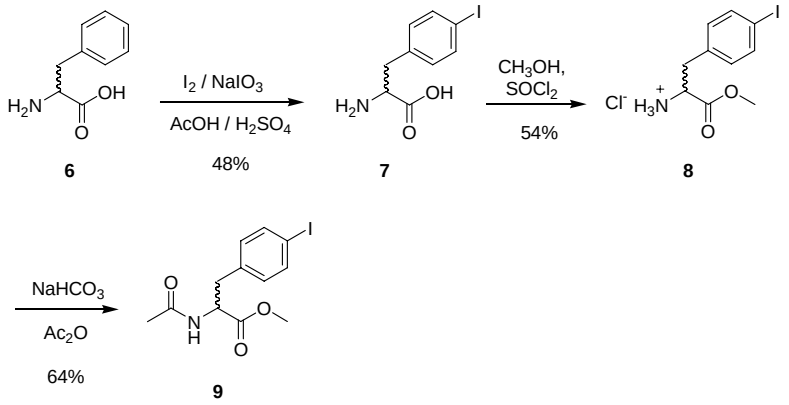


Figure S5. ATR-IR spectrum of peptide conjugate **22**.

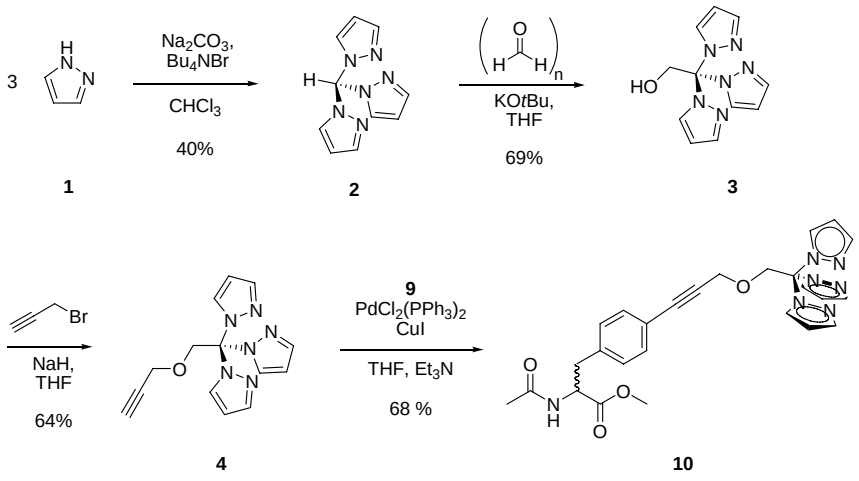


Scheme S1. Synthesis of *N*-Acetyl-4-iodo-*DL*-phenylalaninemethylester (**9**).

4-Iodo-*DL*-phenylalanine (7).[1] *DL*-Phenylalanine (**6**) (10.0 g, 60.8 mmol) was dissolved in a mixture of concentrated acetic acid (55 ml) and concentrated sulphuric acid (7.3 ml). Under stirring, powderized iodine (6.16 g, 24.3 mmol) and sodium iodate (2.55 g, 13.9 mmol) were added to the colorless solution. The mixture turned deep purple and was heated to 70 °C for 18 h until a change of color to orange indicated the end of the reaction. The acetic acid was removed *in vacuo* and the viscous residue treated with water (100 ml) and extracted with diethylether (2x 25 ml) and dichlormethane (2x 25 ml). For decolorization, the aequeous phase was then treated with charcoal (Norit®, 1.5 g) and filtered. After adjusting the pH to 5 with a concentrated solution of sodium hydroxide, a white precipitate formed, which was filtered off and washed with water (200 ml) followed by ethanol (75 ml). The white powder obtained was dried in a dessicator over calcium cloride. Yield: 48% (8.56 g, 29.0 mmol). MS (ESI^+, CH_3OH): *m/z* 292 $[M+H]^+$, 314 $[M+Na]^+$; IR (ATR, cm^{-1}): 3020 (m), 2927 (m), 2721 (m), 2601 (m), 1584 (s) ν(C=O); ^{1}H-NMR (400.13 MHz, D_2O/DCl): δ 7.76 (d, 2H, H-2, H-6, ^3J = 8.2 Hz), 7.08 (d, 2H, H-3, H-5, ^3J = 8.2 Hz), 4.31 (dd, 1H, H-α, $^3J_{\alpha,\beta}$ = 5.9 Hz, $^3J_{\alpha,\beta'}$ = 7.5 Hz), 3.28 (dd, 1H, H-β, $^3J_{\alpha,\beta}$ = 5.9 Hz, $^2J_{\beta,\beta'}$ = 14.6 Hz), 3.03 (dd, 1H, H-β', $^3J_{\alpha,\beta'}$ = 7.5 Hz, $^2J_{\beta,\beta'}$ = 14.6 Hz) ppm; ^{13}C-NMR (100.62 MHz, D_2O/DCl): δ 171.05 (C=O), 138.05 (C-2, C-6), 133.61 (C-4), 131.28 (C-3, C-5), 92.87 (C-1), 53.70 (C_α), 35.03 (C_β) ppm.

4-Iodo-*DL*-phenylalaninemethylester hydrochloride (8).[1] Under cooling with ice, thionylchloride (5.00 ml, 8.22 g, 69.0 mmol) was added to methanol (50 ml). Then, 4-iodo-*DL*-phenylalanine (**7**) (4.00 g, 13.7 mmol) was added and the mixture heated to reflux for 2 h. After cooling to room temperature, the solvent was completely evaporated under reduced pressure and the yellowish residue again dissolved in methanol and added with stirring to diethylether (300 ml). The white precipitate formed was filtered off, washed with a small amount of diethylether, and dried under vacuum at 40 °C. Yield: 54% (2.25 g, 7.4 mmol). MS (ESI^+, CH_3OH): *m/z* 306 $[M-Cl]^+$, 328 $[M+Na-HCl]^+$; IR (ATR, cm^{-1}): 2826 (s) ν(NH) , 2632 (w), 2008, (w), 1773 (s) ν(C=O), 1243 (s), 834 (s); ^{1}H-NMR (400.13 MHz, CD_3OD): δ 7.75 (d, 2H, H-2, H-6, ^3J = 8.2 Hz), 7.08 (d, 2H, H-3, H-5, ^3J = 8.2 Hz), 4.34 (dd, 1H, 1H, H-α, $^3J_{\alpha,\beta}$ = 6.3 Hz, $^3J_{\alpha,\beta'}$ = 7.2 Hz), 3.83 (s, 3H, CH_3), 3.24 (dd, 1H, H-β, $^3J_{\alpha,\beta}$ = 6.3 Hz, $^2J_{\beta,\beta'}$ = 14.4 Hz), 3.03 (dd, 1H, H-β', $^3J_{\alpha,\beta'}$ = 7.2 Hz, $^2J_{\beta,\beta'}$ = 14.4 Hz) ppm; ^{13}C-NMR (100.62 MHz, CD_3OD): δ 170.31 (C=O), 139.42 (C-2, C-6), 135.19 (C-4), 132.56 (C-3, C-5), 94.14 (C-1), 54.97 (C_α), 53.72 (OCH_3), 36.91 (C_β) ppm.

***N*-Acetyl-4-iodo-*DL*-phenylalaninemethylester (9)**.[2] 4-Iodo-*DL*-phenylalaninemethylester hydrochloride (**8**) (650 mg, 1.90 mmol) was dissolved in a mixture of methanol (20 ml) and acetic anhydride (0.45 ml, 4.76 mmol). Then, sodium hydrogencarbonate (430 mg, 5.12 mmol) was added. After stirring the mixture for 3.5 h at room temperature, the remaining sodium hydrogencarbonate was filtered off and the solvent removed under reduced pressure. The white residue was washed with water (2x 5 ml) followed by diethylether (1x 5 ml) and dried *in vacuo* to gibe a white powder. R_f = 0.76 (silica, CH_2Cl_2/CH_3OH 9:1,). Yield: 64% (420 mg, 1.21 mmol). Elemental analysis calculated for $C_{12}H_{14}INO_3$ (%): C 41.52, H 4.06, N 4.03, found: C 41.14, H 4.11, N 3.95; MS (ESI^+, CH_3OH): *m/z* 370 $[M+Na]^+$; IR (ATR, cm^{-1}): 3292 (m) ν(NH), 2951 (w), 1735 (s) ν(C=O, ester), 1649 (s) ν(C=O, amide), 1537 (s), 1484 (s), 1247 (s), 1027 (s), 1004 (s); ^{1}H-NMR (400.13 MHz, $CDCl_3$): δ 7.61 (d, 2H, H-2, H-6, ^3J = 8.3 Hz), 6.84 (d, 2H, H-3, H-5, ^3J = 8.3 Hz), 5.91 (d, 1H, NH, $^3J_{CH,NH}$ = 6.9 Hz), 4.86 (ddd, 1H, H-α, $^3J_{CH,NH}$ = 6.9 Hz, $^3J_{\alpha,\beta}$ = 5.9 Hz, $^3J_{\alpha,\beta'}$ = 5.5 Hz), 3.73 (s, 3H, OCH_3), 3.11 (dd, 1H, H-β, $^3J_{\alpha,\beta}$ = 5.9 Hz, $^2J_{\beta,\beta'}$ = 13.9 Hz), 3.03 (dd, 1H, H-β', $^3J_{\alpha,\beta'}$ = 5.5 Hz, $^2J_{\beta,\beta'}$ = 13.9 Hz), 1.99 (s, 3H, $NHCOCH_3$) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$): δ 171.82, 169.53 (C=O), 137.64 (C-2, C-6), 135.55 (C-4), 131.28 (C-3, C-5), 92.06 (C-1), 52.92 (C_α), 52.41 (OCH_3), 37.04 (C_β), 23.13 ($NHCOCH_3$) ppm.



Scheme S2. Synthesis of model conjugate tpm-L1 (**10**).

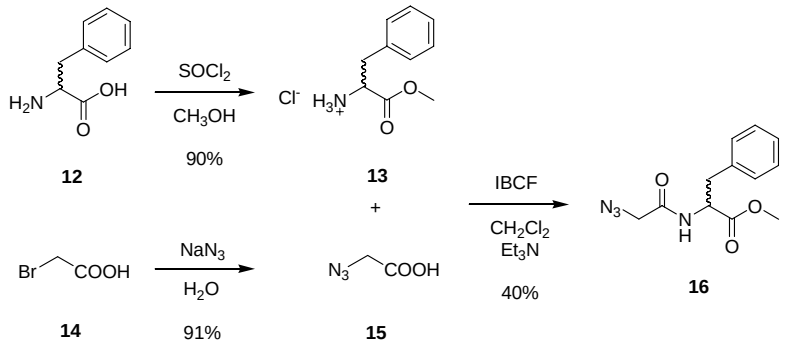
Tris(pyrazol-1-yl)methan (2).[3] Pyrazole (**1**) (15.0 g, 220 mmol) and tetra-*n*-butylammoniumbromide (3.54 g, 11.0 mmol) were dissolved in water (250 ml) and then, sodium carbonate (140.0 g, 1.32 mol) was carefuly added in small portions with vigorous stirring (exothermal reaction!). After cooling, chloroform (120 ml) was added to the colorless solution and heated to reflux for 3 d. After cooling to room temperature, the layers were separated and the aqueous phase was extracted with diethylether (3x 200 ml). The combined organic layers were washed with water (5x 200 ml) and dried over magnesium sulfate. Evaporation of the solvent yielded a light brown solid. For recrystallisation, the solid was dissolved in boiling cyclohexane, treated with charcoal for decolorization (Norit®, 1 g) and filtered off while still hot. After cooling to RT, the crystalline precipitate formed was isolated and dried under vacuum. Yield: 36% (5.67 g, 26.5 mmol). Elemental analysis calculated for $C_{10}H_{10}N_6$ (%): C 56.07, H 4.70, N 39.23, found: C 55.94, H 4.62, N 39.07; MS (FAB$^+$): *m/z* 215 $[M+H]^+$, 237 $[M+Na]^+$; IR (ATR, cm^{-1}): 3121 (m), 2977 (m), 1514 (s), 1427 (s), 1385 (s); ^{1}H-NMR (200.13 MHz, $CDCl_3$): δ 8.41 (s, 1H, H_q), 7.65 (dd, 3H, H(3-pz), $^3J_{4\text{-pz},3\text{-pz}}$ = 1.8 Hz, $^4J_{5\text{-pz},3\text{-pz}}$ = 0.6 Hz), 7.56 (dd, 3H, H(5-pz), $^3J_{4\text{-pz},5\text{-pz}}$ = 2.6 Hz, $^4J_{3\text{-pz},5\text{-pz}}$ = 0.6 Hz), 6.35 (dd, 3H, H(4-pz), $^3J_{3\text{-pz},4\text{-pz}}$ = 1.8 Hz, $^3J_{5\text{-pz},4\text{-pz}}$ = 2.6 Hz) ppm; ^{13}C-NMR (50.32 MHz, $CDCl_3$): δ 141.78 ($C_{3\text{-pz}}$), 129.49 ($C_{5\text{-pz}}$), 107.28 ($C_{4\text{-pz}}$), 83.32 (C_q) ppm.

Tris-2,2,2-(pyrazol-1-yl)ethanol (3).[3] Tris(pyrazol-1-yl)methane (**2**) (5.60 g, 26.0 mmol), paraformaldehyde (2.73 g, 91.0 mmol) and potassium *tert*-butanolate (10.2 g, 91.0 mmol) were dissolved in anhydrous tetrahydrofuran (400 ml) and the brown-orange solution stirred for 2 d at RT. Subsequently, water was added (150 ml) and the mixture was then extracted with diethylether (4x 150 ml). The combined organic phases were dried over magnesium sulfate and the solvent evaporated under reduced pressure. Recrystallisation of the yellowish residue from methanol yielded a white crystalline solid. Yield: 69% (4.34 g, 18.0 mmol). Elemental analysis calculated for $C_{11}H_{12}N_6O$ (%): C 54.09, H 4.95, N 34.41, found: C 53.99, H 4.95, N 34.43; MS (FAB$^+$): *m/z* 267 $[M+Na]^+$, 245 $[M+H]^+$; IR (ATR, cm^{-1}): 3259 (w), 3156 (w), 3132 (w), 3067 (w), 2961 (w), 1513 (m); ^{1}H-NMR (400.13 MHz, $CDCl_3$): δ 7.68 (dd, 3H, H(3-pz), $^3J_{4\text{-pz},3\text{-pz}}$ = 1.8 Hz, $^4J_{5\text{-pz},3\text{-pz}}$ = 0.6 Hz), 7.10 (dd, 3H, H(5-pz), $^3J_{4\text{-pz},5\text{-pz}}$ = 2.6 Hz, $^4J_{3\text{-pz},5\text{-pz}}$ = 0.6 Hz), 6.34 (dd, 3H, H(4-pz), $^3J_{3\text{-pz},4\text{-pz}}$ = 1.8 Hz, $^3J_{5\text{-pz},4\text{-pz}}$ = 2.6 Hz), 5.06 (s, 2H, CH_2) ppm; ^{13}C-NMR (100.61 MHz, $CDCl_3$): δ 141.85 ($C_{3\text{-pz}}$), 130.32 ($C_{5\text{-pz}}$), 107.03 ($C_{4\text{-pz}}$), 89.67 (C_q), 68.20 (CH_2) ppm.

Tris-2,2,2-(pyrazol-1-yl)ethoxypropargylether (4).[4] Tris-2,2,2-(pyrazol-1-yl)ethanol (**3**) (3.48 g, 14.3 mmol) was dissolved in anhydrous tetrahydrofuran (50 ml) and added dropwise over 15 min to a suspension of sodium hydride (99%) (342 mg, 14.3 mmol) in anhydrous tetrahydrofuran (80 ml). After heating the suspension to reflux for 1.5 h, propargylbromide (1.69 g, 14.3 mmol) was added and the heating continued for another 40 h. After cooling to RT, water was added to the mixture, the phases separated and the aqueous phase extracted with dichloromethane (3x 100 ml). The combined organic phases were washed with saturated sodium hydrogencarbonate solution (1x 100 ml) and water (4x 100 ml) and dried over magnesium sulfate. After evaporation of the solvent, the brown residue was purified by column chromatography on silica with *n*-hexane/ethylacetate (1:1) as the eluent (R_f = 0.61) to obtain a colorless crystalline solid. Yield: 64% (2.58 g, 9.20 mmol). Elemental analysis calculated for $C_{14}H_{14}N_6O$ (%): C 59.56, H 5.00, N 29.77, found: C 59.34, H 5.08, N 29.60; MS (FAB$^+$): *m/z* 147 $[M-2pz+H]^+$, 215 $[M-pz+H]^+$, 283 $[M+H]^+$, 305 $[M+Na]^+$; IR (ATR, cm^{-1}): 3263 (s) ν(CC-H), 2112 (w) ν(C≡C); ^{1}H-NMR (400.13 MHz, $CDCl_3$): δ 7.68 (dd, 3H, H(3-pz), ^3J = 1.7 Hz, ^4J = 0.6 Hz), 7.40 (dd, 3H, H(5-pz), ^3J = 2.6 Hz, ^4J = 0.6 Hz), 6.34 (dd, 3H, H(4-pz), ^3J = 2.6 Hz, ^3J = 1.7 Hz), 5.20 (s, 2H, $OCH_2C(pz)_3$), 4.19 (d, 2H, $OCH_2C{\equiv}C$, ^4J = 2.4 Hz), 2.50 (t, 1H, C≡CH, ^4J = 2.4 Hz) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$): δ 141.3 ($C_{3\text{-pz}}$), 130.8 ($C_{5\text{-pz}}$), 106.5 ($C_{4\text{-pz}}$), 89.6 ($C_{q\text{-tpm}}$), 78.5 (*C*≡C), 75.7 (C≡*C*), 72.8 ($OCH_2C(pz)_3$), 59.2 (OCH_2-C≡C) ppm.

***cis*-Dichlorobis(triphenylphosphine)palladium(II).**[5] Palladium(II)chloride (250 mg, 1.50 mmol) and lithium chloride (280 mg, 6.60 mmol) were dissolved in anhydrous methanol (100 ml). Triphenylphosphine (0.90 g, 3.00 mmol) was added to the orange solution and the mixture heated to reflux for 1.5 h. The light yellow preciptate was filtered off, recrystallized from chloroform, and dried under vacuum. Yield: 41% (429 mg, 0.61 mmol). IR (ATR, cm^{-1}): 1729 (m), 1480 (m), 1435 (m), 1095 (s), 690 (s); MS (ESI^+, CH_3OH): *m/z* 1104 $[(PPh_3)_2Pd(\mu\text{-}Cl)_2Pd(PPh_3)Cl]^+$, 665 $[M\text{-}Cl]^+$, 649 $[M\text{-}2Cl\text{+}OH]^+$; ^{1}H-NMR (400.13 MHz, $CDCl_3$): δ 7.73 - 7.69 (m, 9H, H-3, H-4, H-5), 7.45 - 7.36 (m, 6H, H-2, H-6) ppm; ^{31}P-NMR (161.98 MHz, $CDCl_3$): δ 24.46 ppm.

tpm-L1 (10). *N*-Acetyl-4-iodo-*DL*-phenylalaninemethylester (**9**) (250 mg, 0.72 mmol) und tris-2,2,2-(pyrazol-1-yl)ethoxypropargylether (**4**) (203 mg, 0.72 mmol) were dissolved in a triethylamine/tetrahydrofuran mixture (13 ml, 1:2.25) and subsequently degassed by two "freeze-pump-thaw" cycles. Then, copper(I) iodide (6.9 mg, 0.036 mmol, 5 mol-%) und *cis*-dichlorobis(triphenylphosphine)palladium(II) (10.1 mg, 0.014 mmol, 2 mol-%) were added and the clear yellow solution stirred for 24 h under a nitrogen atmosphere at RT. After evaporation of the solvent at ambient temperature(!), the off-white residue was purified by column chromatography on silica with *n*-hexane/ethylacetate (1:4) as the eluent (R_f = 0.21). Yield: 68% (244 mg, 0.49 mmol). Elemental analysis calculated for $C_{26}H_{27}N_7O_4\cdot H_2O$ (%): C 60.11, H 5.63, N 18.87, found: C 59.69, H 5.50, N 18.85; MS (ESI^+, THF): *m/z* 524 $[M\text{+}Na]^+$; IR (ATR, cm^{-1}): 3284 (w) ν(NH), 3150 (w), 3130 (w), 2952 (w), 2239 (w) ν(C≡C), 1741 (s) ν(C=O, ester), 1656 (s) ν(C=O, amide), 1091 (s), 750 (s); ^{1}H-NMR (400.13 MHz, $CDCl_3$): δ 7.64 (dd, 3H, H(3-pz), ^4J = 0.6 Hz, ^3J = 1.7 Hz), 7.44 (dd, 3H, H(5-pz), ^4J = 0.6 Hz, ^3J = 1.7 Hz), 7.36 (d, 2H, H-$Ar_{2,6}$), ^3J = 8.3 Hz), 7.05 (d, 2H, H-$Ar_{3,5}$), ^3J = 8.3 Hz), 6.33 (dd, 3H, H(4-pz), ^3J = 1.7 Hz, ^3J = 2.6 Hz), 5.97 (s, 1H, NH, $^3J_{CH,NH}$ = 8.3 Hz), 5.25 (s, 2H, $OCH_2C(pz)_3$), 4.87 (ddd, 1H, H-α, $^3J_{CH,NH}$ = 7.8 Hz, $^3J_{\alpha,\beta}$ = 5.9 Hz, $^3J_{\alpha,\beta'}$ = 5.5 Hz), 4.37 (s, 2H, C≡C-CH_2), 3.72 (s, 3H, OCH_3), 3.15 (dd, 1H, H-β, $^3J_{\alpha,\beta}$ = 5.9 Hz, $^2J_{\beta,\beta'}$ = 13.9 Hz), 3.08 (dd, 1H, H-β', $^3J_{\alpha,\beta'}$ = 5.5 Hz, $^2J_{\beta,\beta'}$ = 13.9 Hz), 1.98 (s, 3H, NHCO-C*H*$_3$) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$): δ 171.83 (C=O, ester), 169.54 (C=O, amide), 141.30 ($C_{3\text{-}pz}$), 136.68 ($C_{1\text{-}Ar}$), 131.96 ($C_{2,6\text{-}Ar}$), 130.81 ($C_{5\text{-}pz}$), 129.20 ($C_{3,5\text{-}Ar}$), 121.07 ($C_{4\text{-}Ar}$), 106.49 ($C_{4\text{-}pz}$), 89.65 ($C_{q\text{-}tpm}$), 86.89 (Ar-*C*≡C), 84.12 (Ar-C≡*C*), 72.81 (O*C*H$_2$-(pz)$_3$), 59.91 (C≡C-*C*H$_2$-O), 52.96 ($C_α$), 52.35 (OCH_3), 37.75 ($C_β$), 23.07 (NHCO*C*H$_3$) ppm.



Scheme S3. Synthesis of *N*-Azidoacetyl-*DL*-phenylalaninemethylester (**16**).

***DL*-Phenylalaninemethylester hydrochloride (13).**[1] Under cooling with ice, thionylchloride (10.0 ml, 16.4 g, 0.14 mol) was dropped into methanol (60 ml). Then, a suspension of *DL*-phenylalanine (**12**) (5.0 g, 30.0 mmol) in methanol (30 ml) was added and the mixture heated to reflux for 14 h. After cooling to room temperature, the solvent was evaporated under vaccum and the white residue redissolved in methanol and added with stirring to diethylether (250 ml). The white precipitate was filtered off, washed with diethylether (3x 25 ml) and dried under vacuum. Yield: 90% (5.80 g, 27.0 mmol). Elemant alanalysis calculated for $C_{10}H_{14}ClNO_2$ (%): C 55.69, H 6.54, N 6.49, found: C 55.39, H 6.57, N 6.48; MS (ESI^+, CH_3OH): *m/z* 180 $[M\text{-}Cl]^+$; IR (ATR, cm^{-1}): 2914 (s) ν(NH), 2840 (s) ν(NH), 2620 (m), 1744 (s) ν(C=O), 1238 (s), 741 (s), 701(s); ^{1}H-NMR (400.13 MHz, DMSO-d_6): δ 8.78 (s, 2H, NH_2), 7.35 - 7.23 (m, 5H, H-Ar), 4.22 (dd, 1H, H-α, $^3J_{\alpha,\beta}$ = 5.7 Hz, $^3J_{\alpha,\beta'}$ = 7.5 Hz), 3.65 (s, 3H, CH_3), 3.22 (dd, 1H, H-β, $^3J_{\alpha,\beta}$ = 5.7 Hz, $^2J_{\beta,\beta'}$ = 14.0 Hz), 3.10 (dd, 1H, H-β', $^3J_{\alpha,\beta'}$ = 7.5 Hz, , $^2J_{\beta,\beta'}$ = 14.0 Hz) ppm; ^{13}C-NMR (100.62 MHz, DMSO-d_6): δ 169.27 (C=O), 134.71 (C-1), 129.33 (C-3, C-5), 128.52 (C-2, C-6), 127.19 (C-4), 53.22 ($C_α$), 52.45 (OCH_3), 35.79 ($C_β$) ppm.

Azidoacetic acid (15).[6] Bromoacetic acid (**14**) (7.0 g, 50 mmol) und sodium azide (6.5 g, 100 mmol) were dissolved in water (30 ml) and stirred for 48 h at RT. To the clear colorless solution, concentrated hydrochloric acid (25 ml) was added and the mixture extracted with diethylether (4x 50 ml). The combined organic phases were dried over magnesium sulfate and the solvent evaporated under reduced pressure. The yellow oil obtained was dried under vacuum. Yield: 91% (4.62 g, 46 mmol). Elemental analysis calculated $C_2H_3N_3O_2$ (%): C 23.77, H 2.99, found: C 23.33, H 3.18; Mr MS (ESI^-, CH_3OH): *m/z* 100 $[M\text{-}H]^-$, 223 $[2M\text{-}2H\text{+}Na]^-$; IR (ATR, cm^{-1}): 3048 (m) ν(OH), 2105 (s) ν(N_3), 1717 (s) ν(C=O), 1415 (m), 1278 (m), 1220 (m), 1182 (m): ^{1}H-NMR (200.13 MHz, CD_3OD): δ 3.91 (s, 2H, CH_2) ppm. ^{13}C-NMR (50.32 MHz, CD_3OD): δ 171.98 (C=O), 50.92 (CH_2) ppm.

***N*-Azidoacetyl-*DL*-phenylalaninemethylester (16)**.[7] To a solution of azidoacetic acid (**15**) (505 mg, 5.00 mmol) and *N*-methylmorpholine (0.55 ml, 0.51 g, 5.00 mmol) in chloroform (10 ml), isobutylchloroformate (0.65 ml, 0.68 g, 5.00 mmol) was added dropwise at -78 °C under a nitrogen atmosphere and stirred at this temperatur for 30 min. Then, a mixture of *DL*-phenylalaninemethylester hydrochlorid (**13**) (1.08 g, 5.00 mmol) and triethylamine (0.70 ml, 0.51 g, 5.00 mmol) in chloroform (20 ml) was added and the clear solution stirred at room temperature for 24 h. Then, the reaction mixture was extracted with 2.5% hydrochloric acid (2x 30 ml) and saturated sodium hydrogencarbonate solution (2x 30 ml). The organic phase was washed with water (1x 40 ml) and dried over magnesium sulfate. After evaporating the solvent, the white crystalline residue obtained, was recystallized from ethanol and dried under vaccum. Yield: 40% (0.53 g, 2.02 mmol). Elemental analysis calculated for $C_{12}H_{14}N_4O_3$ (%): C 54.96, H 5.38, N 21.36, found: C 55.04, H 5.68, N 21.23; MS (ESI^+, CH_3OH): *m/z* 263 $[M+H]^+$, 285 $[M+Na]^+$, 301 $[M+K]^+$; IR (ATR, cm^{-1}): 3348 (m) ν(NH), 3029 (w), 2960 (w), 2101 (s) ν(N_3), 1738 (s) ν(C=O, ester), 1652 (s) ν(C=O, amide), 1531 (s); ^{1}H-NMR (400.13 MHz, DMSO-d_6): δ 8.58 (d, 1H, NH, $^3J_{CH,NH}$ = 7.7 Hz), 7.32 - 7.25 (m, 2H, H-$Ar_{2,6}$), 7.24 - 7.19 (m, H, H-$Ar_{3,4,5}$), 4.53 (ddd, 1H, H-α, $^3J_{CH,NH}$ = 7.7 Hz, $^3J_{\alpha,\beta}$ = 9.2 Hz, $^3J_{\alpha,\beta'}$ = 5.6 Hz), 3.84 (d, 1H, CH_2^a-N_3, $^2J_{Ha,Hb}$ = 15.6 Hz), 3.79 (d, 1H, CH_2^b-N_3, $^2J_{Ha,Hb}$ = 15.6 Hz), 3.62 (s, 3H, OCH_3), 3.06 (dd, 1H, H-β, $^3J_{\alpha,\beta}$ = 9.2 Hz, $^2J_{\beta,\beta'}$ = 13.8 Hz), 2.93 (dd, 1H, H-β', $^3J_{\alpha,\beta'}$ = 5.6 Hz, $^2J_{\beta,\beta'}$ = 13.8 Hz) ppm; ^{13}C-NMR (100.62 MHz, DMSO-d_6): δ 171.54 (C=O, ester), 167.43 (C=O, amide), 136.87 ($C_{1\text{-}Ar}$), 128.98 ($C_{2,6\text{-}Ar}$), 128.23 ($C_{3,5\text{-}Ar}$), 126.53 ($C_{4\text{-}Ar}$), 53.33 (CH_2N_3), 51.91 (C_α), 50.37 (OCH_3), 36.57 (C_β) ppm.

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