Supplementary Material

Pseudo-enantiomeric coupling reagents for predictable incorporation into the peptide chain D and/or L amino acid residue of racemic substrates

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Syntheses of 14b-g using 2DMT/quinine/2BF_4^- (4) as coupling reagent.

S1. Synthesis of Z-D-Ala-Leu-OMe (**14b**) using 2DMT/quinine/2BF_4^- **(4)** as coupling reagent.

In the synthesis according to typical procedure 2 were used: 2DMT/quinine/2BF_4^- (0.780 g, 1 mmol), quinine (0.101 g, 0,31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Leu-OMe (0.182 g, 1 mmol). Z-D-Ala-Leu-OMe (0.214 g, yield 61%) was obtained, mp 68-70 °C, lit. mp 72-73 °C.[s1]

GC: R_t 8.33 (L-Leu); R_t 3.54 (L-Ala); R_t 3.41 (D-Ala); L-Ala/D-Ala= 1/99.

S2. Synthesis of Z-D-Ala-Tyr-OMe (**14c)** using 2DMT/quinine/2BF_4^- **(4)** as coupling reagent**.**

In the synthesis according to typical procedure 2 were used: 2DMT/quinine/2BF_4^- (0.780 g, 1 mmol), quinine (0.101 g, 0,31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Tyr-OMe (0.232 g, 1 mmol). Z-D-Ala-Tyr-OMe (0.228 g, yield 57%) was obtained, mp 102-105 °C, lit. mp 105-107 °C.[s2]

GC: R_t 23.12 (L-Tyr); R_t 4.65 (L-Ala); R_t 3.53 (D-Ala); L-Ala/D-Ala= 0.5/99.5.

S3. Synthesis of Z-D-Ala-Ser-OMe (**14d**) using 2DMT/quinine/2BF_4^- **(4)** as coupling reagent.

In the synthesis according to typical procedure 2 were used: 2DMT/quinine/2BF_4^- (0.780 g, 1 mmol), quinine (0.101 g, 0,31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Ser-OMe (0.156 g, 1 mmol). Z-D-Ala-Ser-OMe (0.191 g, yield 59%) was obtained, mp 128-130 °C, lit. mp 128-130 °C.[s3]

GC: R_t 7.29 (L-Ser); R_t 3.56 (L-Ala); R_t 3.35 (D-Ala); L-Ala/D-Ala= 2/98.

S4. Synthesis of Z-D-Ala-Val-OMe (**14e**) using 2DMT/quinine/2BF_4^- **(4)** as coupling reagent.

In the synthesis according typical procedure 2 were used 2DMT/quinine/2BF_4^- **(4)** (0.780 g, 1 mmol), quinine (0.101 g, 0.31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol), HCl*Val-OMe (0.168 g, 1 mmol). Z-D-Ala-Val-OMe (0.202 g, yield 60%) was obtained, mp 85-87 °C, lit mp 79-82 °C.[s3]

GC: R_t 4.76 (L-Val); R_t 3.56 (L-Ala); R_t 3.35 (D-Ala); L/D = 0.5/99.5.

S5. Synthesis of Z-D-Ala-Ala-OMe (**14f**) using 2DMT/quinine/2BF_4^- **(4)** as coupling reagent .

In the synthesis according to typical procedure 2 were used: 2DMT/quinine/2BF_4^- (0.780 g, 1 mmol), quinine (0.101 g, 0,31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Ala-OMe (0.140, 1 mmol). Z-D-Ala-Ala-OMe (0.191, yield 62%) was obtained, mp 85-87 °C, lit. mp 105-106 °C.[s4]

GC: R_t 3.57 (L-Ala); R_t 3.31 (D-Ala); L/D = 50.5/49.5.

S6. Synthesis of Z-D-Ala-Gly-OMe (**14g**) using 2DMT/quinine/2BF_4^- **(4)** as coupling reagent .

I n the synthesis according to typical procedure 2 were used: 2DMT/quinine/2BF_4^- (0.780 g, 1 mmol), quinine (0.101 g, 0,31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Gly-OMe (0.125 g, 1 mmol). Z-D-Ala-Gly-OMe (0.165 g, yield 56%) was obtained, mp 90-91 °C, lit. mp 94-96 °C.[s5]

GC: R_t 4.82 (Gly); R_t 3.69 (L-Ala); R_t 3.41 (D-Ala); L-Ala/D-Ala= 2/98.

Syntheses of 15b-g using 2DMT/quinine/2BF_4^- (4) as coupling reagent.

S7. Synthesis of Z-Phe-Leu-OMe (**15b**) using 2DMT/quinine/2BF_4^- **(4)** as coupling reagent.

In the synthesis according to typical procedure 2 were used: 2DMT/quinine/2BF_4^- (0.780 g, 1 mmol), quinine (0.101 g, 0,31 mmol), *rac*-Z-Phe-OH (0.599 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Leu-OMe (0.182 g, 1 mmol). Z-Phe-Leu-OMe (0.260 g, yield 61%) was obtained, mp 109-112 °C, lit. mp 111 °C.[s6]

GC: R_t 8.36 (L-Leu); R_t 18.72 (L-Phe); R_t 18.19 (D-Phe); L-Phe/D-Phe = 99.5/0.5.

S8. Synthesis of Z-Phe-Tyr-OMe (**15c**) using 2DMT/quinine/2BF_4^- **(4)** as coupling reagent.

In the synthesis according to typical procedure 2 were used: 2DMT/quinine/2BF_4^- (0.780 g, 1 mmol), quinine (0.101 g, 0,31 mmol), *rac*-Z-Phe-OH (0.599 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Tyr-OMe (0.232 g, 1 mmol). Z-Phe-Tyr-OMe (0.272 g, yield 57%) was obtained, mp 154-157 °C, lit. mp 158 °C.[s7]

GC: R_t 23.10 (L-Tyr); R_t 18.71 (L-Phe); R_t 18.14 (D-Phe); L-Phe/D-Phe = 99/1.

S9. Synthesis of Z-Phe-Ser-OMe (**15d**) using 2DMT/quinine/2BF_4^- **(4)** as coupling reagent.

In the synthesis according to typical procedure 2 were used: 2DMT/quinine/2BF_4^- (0.780 g, 1 mmol), quinine (0.101 g, 0,31 mmol), *rac*-Z-Phe-OH (0.599 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Ser-OMe (0.156 g, 1 mmol). Z-Phe-Ser-OMe (0.236 g, yield 59%) was obtained, mp 86-77 °C, lit. mp 83-84 °C.[s8]

GC: R_t 7.20 (L-Ser); R_t 18.51 (L-Phe); R_t 18.14 (D-Phe); L-Phe/D-Phe = 98/2.

S10. Synthesis of Z-Phe-Val-OMe (**15e**) using 2DMT/quinine/2BF_4^- **(4)** as coupling reagent.

In the synthesis according to typical procedure 2 were used: 2DMT/quinine/2BF_4^- (0.780 g, 1 mmol), quinine (0.101 g, 0,31 mmol), *rac*-Z-Phe-OH (0.599 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Val-OMe (0.168 g, 1 mmol). Z-Phe-Val-OMe (0.247 g, yield 60%) was obtained, mp 110-113 °C, lit. mp 114-115 °C.[s9]

GC: R_t 4.76 (L-Val); R_t 18.58 (L-Phe); R_t 18.14 (D-Phe); L-Phe/D-Phe = 98/2.

S11. Synthesis of Z-Phe-Ala-OMe (**15f**) using 2DMT/quinine/2BF_4^- **(4)** as coupling reagent.

In the synthesis according to typical procedure 2 were used: 2DMT/quinine/2BF_4^- (0.780 g, 1 mmol), quinine (0.101 g, 0,31 mmol), *rac*-Z-Phe-OH (0.599 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Phe-OMe (0.139 g, 1 mmol). Z-Phe-Ala-OMe (0.238 g, yield 62%) was obtained, mp 121-123 °C, lit. mp 122-125 °C.[s10]

GC: R_t 3.64 (L-Ala); R_t 18.58 (L-Phe); R_t 18.15 (D-Phe); L-Phe/D-Phe = 99/1.

S12. Synthesis of Z-Phe-Gly-OMe (**15g**) using 2DMT/quinine/2BF_4^- **(4)** as coupling reagent.

In the synthesis according to typical procedure 2 were used: 2DMT/quinine/2BF_4^- (0.780 g, 1 mmol), quinine (0.101 g, 0,31 mmol), *rac*-Z-Phe-OH (0.599 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Gly-OMe (0.125 g, 1 mmol). Z-Phe-Gly-OMe (0.207 g, yield 56%) was obtained, mp 120-121 °C, lit. mp 120 °C.[s11]

GC: R_t 4.74 (Gly); R_t 18.58 (L-Phe); R_t 18.14 (D-Phe); L-Phe/D-Phe = 97/3.

Syntheses of 14b-g using 2DMT/quinidine/2BF_4^- (7) as coupling reagent.

S13. Synthesis of Z-Ala-Phe-OMe (**14a**) using 2DMT/quinidine/2BF_4^- **(7)** as coupling reagent.

In the synthesis according to typical procedure 3 were used: 2DMT/quinidine/2BF_4^- (0.780 g, 1 mmol), quinidine (0.101 g, 0,31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Phe-OMe (0.216 g, 1 mmol). Z-Ala-Phe-OMe (0.210 g, yield 55%) was obtained, mp 100-102 °C. lit. mp 103-104 °C.[s12]

GC: R_t 18.71 (L-Phe); R_t 3.54 (L-Ala); R_t 3.30 (D-Ala); L-Ala/D-Ala = 99.5/0.5.

S14. Synthesis of Z-Ala-Leu-OMe (**14b**) using 2DMT/quinidine/2BF_4^- **(7)** as coupling reagent.

In the synthesis according to typical procedure 3 were used: 2DMT/quinidine/2BF_4^- (0.780 g, 1 mmol), quinidine (0.101 g, 0,31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Leu-OMe (0.182 g, 1 mmol). Z-Ala-Leu-OMe (0.210 g, yield 60%) was obtained, mp 69-71 °C. lit. mp 72-73 °C.[s13]

GC: R_t 18.71 (L-Phe); R_t 3.54 (L-Ala); R_t 3.30 (D-Ala); L-Ala/D-Ala = 99.5/0.5.

S15. Synthesis of Z-Ala-Tyr-OMe (**14c**) using 2DMT/quinidine/2BF_4^- **(7)** as coupling reagent.

In the synthesis according to typical procedure 3 were used: 2DMT/quinidine/2BF_4^- (0.780 g, 1 mmol), quinidine (0.101 g, 0,31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Leu-OMe (0.182 g, 1 mmol). Z-Ala-Tyr-OMe (0.240 g, yield 60%) was obtained, mp 132-134 °C. lit. mp 122 °C.[s14]

GC: R_t 23.28 (L-Tyr); R_t 4.61 (L-Ala); R_t 3.58 (D-Ala); L-Ala/D-Ala = 99.5/0.5.

S16. Synthesis of Z-Ala-Ser-OMe (**14d**) using 2DMT/quinidine/2BF_4^- **(7)** as coupling reagent.

In the synthesis according to typical procedure 3 were used: 2DMT/quinidine/2BF_4^- (0.780 g, 1 mmol), quinidine (0.101 g, 0,31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Ser-OMe (0.156 g, 1 mmol). Z-Ala-Ser-OMe (0.188 g, yield 58%) was obtained, mp 130-132 °C. lit. mp 134-135 °C.[s15]

GC: R_t 7.27 (L-Ser); R_t 3.55 (L-Ala); R_t 3.35 (D-Ala); L-Ala/D-Ala = 99/1.

S17. Synthesis of Z-Ala-Val-OMe (**14e**) using 2DMT/quinidine/2BF_4^- **(7)** as coupling reagent.

In the synthesis according to typical procedure 3 were used: 2DMT/quinidine/2BF_4^- (0.780 g, 1 mmol), quinidine (0.101 g, 0,31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Val-OMe (0.168 g, 1 mmol). Z-Ala-Val-OMe (0.209 g, yield 62%) was obtained, mp 81-83 °C. lit. mp 82-84 °C.[s16]

GC: R_t 4.75 (L-Val); R_t 3.55 (L-Ala); R_t 3.35 (D-Ala); L-Ala/D-Ala = 99/1.

S18. Synthesis of Z-Ala-Ala-OMe (**14f**) using 2DMT/quinidine/2BF_4^- **(7)** as coupling reagent.

In the synthesis according to typical procedure 3 were used: 2DMT/quinidine/2BF_4^- (0.780 g, 1 mmol), quinidine (0.101 g, 0,31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Ala-OMe (0.139 g, 1 mmol). Z-Ala-Ala-OMe (0.188 g, yield 61%) was obtained, mp 109-113 °C. lit. mp 109-112 °C.[s17]

GC: R_t 3.55 (L-Ala); R_t 3.33 (D-Ala); L-Ala/D-Ala = 99.5/0.5.

S19. Synthesis of Z-Ala-Gly-OMe (**14g**) using 2DMT/quinidine/2BF_4^- **(7)** as coupling reagent.

In the synthesis according to typical procedure 3 were used: 2DMT/quinidine/2BF_4^- (0.780 g, 1 mmol), quinidine (0.101 g, 0,31 mmol), *rac*-Z-Ala-OH (0.446 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Gly-OMe (0.125 g, 1 mmol). Z-Ala-Gly-OMe (0.168 g, yield 57%) was obtained, mp 95-97 °C. lit. mp 97-98 °C.[s18]

GC: R_t 4.85 (Gly); R_t 3.67 (L-Ala); R_t 3.40 (D-Ala); L-Ala/D-Ala = 99.5/0.5.

Syntheses of 15b-g using 2DMT/quinidine/2BF_4^- (7) as coupling reagent.

S20. Synthesis of Z-D-Phe-Leu-OMe (**15b**) using 2DMT/quinidine/2BF_4^- **(7)** as coupling reagent.

In the synthesis according to typical procedure 3 were used: 2DMT/quinidine/2BF_4^- (0.780 g, 1 mmol), quinidine (0.101 g, 0,31 mmol), *rac*-Z-Phe-OH (0.599 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Leu-OMe (0.182 g, 1 mmol). Z-D-Phe-Leu-OMe (0.268 g, yield 63%) was obtained, mp 139-141 °C. lit. mp 124-125 °C.[s19]

GC: R_t 8.35 (L-Leu); R_t 18.70 (L-Phe); R_t 18.15 (D-Phe); L-Phe/D-Phe = 2/98.

S21. Synthesis of Z-D-Phe-Tyr-OMe (**15c**) using 2DMT/quinidine/2BF_4^- **(7)** as coupling reagent.

In the synthesis according to typical procedure 3 were used: 2DMT/quinidine/2BF_4^- (0.780 g, 1 mmol), quinidine (0.101 g, 0,31 mmol), *rac*-Z-Phe-OH (0.599 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Tyr-OMe (0.232 g, 1 mmol). Z-D-Phe-Tyr-OMe (0.310 g, yield 65%) was obtained, mp 159-163 °C. lit. mp 131-132 °C for Z-Phe-Tyr-OMe.[s20]

GC: R_t 23.12 (L-Tyr); R_t 18.70 (L-Phe); R_t 18.15 (D-Phe); L-Phe/D-Phe = 0.5/99.5.

S22. Synthesis of Z-D-Phe-Ser-OMe (**15d**) using 2DMT/quinidine/2BF_4^- **(7)** as coupling reagent.

In the synthesis according to typical procedure 3 were used: 2DMT/quinidine/2BF_4^- (0.780 g, 1 mmol), quinidine (0.101 g, 0,31 mmol), *rac*-Z-Phe-OH (0.599 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Ser-OMe (0.182 g, 1 mmol). Z-D-Phe-Ser-OMe (0.156 g, yield 39%) was obtained, mp 145-147 °C. lit. mp 146-147 °C.[s21]

GC: R_t 7.20 (L-Ser); R_t 18.50 (L-Phe); R_t 18.14 (D-Phe); L-Phe/D-Phe = 1/99.

S23. Synthesis of Z-D-Phe-Val-OMe (**15e**) using 2DMT/quinidine/2BF_4^- **(7)** as coupling reagent.

In the synthesis according to typical procedure 3 were used: 2DMT/quinidine/2BF_4^- (0.780 g, 1 mmol), quinidine (0.101 g, 0,31 mmol), *rac*-Z-Phe-OH (0.599 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Val-OMe (0.168 g, 1 mmol). Z-D-Phe-Val-OMe (0.247 g, yield 60%) was obtained, mp 99-101 °C. 139-132 °C.[s22]

GC: R_t 4.75 (L-Val); R_t 18.55 (L-Phe); R_t 18.15 (D-Phe); L-Phe/D-Phe = 1/99.

S24. Synthesis of Z-D-Phe-Ala-OMe (**15f**) using 2DMT/quinidine/2BF_4^- **(7)** as coupling reagent.

In the synthesis according to typical procedure 3 were used: 2DMT/quinidine/2BF_4^- (0.780 g, 1 mmol), quinidine (0.101 g, 0,31 mmol), *rac*-Z-Phe-OH (0.599 g, 2 mmol), NMM (0.110 mL, 1 mmol) and HCl*H-Ala-OMe (0.139 g, 1 mmol). Z-D-Phe-Ala-OMe (0.238 g, yield 62%) was obtained, mp 141-143 °C. lit. mp 135-135.5 °C.[s23]

GC: R_t 3.64 (L-Ala); R_t 18.58 (L-Phe); R_t 18.15 (D-Phe); L-Phe/D-Phe = 0.5/99.5.

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