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Palladium-Catalyzed Coupling of a Propargylglycine Derivative.

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Key Words: Palladium-catalyzed; coupling; propargylglycine; aryl and vinyl halide; aryl andvinyl triflate.

Abstract: *The coupling of aryl or vinyl halides and triflates with a propargylglycine derivative under the influence of a palladium catalyst has been described. The coupling is compatible with a variety of structural types and functional groups. The coupling was also carried out on an optically-active propargylglycine derivative and the products were optically active.*

The search for new routes leading to the synthesis of unusual α-amino acids is continuing to attract considerable attention from organic chemists.[1] Modified α-amino acids have been shown to have interesting and potentially useful pharmacological activity, to serve as starting materials for more complex organic structures and to provide useful chiral auxiliaries.[2] In addition, α- amino acids possessing unsaturated side chains such as **D**- and **L**-propargylglycine have been shown to act as irreversible inhibitors of a number of enzyme systems.[3]

As part of our continuing search[4] for conceptually simple approaches for the elaboration of α-amino acids we have chosen to explore the palladium-catalyzed coupling of a propargylglycine derivative **1** with a variety of sp^2 derived halides and triflates (trifluoromethanesulphonates).

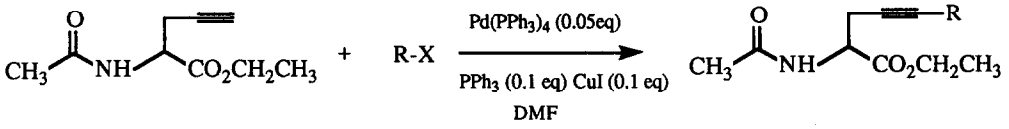
Only a few reports have appeared on the palladium-catalyzed elaboration of α-amino acids. These have included the coupling of α,β-unsaturated esters or tri-*n*-butyl allyl stannane with a tyrosine triflate derivative,[5] the coupling of a β-iodoalanine derivative with aryl halides[6] and the Heck arylation of 2-amidoacrylates.[7]

The palladium-catalyzed coupling of sp^2 halides or triflates with copper acetylides (prepared *in situ* from a terminal alkyne, base and copper(I)iodide) has been well documented.[8] We wish to report that this versatile methodology was applied to the terminal alkyne function of a suitably protected propargylglycine with equal efficacy.

RESULTS AND DISCUSSION.

The preparation of the propargylglycine derivative **1** followed a standard literature procedure.[9] The reaction conditions chosen for the coupling of **1** with various sp^2 halides and triflates was adapted from the literature and is described in the following equation as Condition A.[10]

Condition A



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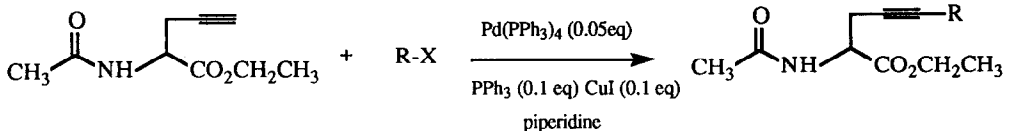
The palladium-catalyzed coupling of **1** with sp^2 halides and triflates was found to be a very general reaction as shown by the summary outlined in Table 1. The reactions described by entries 1, 5 -10, 12-19 and 21 proceeded under the mild conditions as outlined in the above equation and are designated as Condition A in the Table. The mechanism for the coupling presumably involves the expected oxidative-addition, transmetallation and reductive-elimination sequence proposed by previous workers.[8] A minor byproduct from the coupling reaction (under 10% in most cases) was the homo-coupled propargylglycine derivative **24**, presumably arising from a Glaser-type coupling .[11]

When 3-bromopyridine was treated with propargylglycine **1** under reaction Condition A then none of the desired product **12** was formed and 44% of the homo-coupled product **24** was isolated. A similar result was obtained for entries 3, 4, and 20 under reaction Condition A. The reaction conditions were then modified to use piperidine as the solvent and the base[12] as outlined in the following equation and designated as Condition B. Each of the compounds which showed reluctance to couple with **1** under Condition A could be successfully coupled under these modified conditions (see Table 1).

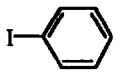
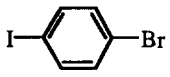
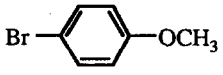
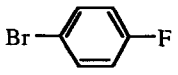
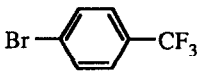
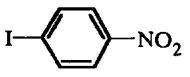
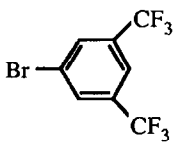
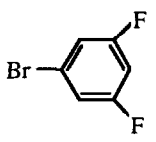
Condition B

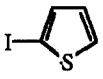
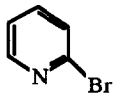
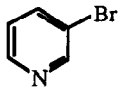
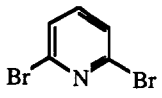
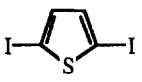
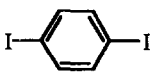
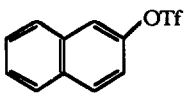
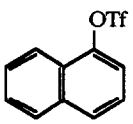


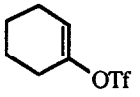
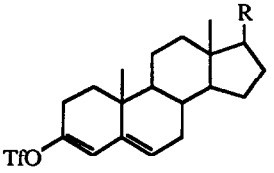
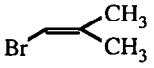
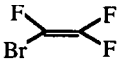
1

The addition of 3 equivalents of **1** to 1,4-diiodobenzene gave the bis-substituted product **16**, entry 14 in Table 1. In order to prepare the mono-substituted benzene derivative 1-bromo-4-iodo benzene was reacted with 1.5 equivalents of **1** and only the more reactive iodo substituent was replaced to yield **3** in 94% yield . When 2,6-dibromopyridine was treated with either 1.5 or 3.0 equivalents of **1** only the mono-substiuted compound **13** was isolated. No evidence for the disubstututed compound was obtained. For 2,5-diiodothiophene both the mono-and bis-substituted compounds could be prepared depending upon the ratio of reactants. Thus addition of 1.5 equivalents of **1** to 2,5-diiodothiophene gave **15** in 53% yield, whilst addition of 3.0 equivalents of **1** to 2,5-diiodothiphene gave **14** in 88% yield.

Table 1. Coupled products and Isolated Yields.

Entry	Halide or Triflate	Conditions[a]	Product	% Isolated Yield
1		A	**2**	94
2		A	**3**	94
3		B	**4**	53
4		B	**5**	52
5		A	**6**	67
6		A	**7**	85
7		A	**8**	65
8		A	**9**	57

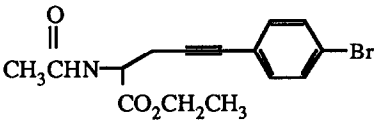
Entry	Halide or Triflate	Conditions	Product	% Isolated Yield
9		A	**10**	93
10		A	**11**	47
11		B	**12**	67
12		A	**13**	67
13		A[b]	**14** **15**	88 53
14		A	**16**	71
15		A	**17**	95
16		A	**18**	95

Entry	Halide or Triflate	Conditions	Product	% Isolated Yield
17		A	**19**	93
18		A	**20**	64
19		A	**21**[c]	61
20		B	**22**	49
21		A	**23**	37

a. Condition A refers to DMF as solvent, triethylamine as base (2.0 equivalents), copper(I)iodide (0.2 equivalents) and $Pd(PPh_3)_4$ (0.1 equivalents).
Condition B refers to piperidine as solvent and base, copper(I)iodide (0.1 equivalents), $Pd(PPh_3)_4$ (0.05 equivalents) and added PPh_3 (0.1 equivalents).

b. Addition of 3.0 equivalents of **1** to 2,5-diiodothiophene gave the disubstituted compound **14** and addition of 1.5 equivalents of **1** gave the mono-substituted compound **15**.

c. R is $-CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2$.



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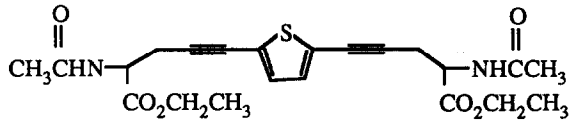
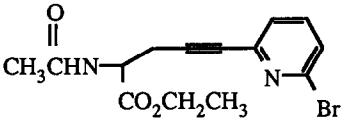


14



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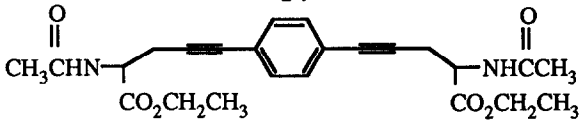
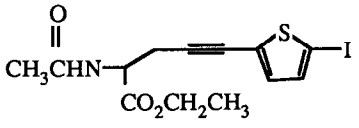
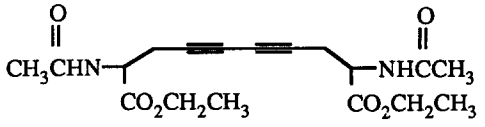


16

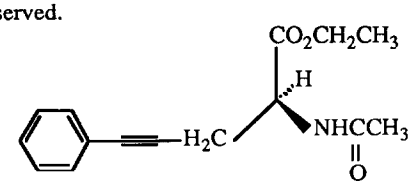


15

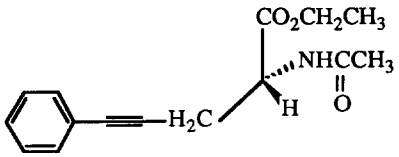


24

In order to determine the compatibility of the coupling reaction with an optically active α-amino acid, racemic *N*-acetyl propargylglycine[9] was resolved into its enantiomers with the acylase enzyme derived from *Aspergillus sp.*[13] Subsequent coupling of **D-1** and **L-1** with iodobenzene under reaction Condition A (as described for entry 1 in Table 1) gave the corresponding optically active products **D-2** and **L-2**. The optical purity of these coupled products was determined with the aid of the chiral shift reagent Eu(tfc)3 and, within the limits of 300 MHz proton n.m.r. spectral analysis, only one enantiomer was observed.



L-2 $[\alpha]_D$ $+103^0$



D-2 $[\alpha]_D$ -99^0

EXPERIMENTAL

General: Infrared spectra were obtained using a Jasco A102 or a Hitachi 270-30 infrared spectrophotometer, as a neat film or a nujol mull . ^1H n.m.r. spectra and ^{13}C n.m.r. spectra were recorded using an ACP 300 Fourier Transform n.m.r. spectrometer. All n.m.r. samples were prepared in deuterochloroform with tetramethylsilane as the internal standard. Optical rotations were obtained using a Perkin Elmer 141 Polarimeter. Electron impact mass spectra and accurate mass measurements were obtained using a AEI-GEC MS3074 mass spectrometer. Where the electron impact technique was unsuccessful in giving a molecular ion, mass spectra were obtained using the FAB technique using a VG ZAB 2HF mass spectrometer. All solvents were distilled prior to use. The analytical t.l.c plates used were Merck Alufolien Kieselgel 60 PF_{254} and were visualized by UV light (254 nm), by staining with iodine vapour or by staining with phosphomolybdic acid followed by development with heat. Preparative radial chromatography plates were prepared using Merck Kieselgel 60 PF_{254} containing gypsum. Melting points were recorded using a Reichert hot stage melting point apparatus and are uncorrected. The following compounds were prepared by literature procedures: **D,L**-Ethyl *N*-acetylpropargyl glycinate[9], **D**-*N*-acetylpropargylglycine,[13] **L**-*N*-acetylpropargylglycine,[13] tetrakis (triphenylphosphine)

palladium(0),[14] 1,3-dibenzyl-5-iodouracil,[15] cyclohex-1-en-1-yl triflate,[16] 1-naphthyl triflate,[16] 2-naphthyl triflate[16] and cholesta-3,5-dien-3-yl triflate.[16]

Coupling Reactions-Condition A.

Ethyl 2-(*N*-Acetyl)-5-(2-thienyl)pent-4-ynote (10)

Ethyl *N*-acetylpropargylglycinate **1** (0.153g, 0.83mmol) was dissolved in dimethylformamide (DMF) (5mL) and 2-iodothiophene (0.060 g, 0.55mmol), triethylamine (0.15mL,) and $Pd(PPh_3)_4$ (0.060g, 0.055mmol) were added. Copper(I) iodide (0.020g, 0.11mmol) was added and the clear brown solution rapidly darkened and the mixture was stirred under nitrogen at room temperature for 15 hours, after which time no 2-iodothiophene could be detected by t.l.c. analysis of the mixture. The solvent was evaporated *in vacuo* and the oily residue purified initially by passing through a small silica gel column (5% CH_3OH/CH_2Cl_2), and then by radial chromatography (1% CH_3OH/CH_2Cl_2). The product **10** was recovered as a brown oil (0.112g, 77%). When the reaction scale was doubled **10** was formed in 93% yield (0.267g). I.R. υ_{max} 3270, 3050, 2220, 1730, 1650cm^{-1}. ^{1}H nmr δ 1.31(3H,t,*J* 7.1Hz, OCH_2CH_3), 2.06(3H,s,C(O)CH_3), 3.00(2H,d,*J* 4.8Hz, $CH_2C{\equiv}C$), 4.27 (2H, m,OCH_2CH_3), 4.79 (1H,dt,*J* 4.9,7.5Hz, N(H)CH), 6.58(1H,d,*J* 7.5Hz,NH), 6.93(1H,dd,*J* 3.6Hz,5.0Hz, Ar), 7.13 (1H, d,*J* 3.6Hz,Ar), 7.21(d,*J* 4.9Hz,Ar); ^{13}C nmr δ 14.0, 22.9, 23.6, 50.8, 61.8, 76.4(C≡C), 87.9 (C≡C), 122.8(Ar), 126.6(Ar), 126.7(Ar), 131.7(Ar), 169.8(C=O), 170.4 (C=O); MS (m/z) 265, 207, 206, 177, 178, 121; HRMS $C_{13}H_{15}NO_3S$ calculated 265.0773, found 265.0762.

Ethyl 2-(*N*-Acetyl)-5-phenylpent-4-ynoate (2)

Ethyl *N*-acetylpropargylglycinate **1** (0.301g, 1.3mol eq.), iodobenzene (140μL, 1.25mmol), triethylamine (0.31mL, 1.8mol eq.), $Pd(PPh_3)_4$ (0.126g, 0.1mol eq.) and copper(I) iodide (0.039g, 0.2mol eq.) were dissolved in DMF (10mL) under Condition A described above. The product **2** was isolated as an oil (0.270g, 94%) which later formed a solid and was recrystallized from ethyl acetate / petroleum ether. M.p. 69-70°C; I.R. υ_{max} 3270, 3140, 2230, 1730, 1650cm^{-1}. ^{1}H nmr δ 1.31(3H,t,*J* 7.1Hz,OCH_2CH_3), 2.07(3H, s,C(O)CH_3), 2.98(2H,d,*J* 4.7Hz, $CH_2C{\equiv}C$), 4.27(2H,m, OCH_2CH_3), 4.81(1H,dt,*J* 4.6,7.6Hz, N(H)CH), 6.46(1H,d,*J* 7.5Hz,NH), 7.27-7.39 (5H,m,Ar); ^{13}C nmr δ 14.0, 22.9, 23.3, 50.9, 61.8, 83.4(C≡C), 83.7 (C≡C), 122.8(Ar), 128.0 (Ar), 128.1(Ar), 131.5(Ar), 170.0 (C=O), 170.5(C=O); MS (m/z) 259, 230, 201, 200, 172, 171, 115; HRMS $C_{15}H_{17}NO_3$ calculated 259.1208, found 259.1216.

Ethyl 2-(*N*-Acetyl)-5-(4-bromophenyl)pent-4-ynoate (3)

Coupling of **1** (0.153g, 0.83mmol) with bromo-4-iodobenzene (0.159g, 0.56mmol) under Condition A yielded **3** as a solid (0.177g, 94%). M.p. 105-106°C; I.R. υ_{max} 3300, 2920, 1752, 1654cm^{-1}. ^{1}H nmr δ 1.30(3H,t,*J* 7.2Hz,OCH_2CH_3), 2.07(3H,s,C(O)CH_3), 2.97(2H,d,*J* 4.8Hz,$CH_2C{\equiv}C$), 4.25(2H,m, OCH_2CH_3), 4.80(1H,dt,*J* 4.8,7.8Hz,N(H)CH), 6.55(1H,d,*J* 7.7Hz,NH), 7.22(2H,d,*J* 8.6Hz,Ar), 7.42 (2H,d,*J* 8.6Hz,Ar).^{13}C nmr δ 14.1, 23.1, 23.4, 50.8, 61.8, 82.3 (C≡C), 85.2(C≡C), 121.8(Ar), 122.2(Ar), 131.4(Ar), 133.0(Ar), 169.8(C=O), 170.5(C=O); MS (m/z) 339, 337, 280, 278, 195, 193, 102; HRMS $C_{15}H_{16}{}^{81}BrNO_3$ calculated 339.0293, found 339.0278.

Ethyl 2-(*N*-Acetyl)-5-(4-trifluoromethylphenyl)pent-4-ynoate (6)

Coupling of **1** (0.153g, 0.83mmol) with bromo-4-trifluoromethylbenzene (77μL, 0.55mmol) under Condition A yielded **6** as a solid (0.120g, 67%). M.p. 113-114°C; I.R. υ_{max} 3300, 2900, 1750, 1650cm^{-1}. ^{1}H nmr δ 1.31(3H,t,*J* 7.3Hz,OCH_2CH_3), 2.08(3H,s,C(O)CH_3), 3.01(2H,d,*J* 4.8Hz, $CH_2C{\equiv}C$), 4.27(2H,m,OCH_2CH_3), 4.83 (1H,dt,*J* 4.8,7.6Hz,N(H)CH), 6.65(1H, d, 7.6Hz,NH), 7.47(2H, d,*J* 8.2Hz,Ar), 7.54(2H,d,*J* 8.3Hz,Ar); ^{13}C nmr δ 14.0, 23.0, 23.4, 50.8, 61.8, 82.0 (C≡C), 86.7(C≡C), 123.7 (q,$^1J_{CF}$ 272.1Hz), 125.0(q,$^3J_{CF}$ 3.5Hz), 126.7(Ar), 129.7 (q,$^2J_{CF}$ 32.9Hz), 131.8 (Ar), 169.8(C=O), 170.4(C=O); MS (m/z) 327, 268, 240, 223, 212, 183; HRMS $C_{16}H_{16}F_3NO_3$ calculated 327.1082, found 327.1096.

Ethyl 2-(*N*-Acetyl)-5-(4-nitrophenyl)pent-4-ynoate (7)
Coupling of **1** (0.153g, 0.83mmol) with iodo-4-nitrobenzene (0.0136g, 0.55mmol) under Condition A yielded **7** as a solid (0.142g, 85%). M.p. 120-122°C; I.R. υ_{max} 3292, 3082, 2230, 1728, 1650cm^{-1}. ^{1}H nmr δ 1.32(3H,t,*J* 7.1Hz,OCH_2CH_3), 2.10(3H,s,$C(O)CH_3$), 3.05(2H,m, $CH_2C{\equiv}C$), 4.29 (2H, m, OCH_2CH_3), 4.84(1H,dt,*J* ,4.9,7.6Hz,N(H)CH, 6.61(1H,d,*J* 7.7Hz,NH), 7.51(2H,d,*J* 8.8Hz,Ar), 8.15(2H,d,*J* 8.8Hz); ^{13}C nmr δ 14.1, 23.0, 23.5, 50.8, 61.9, 87.8(C≡C), 90.0(C≡C), 123.4(Ar), 129.8(Ar), 132.3(Ar),146.8(Ar), 169.8(C=O), 170.3(C=O); MS (m/z) 305(M+H)$^+$, 304, 245, 217, 189, 144, 143, 102; HRMS $C_{15}H_{16}N_2O_5$ calculated 304.1059, found 304.1049.

Ethyl 2-(*N*-Acetyl)-5-[3,5-bis(trifluoromethyl)phenyl]pent-4-ynoate (8)
Coupling of **1**(0.153g, 0.83mmol) with 3,5-bis(trifluoromethyl)bromobenzene (95μL, 0.55mmol) under Condition A yielded **8** as a solid (0.142g, 65%). M.p. 141-144°C; I.R. υ_{max} 3300, 2900, 2200, 1750, 1650cm^{-1}. ^{1}H nmr δ 1.32(3H,t,*J* 7.1Hz,OCH_2CH_3), 2.09(3H,s, $C(O)CH_3$), 3.04(2H, m, $CH_2C{\equiv}C$), 4.30(2H,m,OCH_2CH_3), 4.83(1H,dt,*J* 4.6,7.7Hz, N(H)CH), 6.6(1H,d,*J* 7.6Hz,NH), 7.79(3H,bs,Ar); ^{13}C nmr δ 14.0, 23.0, 23.4, 50.8, 62.0, 80.5(C≡C), 88.1(C≡C), 121.5 (m, $^3J_{CF}$ 3.6Hz), 122.8 (q, $^1J_{CF}$ 273.0Hz), 125.2 (Ar), 131.5(broad s,Ar), 131.8 (q, $^2J_{CF}$ 33.9Hz), 169.9(C=O), 170.4(C=O); MS (m/z) 395, 376, 337, 336, 308, 280, 251; HRMS $C_{17}H_{15}F_6NO_3$ calculated 395.0956, found 395.0942.

Ethyl 2-(*N*-Acetyl)-5-(3,5-difluorophenyl)pent-4-ynoate (9)
Coupling of **1** (0.153g, 0.83mmol) with bromo-3,5-difluorobenzene (64μL, 0.56mmol) under Condition A yielded **9** as a solid (0.094g, 57%). M.p. 94-97°C; I.R. υ_{max} 3270, 2900, 2200, 1720, 1645cm^{-1}. ^{1}H nmr δ 1.31(3H,t,*J* 7.2Hz,OCH_2CH_3), 2.07(3H, s,$C(O)CH_3$), 2.98(2H,d,*J* 4.7Hz, $CH_2C{\equiv}C$), 4.27(2H,m, OCH_2CH_3), 4.81(1H,dt,*J* 4.6,7.6Hz,N(H)CH), 6.61(1H,d, *J* 7.5Hz,NH), 6.73-6.91 (3H,m,Ar); ^{13}C nmr δ 14.1, 23.0, 23.3, 50.8, 61.9, 81.2(C≡C), 86.4 (C≡C), 104.2 (t,$^2J_{CF}$ 25.1Hz),114.5(dd,$^2J_{CF}$ 17.4Hz,$^4J_{CF}$8.5Hz), 125.5 (t, $^3J_{CF}$ 12.0Hz), 162.5 (dd,$^1J_{CF}$ 249.0 Hz, $^3J_{CF}$ 13.4Hz), 169.8(C=O), 170.4(C=O); MS (m/z) 295, 237, 236, 208, 180, 151. HRMS $C_{15}H_{15}F_2NO_3$ calculated 295.1020, found 295.1022.

Ethyl 2-(*N*-Acetyl)-5-(2-pyridyl)pent-4-ynoate (11)
Coupling between **1** (0.153g, 0.83mmol) and 2-bromopyridine (52μL, 0.55 mmol) under Condition A yielded **11** as a brown oil (0.068mg, 47%). I.R.υ_{max} 3240, 3110, 2240, 1735, 1655cm^{-1}. ^{1}H nmr δ 1.31 (3H,t,*J* 7.2Hz,OCH_2CH_3), 2.07(3H,s,$C(O)CH_3$), 3.02(2H,d,*J* 4.8Hz,$CH_2C{\equiv}C$), 4.26 (2H,m, OCH_2CH_3), 4.84(1H,dt,*J* 4.8,7.8Hz,N(H)CH), 6.93(1H,d,*J* 7.7Hz,NH), 7.23(1H,m, Ar), 7.35 (1H,d,*J* 7.9Hz,Ar), 7.63(1H,dt,*J* 1.8,7.8Hz,Ar), 8.55(1H,d,*J* 3.9Hz,Ar); ^{13}C nmr δ 14.0, 22.9, 23.2, 50.7, 61.8, 81.7(C≡C), 84.7(C≡C), 122.8(Ar), 127.0 (Ar), 136.1(Ar), 142.8 (Ar), 149.6(Ar), 170.0 (C=O), 170.3(C=O); MS (m/z) 261, 202, 201, 173, 117; HRMS $C_{14}H_{16}N_2O_3$ calculated (M^++H) 261.1239, found 261.1228.

Ethyl 2-(*N*-Acetyl)-5-[2-(6-bromopyridyl)]pent-4-ynoate (13)
Coupling of **1** (0.145g, 3.0 mol. eq.) with 2,6-dibromopyridine (0.063g, 0.27mmol) under Condition A yielded **13** as a solid (0.062g, 67%) and dimer **24** as a solid (0.043g,30%). Compound **13** M.p. 83-85°C; I.R. υ_{max} 3296, 3000, 2230, 1746, 1654cm^{-1}. ^{1}H nmr δ 1.29(3H,t,*J* 7.2Hz, OCH_2CH_3), 2.10 (3H,s,$C(O)CH_3$), 3.01(2H,d,*J* 4.5Hz, $CH_2C{\equiv}C$), 4.25 (2H,q,*J* 7.2Hz, OCH_2CH_3), 4.75(1H,m, N(H)CH), 7.29-7.32(2H,m,Ar), 7.44(1H,d,*J* 7.8Hz,NH), 7.63(1H,t,*J* 7.8Hz); ^{13}C nmr δ 14.1, 23.1, 23.4, 50.7, 61.9, 82.0(C≡C), 86.7(C≡C), 125.9(Ar), 137.0(Ar), 142.8(Ar), 170.2, 170.4 (2xC=O); MS (m/z) 340($M-CH_3$)$^+$, 338, 325, 323, 267, 265, 197, 195, 102; HRMS $C_{14}H_{15}{}^{79}BrN_2O_3$ calculated (M^+-CH_3)323.0031, found 323.0005.

2,5-bis[4-Ethoxycarbonyl-4-(*N*-acetyl)pent-1-yn-1-yl]thiophene (14)
Coupling of **1** (0.203g, 3.0 mol eq.) with 2,5-diiodothiophene (0.092g, 0.27mmol, 1.0mol eq.) under Condition A yielded **14** as a solid (0.106g, 88%). M.p. 107-110°C; I.R. υ_{max} 3300, 2984, 2250, 1738, 1658cm^{-1}. ^{1}H nmr δ 1.30(6H,t,*J* 7.2Hz, OCH_2CH_3), 2.06(6H,s,C(O)CH_3), 2.99(4H,d,*J* 5.1Hz, $CH_2C{\equiv}C$), 4.25(4H,m, OCH_2CH_3), 4.78(2H,dt,*J* 5.1,7.5Hz,N(H)**CH**), 6.93(4H,broad s,**NH**&Ar); ^{13}C nmr δ 13.9, 22.7, 23.4, 50.7, 61.6, 75.7(C≡C), 89.0(C≡C), 123.5 (Ar), 131.2(Ar), 169.8 (C=O), 170.2(C=O); MS (m/z) 446, 403, 387, 328, 243; HRMS $C_{22}H_{26}N_2O_6S$ calculated 446.1512, found 446.1494.

Ethyl 2-(*N*-Acetyl)-5-[2-(5-iodothiophenyl)]pent-4-ynoate (15)
Coupling of **1** (0.153g, 0.83mmol) with 2,5-diiodothiophene (0.182g, 0.54mmol) under Condition A yielded **15** as an oil which slowly solidified (0.084g,53%). M.p.95-97°C; I.R. υ_{max} 3280, 2924, 1722, 1648cm^{-1}. ^{1}H nmr δ 1.30(3H,t,*J* 7.1Hz,OCH_2CH_3), 2.06(3H, s,C(O)CH_3), 3.00(2H,d,*J* 4.9Hz, $CH_2C{\equiv}C$), 4.27(2H,m,OCH_2CH_3), 4.78 (1H,dt,*J* 4.8,7.7Hz,N(H)**CH**), 6.61(2H,d,*J* 7.6 Hz,**NH**), 6.78(1H, d,*J* 3.8Hz,Ar),7.08(1H,d,*J* 3.8Hz,Ar); ^{13}C nmr δ 14.1, 23.0, 23.6, 50.8, 61.8, 73.9(C≡C), 75.4(C≡C), 90.1(C-I), 128.9(Ar), 133.0 (Ar), 136.7(Ar), 169.8 (C=O), 170.3 (C=O); $C_{13}H_{14}INO_3S$ FAB MS 392(M+H)$^+$.

1,4-bis[4-Ethoxycarbonyl-4-(*N*-acetyl)pent-1-yn-1-yl]benzene (16)
Coupling of **1** (0.203g, 3.0 mol. eq.) with 1,4-diiodobenzene (0.120g, 0.36mmol), under Condition A yielded **16** as a solid (0.113g, 71%). M.p. 174-177°C; I.R. υ_{max} 3270, 2930, 1750, 1640cm^{-1}. ^{1}H nmr δ 1.31 (6H,t,*J* 7.1Hz,OCH_2CH_3), 2.07(6H,s,C(O)CH_3), 2.99(4H,d,*J* 4.8Hz, $CH_2C{\equiv}C$), 4.27 (4H, m,OCH_2CH_3), 4.80(2H,dt,*J* 4.8,7.8Hz,N(H)**CH**), 6.48(2H,d,*J* 7.7 Hz, **NH**), 7.28 (4H,s,Ar); ^{13}C nmr δ 14.1, 23.1, 23.5, 50.9, 61.9, 83.0(C≡C), 85.7 (C≡C), 122.6(Ar), 131.4 (Ar), 169.7(C=O), 170.5(C=O); MS (m/z) 440, 398, 381, 355, 322, 237. HRMS $C_{24}H_{28}N_2O_6$ calculated 440.1947, found 440.1936.

Ethyl 2-(*N*-acetyl)-5-(2-naphthyl)pent-4-ynoate (17)
Coupling of **1** (0.153g, 0.83mmol) with 2-naphthyl triflate (0.154g, 0.58mmol) under Condition A yielded **17** as an oil which slowly solidified (0.177g, 95%). M.p. 74-77°C; I.R. υ_{max} 3300, 2924, 1752, 1654cm^{-1}. ^{1}H nmr δ 1.27(3H,t,*J* 7.1Hz,OCH_2CH_3), 2.06(3H,s,C(O)CH_3), 3.02(2H,d,*J* 4.9Hz, $CH_2C{\equiv}C$), 4.24(2H,m,OCH_2CH_3), 4.85(1H,dt,*J* 4.9,7.6Hz,N(H)**CH**), 6.88(1H,d,*J* 7.6Hz, **NH**), 7.28-7.77(7H,m,Ar), 7.88(1H,s,Ar); ^{13}C nmr δ 13.9, 22.7, 23.3, 50.9, 61.5, 83.5(C≡C), 84.2 (C≡C), 120.0(Ar), 126.3(Ar), 127.3(Ar), 127.4(Ar), 127.6(Ar), 128.2(Ar), 1301.1 (Ar), 132.4 (Ar), 132.6 (Ar), 169.8(C=O), 170.5(C=O); MS (m/z) 309, 250, 221, 205, 165; HRMS $C_{19}H_{19}NO_3$ calculated 309.1365, found 309.1351.

Ethyl 2-(*N*-Acetyl)-5-(1-naphthyl)pent-4-ynoate (18)
Coupling of **1** (0.153g, 0.83mmol)with 1-naphthyl triflate (0.152g, 0.55mmol) under Condition A yielded **18** as an oil which slowly solidified (0.170g, 95%). M.p. 101-102°C; I.R. υ_{max} 3292, 2980, 2230, 1742, 1655cm^{-1}. ^{1}H nmr δ 1.25(3H,t,*J* 7.1Hz,OCH_2CH_3), 2.04 (3H,s,C(O)CH_3), 3.12 (2H, d,*J* 5.0Hz,$CH_2C{\equiv}C$), 4.23(2H,m,OCH_2CH_3), 4.88(1H,dt,*J* 5.0,7.8Hz,N(H)**CH**), 6.99 (1H,d,*J* 7.7Hz,**NH**), 7.33-7.61(4H,m,Ar), 7.78(2H,t,*J* 9.2Hz), 8.26(1H,d,*J* 8.0Hz); ^{13}C nmr δ 13.9, 22.7, 23.4, 51.0, 61.6, 81.1(C≡C), 88.8(C≡C), 120.3(Ar), 124.8(Ar), 125.7(Ar), 126.1(Ar), 126.4(Ar), 128.0(Ar), 128.3(Ar), 130.1(Ar), 132.8(Ar), 133.0 (Ar), 169.9(C=O), 170.6(C=O); MS (m/z) 309, 250, 221, 194, 165; HRMS $C_{19}H_{19}NO_3$ calculated 309.1365, found 309.1351.

Ethyl 2-(*N*-Acetyl)-4-[5-(1,3-dibenzyluracil)]pent-4-ynoate (19)
Coupling of **1** (0.153g, 0.83mmol) with 1,3-dibenzyl-5-iodouracil (0.203g, 0.55mmol) under Condition A yielded **19** as an oil (245mg, 94%). I.R. υ_{max} 3320, 3060, 1740-1640(broad) cm^{-1}. ^{1}H nmr δ 1.22 (3H,t,*J* 6.9Hz,OCH_2CH_3), 2.03(3H,s,C(O)CH_3), 2.89(2H,d,*J* 4.9Hz, $CH_2C{\equiv}C$), 4.16(2H,q,*J*

7.0Hz,OCH_2CH_3), 4.78(1H,dt,*J* 5.2,7.9Hz,N(H)**CH**), 4.86(2H,s,CH_2Ar), 5.11 (2H,s,CH_2Ar), 7.15 (1H,d,*J* 8.0Hz,**NH**), 7.20-7.51(11H,m,Ar); ^{13}C nmr δ 13.8, 22.7, 23.2, 44.8, 50.4, 52.3, 61.4, 75.0 (C≡C), 89.3(C≡C), 98.9, 127.5(Ar), 127.8(Ar), 128.1(Ar),128.3(Ar), 128.8 (Ar), 131.7(Ar), 134.6 (Ar), 136.1(Ar), 143.8(Ar), 150.4(C=O), 161.6(C=O), 170.0(C=O), 170.2 (C=O); MS (m/z) 473, 414, 357, 329; HRMS $C_{27}H_{27}N_3O_5$ calculated 473.1951, found 473.1936.

Ethyl 2-(*N*-Acetyl)-5-(cyclohex-1-en-1-yl)pent-4-ynoate (20)
Coupling of **1** (0.153g, 0.83mmol) with cyclohex-1-en-1-yl triflate (0.126g, 0.55mmol) under Condition A yielded **20** as an oil which slowly solidified (0.093g, 64%). M.p. 68-71°C; I.R. υ_{max} 3260, 2928, 1750, 1646 cm^{-1}. ^1H nmr δ 1.30(3H,t,*J* 7.2Hz,OCH_2CH_3), 1.59(4H,m,CH_2CH_2), 2.06(7H,broad s, $CH_2C{=}CHCH_2$,$C(O)CH_3$), 2.86(2H,m,$CH_2C{\equiv}C$), 4.24(2H,m,*J* 7.1Hz, OCH_2CH_3), 4.73(1H, dt,*J* 4.7,7.9Hz,N(H)**CH**), 6.02(1H,bs,**CH**=C), 6.37(1H,d,*J* 7.9Hz,**NH**); ^{13}C nmr δ 14.1, 21.4, 22.2, 23.1, 23.3, 25.4, 29.2, 51.0, 61.7, 80.6(C≡C), 85.3 (C≡C), 120.2 (C=**CH**), 134.5(**C**=CH), 169.7(C=O), 170.6(C=O); MS (m/z) 263, 204, 176, 175, 148, 147, 102; HRMS $C_{15}H_{21}NO_3$ calculated 263.1521, found 263.1513.

Ethyl 2-(*N*-Acetyl)-5-(cholesta-3,5-dien-3-yl)pent-4-ynoate (21)
Coupling of **1** (0.075g, 1.5 mol. eq.) with cholesta-3,5-dien-3-yl triflate (0.145g, 0.28mmol) under Condition A yielded **21** as an oil (0.094g, 61%). I.R. υ_{max} 3330, 2924, 1755, 1700, 1660cm^{-1}. ^1H nmr δ 0.67-2.29(48H,many m), 2.89(1H,m,$CH_2C{\equiv}C$), 4.27(2H,m,OCH_2CH_3), 4.75 (1H,dt,*J* 4.7, 7.9Hz, N(H)**CH**), 5.48(1H,broad,**CH**=C), 6.18 (1H,sCH=C), 6.51(1H,d,*J* 7.9Hz,**NH**); ^{13}C nmr, two diasteriomers were observed, δ 11.8,14.1,18.6,19.4,22.5, 22.7,23.0,23.7,24.0,27.0, 27.9, 28.1, 31.5,31.9,33.4,34.3,36.0,39.4,39.6,42.3,47.9,51.0,56.0,56.7,61.7,78.3(C≡C), 83.0(C≡C), 85.5 (C≡C),88.0(C≡C),116.6, 126.1,131.0,135.1, 141.0,170.0(C=O),170.6(C=O); MS (m/z) 549, 521, 520, 504, 490, 405 ; HRMS $C_{36}H_{55}NO_3$ calculated 549.4182, found 549.4220.

Ethyl 2-(*N*-Acetyl)-6,7,7-trifluorohept-6-en-4-ynoate (23)
DMF was initially degassed with nitrogen. Coupling of **1** (0.153g, 0.83mmol) under Condition A with bromotrifluoroethylene was accomplished by bubbling the gas through the DMF solution for 10 minutes prior to and 5 minutes after the reaction commenced. Compound **23** was isolated as a brown oil (0.081g,37%). I.R.υ_{max} 3300, 3000, 2250, 1736, 1656cm^{-1}. ^1H nmr δ 1.31(3H,t,*J* 7.1Hz, OCH_2CH_3), 2.07(3H,s,$C(O)CH_3$), 3.05(2H,m,$CH_2C{\equiv}C$), 4.27(2H,m, OCH_2CH_3), 4.77(1H,m, N(H)**CH**), 6.64(1H,d,*J* 7.2Hz,**NH**); MS (m/z) 263, 204, 175, 148, 144, 102; HRMS $C_{11}H_{12}F_3NO_3$ calculated 263.0769, found 263.0777.

Diethyl-2,9-bis(*N*-Acetyl)deca-4,6-diynoate (24)
Coupling of **1** with 3-bromopyridine under Condition A yielded homo-coupled dimer, diethyl-2,9-bis(N-acetyl)deca-4,6-diynoate **24** as a white solid which rapidly coloured red on exposure to air (44%). M.p. 120-122°C; I.R.υ_{max} 3300, 2910, 1730, 1640cm^{-1}. ^1H nmr δ 1.30(6H,t,*J* 7.1Hz, OCH_2CH_3), 2.07 (6H,s,$C(O)CH_3$), 2.85(4H,d,*J* 4.4Hz, $CH_2C{\equiv}C$), 4.25 (4H, m,OCH_2CH_3), 4.71 (2H,dt,*J* 4.5, 7.6Hz, N(H)**CH**), 6.80(2H,d,*J* 7.4Hz, **NH**); ^{13}C nmr δ 14.0, 23.0, 23.2, 50.6, 62.0, 67.6(C≡C), 72.4(C≡C), 169.9(C=O), 170.1 (C=O); FAB MS $C_{18}H_{24}N_2O_6$ (M^+)364.

Coupling Reactions-Condition B
Ethyl 2-(*N*-Acetyl)-7-methylocta-6-en-4-ynoate (22)
Ethyl *N*-acetylpropargylglycinate **1** (0.150g, 0.82mmol,1.0mol eq.), 1-bromo-2-methylpropene (92μL, 1.1mol eq.), triphenylphosphine (0.021g, 0.1mol eq.) and $Pd(PPh_3)_4$ (0.051g, 0.05mol eq.) were dissolved in degassed piperidine (10mL). Copper(I) iodide (0.015g, 0.1mol eq.) was added and the clear light brown solution rapidly darkened. The mixture was heated at reflux under nitrogen for 45 minutes. TLC (5% CH_3OH/CH_2Cl_2) indicated that no starting material **1** was present. The solvent was evaporated *in vacuo* and the residue was purified by initially passing through a short column of silica gel (5% CH_3OH/CH_2Cl_2), then by radial chromatography (1%CH_3OH/CH_2Cl_2) to yield **22** as a brown oil

(0.096g,49%). I.R. υ_{max} 3300, 2980, 1742, 1656cm^{-1}. ^{1}H nmr δ 1.29(3H,t,*J* 7.2Hz,OCH_2CH_3), 1.78(3H,s), 1.84(3H,s), 2.05(3H,s,C(O)CH_3), 2.90(2H,m,$CH_2C{\equiv}C$), 4.23 (2H,m,OCH_2CH_3), 4.73(1H,dt,*J* 4.8,7.9Hz,N(H)CH), 6.63(1H,broad s,NH); ^{13}C nmr δ 13.9, 20.5, 22.8, 23.3, 24.4, 50.9, 61.4, 81.1(C≡C), 85.2(C≡C), 104.6(HC=C), 148.0(HC=C), 169.6(C=O), 170.5(C=O); MS (m/z) 237, 222, 195, 178, 149, 102; HRMS $C_{13}H_{19}NO_3$ calculated 237.1365, found 237.1357.

Ethyl 2-(*N*-Acetyl)-5-(4-methoxyphenyl)pent4-ynoate (4)

Coupling of 1 (0.153g, 0.83mmol) under Condition B with 4-bromoanisole (112μL, 1.1mol eq.) yielded **4** as an oil (0.129g, 53%). I.R. υ_{max} 3288, 3000, 2250, 1734, 1656 cm^{-1}. ^{1}H nmr δ 1.30(3H,t,*J* 7.1 Hz,OCH_2CH_3), 2.06(3H,s,C(O)CH_3), 2.96(2H,m,$CH_2C{\equiv}C$), 3.81(3H,s,OCH_3), 4.26(2H,m, OCH_2CH_3), 4.79(1H,dt,*J* 4.8,7.9Hz,N(H)CH), 6.56 (1H,d,*J* 7.8Hz,NH), 6.81(2H,d,8.8Hz,Ar), 7.30(2H,d,8.8Hz); ^{13}C nmr δ 14.1, 23.0, 23.4, 51.0, 55.1(OCH_3), 61.7, 82.2(C≡C), 83.2(C≡C), 113.7(Ar), 114.9(Ar), 132.9(Ar), 159.3(Ar), 169.8(C=O), 170.6(C=O); MS (m/z) 289, 246, 231, 230, 201, 174, 145; HRMS $C_{16}H_{19}NO_4$ calculated 289.1314, found 289.1304.

Ethyl 2-(*N*-Acetyl)-5-(4-fluorophenyl)pent-4-ynoate (5)

Coupling of **1** (0.153g, 0.83mmol) under Condition B with bromo-4-fluorobenzene (100μ L, 0.91 mmol) yielded **5** as a solid (0.118g, 52%). M.p. 64-64°C; I.R. υ_{max} 3280, 3060, 1736, 1676cm^{-1}. ^{1}H nmr δ 1.29(3H,t,*J* 7.2Hz,OCH_2CH_3), 2.06(3H,s,C(O)CH_3), 2.96(2H,d,*J* 4.8Hz, $CH_2C{\equiv}C$), 4.25 (2H,m,OCH_2CH_3), 4.80(1H,dt,*J* 4.9Hz,7.1Hz,N(H)CH), 6.78(1H,d,*J* 7.1Hz,NH), 6.98 (2H,m,Ar), 7.34(2H,m,Ar); ^{13}C nmr δ 14.1, 23.1, 23.4, 50.8, 61.6, 82.1(C≡C), 83.5 (C≡C), 115.2 (d,$^2J_{CF}$ 22.0Hz), 118.8(d,$^4J_{CF}$ 3.2Hz), 133.3(d,$^3J_{CF}$ 8.5Hz), 162.1(d,$^1J_{CF}$ 249.3Hz), 169.8 (C=O), 170.4 (C=O); MS (m/z) 277, 219, 218, 190, 161, 133; HRMS $C_{15}H_{16}FNO_3$ calculated 277.1114, found 277.1104.

Ethyl 2-(*N*-Acetyl)-5-(3-pyridyl)pent-4-ynoate (12)

Coupling of **1** (0.153g, 0.83mmol) under Condition B with 3-bromopyridine (88μ L, 0.91mmol) yielded **12** as an oil (0.140g, 67%). I.R. υ_{max} 3272, 3025, 2270, 1742, 1664 cm^{-1}. ^{1}H nmr δ 1.31 (3H,t,7.1Hz,OCH_2CH_3), 2.08(3H,s,C(O)CH_3), 3.01(2H,d,*J* 4.8,Hz,$CH_2C{\equiv}C$), 4.27 (2H,m, OCH_2CH_3), 4.85(1H,dt,*J* 4.9,7.7Hz,N(H)CH), 6.93(1H,d,*J* 7.6Hz,NH),7.21(2H,broad s, Ar), 7.62(1H,d,*J* 7.6Hz,Ar), 8.5(2H,broad s,Ar); ^{13}C nmr δ 13.9, 22.7, 23.2, 50.7, 61.6, 79.7 (C≡C), 87.8(C≡C), 128.2(Ar), 131.7(Ar), 138.3(Ar), 147.9(Ar), 151.8(Ar) 169.9(C=O), 170.3 (C=O); MS (m/z) 261, 219, 201, 173, 145, 117; HRMS $C_{14}H_{16}N_2O_3$ calculated $(M+H)^+$ 261.1239, found 261.1246.

L- and D-Ethyl 2-(*N*-Acetyl)pent-4-ynoate (L-1 and D-1)

Crude L-*N*-acetylpropargylglycine[9,17] (0.100g, 0.65mmol) was dissolved in dry ethanol (4mL) and stirred under nitrogen with thionyl chloride (5 drops) for 15 hours. The reaction was followed by TLC (5% CH_3OH/CH_2Cl_2). The product L-ethyl *N*-acetylpropargylglycinate **L-1** was purified by radial chromatography (5% CH_3OH/CH_2Cl_2) and isolated as a white solid (0.56mmol, 87%). M.p. 64-67°C (Lit. 70-72°C)[17]. ^{1}H nmr data identical to racemic **1**.

D-Ethyl *N*-acetylpropargylglycinate **D-1** was prepared from crude D-*N*-acetylpropargylglycine[9,17] in an analogous manner using ethanol and thionyl chloride. M.p. 65-67°C (Lit. 70-72°C)[17]. ^{1}H nmr data identical to racemic **1**.

L- and D-Ethyl 2-(*N*-Acetyl)-5-phenylpent-4-ynoate (L-2 and D-2)

L-Ethyl *N*-acetylpropargylglycinate **L-1** (0.096g, 1.1mol eq.) was coupled with iodobenzene (54μL, 1.0mol eq.) under Condition A to yield **L-2** as a solid (0.096g, 79%). $[\alpha]_D$=+102.7°, (T=20°C, $CHCl_3$, *c* 0.96); M.p. 63-65°C. ^{1}H nmr data identical to racemic **2**.

Similarly, **D**-ethyl *N*-acetylpropargylglycinate **D-1** (0.077g, 1.1mol eq.) was coupled with iodobenzene (43μL, 1.0mol eq.) under Condition A to yield **D-2** as a solid (0.084g, 77%). $[\alpha]_D$=-99.0°, (T=20°C, $CHCl_3$, *c* 0.70); M.p. 63-65°C. ^1H nmr data identical to racemic **2**.

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