Fluorine-containing α-alkynyl amino esters and access to a new family of 3,4-dehydroproline analogues†

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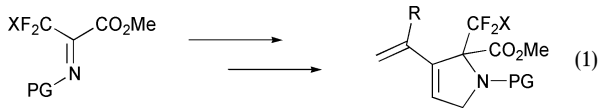
New α-alkynyl, α-CF_3 amino esters have been prepared from electrophilic imines and used to produce 3-alkenyl-3,4-dehydroproline derivatives, *via* enyne metathesis with the precatalyst $[Ru{=}C{=}C{=}CPh_2(Cl)(PCy_3)(arene)]O_3SCF_3$. These new conjugated fluorine-containing dienes are active substrates for the Diels–Alder reaction and lead to a new class of bicyclic amino esters.

α,α-Disubstituted α-amino acids constitute an important class of nonproteinogenic amino acids that has recently received a great deal of attention.[1] In particular, the incorporation of these compounds into peptides results in conformational restrictions and increased rigidity, leading to enhanced resistance towards protease enzymes and to the stabilisation of some secondary structures.[2] Moreover, such α-amino acids bearing an alkynyl or CF_3 group at the α-position irreversibly inhibit the action of various pyridoxal phosphate-dependant enzymes[3] such as alanine racemases[4a] or decarboxylases.[4b] On the other hand, increasing interest in new proline derivatives is connected with the fact that proline is unique among the natural amino acids for its abilities to induce β-turns and initiate peptide folding of the α-helix.[5] Due to these structurally important properties, proline is often regarded as the primary contributor to the biological activity of several proteins, as well as having a key role in biological recognition processes.[5] Structurally modified prolines, especially those containing multiple C–C bonds, have been described as potential enzyme inhibitors.[6] For example, 3,4-dehydro-L-proline is an effective inhibitor of proline dehydrogenase.[7]

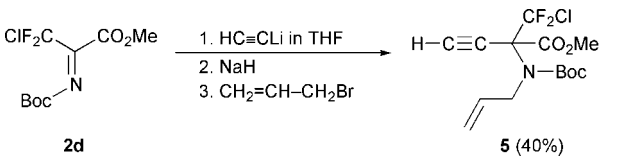
Simple syntheses of new α,α-disubstituted amino acids, containing α-alkynyl and α-CF_3 groups, are of interest as proline derivative precursors. As ruthenium-allenylidene complexes of the type $(LnRu{=}C{=}C{=}CR_2)^+PF_6^-$ were recently shown to be excellent catalyst precursors for enyne metathesis in the synthesis of dihydrofuran derivatives,[8] it might be expected that α-alkynyl, α-CF_3 α-amino esters could offer a direct access to unsaturated cyclic amino esters, and especially to unsaturated proline analogs.

We now report (*i*) general access to a variety of α-CF_3 α-alkynyl amino esters from the readily available electrophilic imines $(CF_3)(CO_2Me)C{=}NR$ and (*ii*) their use for access to 5-membered ring, fluorinated amino esters *via* enyne metathesis performed with the ruthenium-allenylidene precatalyst $[Ru{=}C{=}C{=}CR_2(Cl)(PCy_3)(p\text{-cymene})]^+CF_3SO_3^-$ [eqn. (1)].



(1)

Electrophilic α-CF_3, α-CO_2Me imines constitute excellent starting materials for the formation of bifunctional α-CF_3 α-amino esters.[9] The starting electrophilic imines **2a** and **2b** were prepared in quantitative yields (90–95%) from the fluorinated keto ester CF_3COCO_2Me, **1**,[10] upon addition of H_2NTs, H_2NSO_2Ph or H_2NCbz, followed by dehydration[11] (Scheme 1). The addition of lithium acetylide to an imine **2**, followed by hydrolysis,[12] led to the new α-CF_3, α-alkynyl amino esters **3**. The treatment of the amino esters **3** with NaH, followed by allyl bromide addition in DMF, afforded α-CF_3 amino esters **4** with the 1,6-enyne structure (Scheme 1). Thus, the derivatives **4a** (R = H), **4b** ($R = Bu^n$), **4c** ($R = CH_2OMe$), **4d** (R = cyclopropyl) and **4e** [$R = C(Me){=}CH_2$] were obtained in overall yields of 40, 42, 60, 50 and 28%, respectively, directly from the imines **2a–c** without purification of the intermediates **3**. Similarly, the α-CF_2Cl-containing imine $CF_2Cl(CO_2Me)C{=}N\text{-Boc}$, **2d**,[13] led to the new α-alkynyl-*N*-allyl amino ester **5** [eqn. (2)].



2d **5** (40%)

(2)

The catalytic enyne metathesis on the fluorinated enynes **4** was then attempted. A solution of the α-CF_3 amino ester **4a** (0.2 mmol) in toluene (5 mL) with 10 mol.% of catalyst $[Ru{=}C{=}C{=}CPh_2(Cl)(PCy_3)(p\text{-cymene})]^+PF_6^-$, **A**,[14,15] was irradiated at 300 nm for 0.5 h at room temperature and then the mixture was heated at 80 °C for 69 h in order to reach 90% conversion of **4a**. The 5-membered cyclic amino ester **6** resulting from enyne metathesis was isolated in 70% yield (Scheme 2). Thus, the catalyst **A** appears to be less active towards the bulky enynes **4** than in the enyne metathesis of smaller mixed propargyl allyl ethers to give dihydrofurans.[8] The reaction of **4a** was then performed with 5 mol.% of the

† Dedicated to the memory of Professor Olivier Kahn

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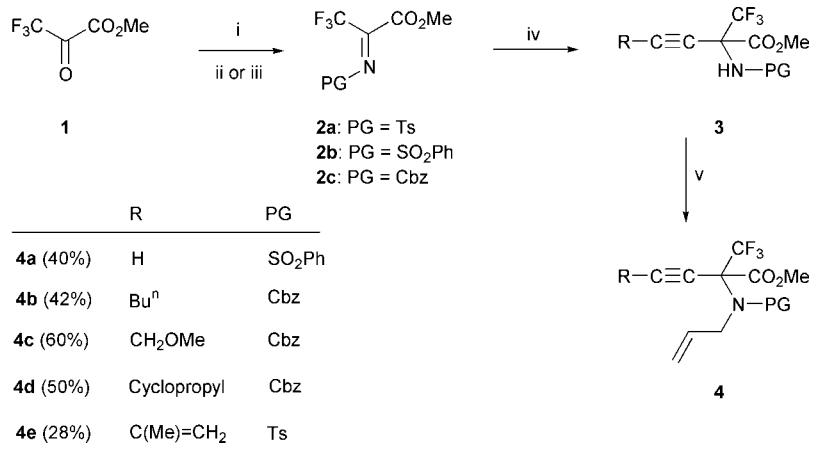
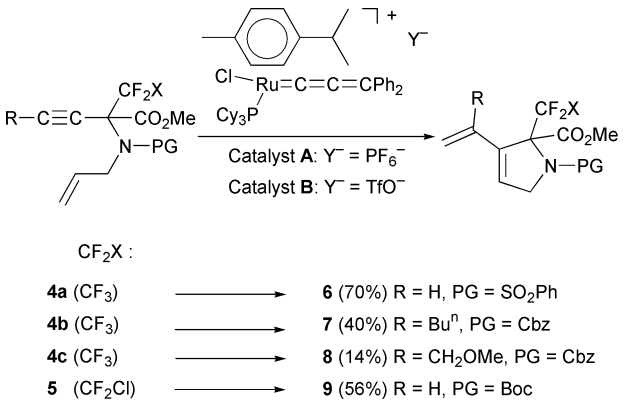


	R	PG
4a (40%)	H	SO_2Ph
4b (42%)	Bu^n	Cbz
4c (60%)	CH_2OMe	Cbz
4d (50%)	Cyclopropyl	Cbz
4e (28%)	$C(Me)=CH_2$	Ts

Scheme 1 *Reagents and conditions*: (i) H_2N-PG [H_2NTs or H_2NSO_2Ph (without solvent) or H_2NBoc or H_2NCbz (both in dichloromethane)]; (ii) $SOCl_2$ in excess (>5 equiv.) with a catalytic amount of pyridine for PG = Ts or SO_2Ph; (iii) 1 equiv. of trifluoroacetic anhydride (TFAA), 2 equiv. of pyridine for PG = Cbz or Boc; (iv) 1 equiv. of RC≡CLi in THF and then hydrolysis; (v) 2 equiv. of NaH and then allyl bromide (3 equiv.) in DMF.



CF_2X :

4a (CF_3) → **6** (70%) R = H, PG = SO_2Ph

4b (CF_3) → **7** (40%) R = Bu^n, PG = Cbz

4c (CF_3) → **8** (14%) R = CH_2OMe, PG = Cbz

5 (CF_2Cl) → **9** (56%) R = H, PG = Boc

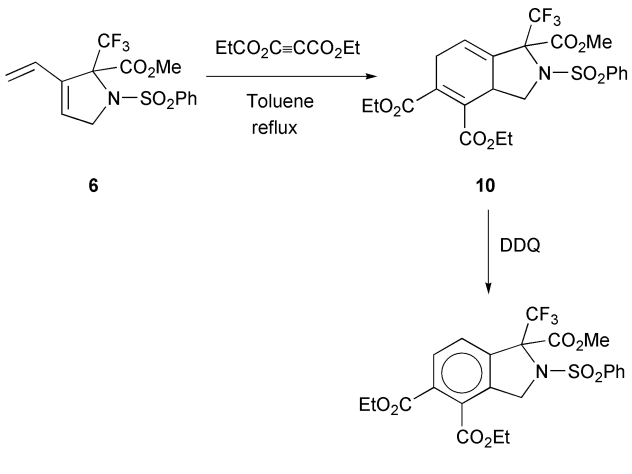
Scheme 2

salt catalyst, but with a different counter anion, $[Ru{=}C{=}C{=}CPh_2(Cl)(PCy_3)(p\text{-cymene})]^+CF_3SO_3^-$, **B**.[15,16] After irradiation for 0.5 h at room temperature, only 24 h of heating in toluene at 80 °C led to 95% conversion of **4a** and to the isolation of **6** in 58% yield. Thus, the triflate catalyst **B** appeared to tolerate the CF_3 group as well, brought the best compromise for this enyne metathesis and was selected for further use.

Catalyst **B** is easily prepared *in situ*, just before use for the transformation of 0.2 mmol of enyne, from 14 mg (2×10^{-2} mmol) of the very stable salt $[RuCl(PCy_3)(p\text{-cymene})]^+TfO^-$, **C**,[16] and 4 mg of HC≡C–CPh_2OH (1 equiv.) in 2 mL of toluene. After 30 min of stirring at room temperature, the enyne (0.2 mmol) was then introduced and the enyne metathesis performed as described above. The stable salt **C** simply results from the quantitative one-pot transformation of the commercial precursor $[RuCl_2(p\text{-cymene})]_2$ on addition of 1 equiv. of PCy_3, to produce $RuCl_2(PCy_3)(p\text{-cymene})$,[16] followed by the reaction with 1 equiv. of AgOTf. The metathesis of enynes **4b** and **4c**, containing a disubstituted C≡C bond, required more forcing conditions. Enyne **4b** (0.2 mmol) with 10 mol.% of catalyst **B** in toluene, after 0.5 h UV irradiation followed by 4 days at 80 °C, led to 86% conversion and 40% of isolated derivative **7**. Analogously, after 3 days at 80 °C, **4c** led to 48% conversion into **8** isolated in 14% yield (Scheme 2).

In contrast, the novel cyclopropyl (**4d**) and isopropenyl (**4e**) derivatives were not transformed under these conditions. This is likely due to the bulkiness of the cyclopropyl and isopropenyl groups, since the C≡C bond is expected to initially interact with the catalyst.[17] The N-Boc-protected α-CF_2Cl enyne **5** containing the α-HC≡C group is transformed under similar conditions as for **4a** (5 mol.% of **B**, 0.5 h irradiation, and 25 h at 80 °C) to yield the cyclic amino ester **9** (56%) (Scheme 2). The amino esters **6–9** contrast well with the cyclic amino esters obtained *via* alkene metathesis[18] as they contain a diene moiety and are potentially suitable precursors for Diels–Alder reactions. Thus, the diene **6** was refluxed with 3 equiv. of $EtO_2CC{\equiv}CCO_2Et$ in toluene for 18 h and the Diels–Alder adduct **10** was isolated in 77% yield, showing the presence of two diastereoisomers in a 7 : 1 ratio. Compound **10** was aromatized on treatment with dichlorodicyanobenzoquinone (DDQ; 5 equiv.). After 24 h of reflux in toluene only 50% of **10** was converted, however, the new fluorine-containing bicyclic amino ester **11** was isolated in 37% yield (Scheme 3).

The above reactions show that the ruthenium-allenylidene complex **B** is a useful catalyst for access to bicyclic amino esters.



Scheme 3

Experimental

General procedure for the preparation of 3

The imine **2** (5 mmol) in dry THF (15 ml) was added dropwise to a stirred solution of 6 mmol of lithium acetylide at −78 °C. After 1 h at −78 °C the reaction mixture was allowed to warm up to room temperature and stirred for 5 h. The reaction was quenched with a saturated solution of NH_4Cl and extracted with diethyl ether (2 × 20 ml). The organic layer was washed with brine (25 ml), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product, characterized by ^1H NMR, was used directly without purification.

General procedure for the preparation of 4 and 5

A solution of **3** (3 mmol) in dry DMF (9 ml) was added to a suspension of NaH (6 mmol) in dry DMF (15 ml) at 0 °C. The mixture was stirred at room temperature for 0.5 h and then 9 mmol of allyl bromide (in solution in 6 ml of DMF) were added. After stirring for an additional 5 h, the mixture was hydrolyzed with water (20 ml) and extracted with diethyl ether (2 × 20 ml). The organic layer was washed with water (4 × 20 ml), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (diethyl ether–pentane). Compounds **4a–e** and **5** were characterized by ^1H, ^{13}C and ^{19}F NMR and gave satisfactory elemental analyses.

4a. ^1H NMR ($CDCl_3$, 200.132 MHz): δ 2.75 (s, 1 H, C≡CH), 3.97 (s, 3 H, OCH_3), 4.00–4.27 (m, 2 H, CH_2N), 4.87 (dm, 1 H, $^3J = 10.1$, *cis*-CH_2=CH), 4.94 (dm, 1 H, $^3J = 16.9$ Hz, *trans*-CH_2=CH), 5.52–5.74 (m, 1 H, CH_2=C*H*), 7.44–7.65 (m, 3 H, Ph), 7.88–7.97 (m, 2 H, Ph). ^{19}F NMR ($CDCl_3$, 188.292 MHz): δ −71.9 (s, 3 F, CF_3). ^{13}C NMR ($CDCl_3$, 50.329 MHz): δ 50.60 (NCH_2), 54.35 (OCH_3), 72.59 (quat. C), 80.15 (C≡*C*H), 97.95 (*C*≡CH), 117.44 (*C*H_2=CH), 122.39 (q, $^1J_{CF} = 288.7$ Hz, CF_3), 128.65, 128.99, 133.60 (aromatic CH), 133.48 (CH_2=*C*H), 139.22 (*ipso* C), 163.294 (C=O). Anal. found: C, 49.29; H, 3.68%. Calc. for $C_{15}H_{14}F_3NO_4S$: C, 49.86; H, 3.90%.

5. ^1H NMR ($CDCl_3$, 200.132 MHz): δ 1.39 (s, 9 H, 3 × CH_3 Boc), 2.72 (s, 1 H, C≡C*H*), 3.83 (s, 3 H, OCH_3), 4.10–4.25 (m, 2 H, CH_2N), 5.13 (dm, 1 H, $^3J = 10.2$, *cis*-CH_2=CH), 5.25 (dm, 1 H, $^3J = 17.2$ Hz, *trans*-CH_2=CH), 5.76–6.04 (m, 1 H, CH_2=C*H*). ^{13}C NMR ($CDCl_3$, 50.329 MHz): δ 28.00 (3 × CH_3 Boc), 50.22 (NCH_2), 53.45 (OCH_3), 73.93 (quat. *C*CF_2Cl), 79.14 (C≡*C*H), 82.45 [*C*$(CH_3)_3$], 97.86 (*C*≡CH), 116.19 (*C*H_2=CH), 128.06 (t, $^1J_{CF} = 288.6$ Hz, CF_2Cl), 134.25 (CH_2=*C*H), 152.58 (*C*=O Boc), 163.23 (C=O).

General procedure for the preparation of 6–9

A mixture of enyne **4** or **5** (1 mmol) and catalyst **A** or **B** (5 or 10 mol.%) in toluene was irradiated at room temperature for 0.5 h and then heated at 80 °C. The solvent was removed in vaccum and the crude product was purified by flash chromatography (diethyl ether–pentane). Compounds **6–9** were characterized by ^1H, ^{13}C and ^{19}F NMR and gave satisfactory elemental analyses.

6. ^1H NMR ($CDCl_3$, 200.132 MHz): δ 3.87 (s, 3 H, OCH_3), 4.03 (d, 1 H, $^3J = 14.8$, CH_2N), 4.53 (d, 1 H, $^3J = 14.8$, CH_2N), 5.21 (d, 1 H, $^3J = 11.4$, *cis*-CH_2=CH), 5.47 (d, 1 H, $^3J = 17.6$, *trans*-CH_2=CH), 6.12 (dd, 1 H, $^3J = 11.4$, $^3J = 17.7$ Hz, CH_2=C*H*), 6.19–6.27 (m, 1 H, CH_2C*H*=C), 7.43–7.65 (m, 3 H, Ph), 7.82–7.93 (m, 2 H, Ph). ^{19}F NMR ($CDCl_3$, 188.292 MHz): δ −71.9 (s, 3 F, CF_3). ^{13}C NMR ($CDCl_3$, 50.329 MHz): δ 53.53 (OCH_3), 55.02 (CH_2N), 68.02 (*C*CF_3), 119.16 (*C*H_2=CH), 123.40 (q, $^1J_{CF} = 287.4$ Hz, CF_3), 126.71 (CH_2*C*H=), 128.58 (CH_2=*C*H), 127.40, 129.07, 133.22 (aromatic CH), 135.40 (quat. C=), 139.51 (*ipso* C), 165.65 (C=O). Anal found: C, 49.71; H, 4.17%. Calc. for $C_{15}H_{14}F_3NO_4S$: C, 49.86; H, 3.90%.

Characterization of 10 and 11

10 (major diastereoisomer). ^1H NMR ($CDCl_3$, 200.132 MHz): δ 1.25 (t, 3 H, $^3J = 7.1$, C$H_3$$CH_2$), 1.29 (t, 3 H, $^3J = 7.1$ Hz, C$H_3$$CH_2$), 3.06–3.20 (m, 1 H, =CHCH_2), 3.50–3.64 (m, 1 H, =CHCH_2), 3.84 (m, 3 H, CH_2N and C*H*CH_2N), 5.88 (m, 1 H, CH_2C*H*=), 7.40–7.62 (m, 3 H, Ph), 7.79–7.91 (m, 2 H, Ph). ^{19}F NMR ($CDCl_3$, 282.408 MHz): δ −71.62 (s, 3 F, CF_3). ^{13}C NMR ($CDCl_3$, 50.329 MHz): δ 13.83 (*C*$H_3$$CH_2$), 14.00 (*C*$H_3$$CH_2$), 29.71 (*C*$H_2$CH=), 38.35 (*C*HC$H_2$N), 52.48 ($CH_2N$), 53.43 ($OCH_3$), 61.78 ($CH_3$*C*$H_2$), 62.71 ($CH_3$*C*$H_2$), 72.79 (q, $^2J_{CF} = 29.7$, *C*CF_3), 122.21 (CH_2*C*H=C), 128.43 (q, $^1J_{CF} = 285.5$ Hz, CF_3), 127.26, 129.15, 133.33 (aromatic CH), 133.83 [CH_2*C*(CO)=C], 135.60 (*ipso* C), 139.85 [CH*C*(CO)=C], 165.70 (quat. CH=*C*), 164.87, 166.39, 167.21 (C=O).

11. ^1H NMR ($CDCl_3$, 200.132 MHz): δ 1.33 (t, 3 H, $^3J = 7.1$, C$H_3$$CH_2$), 1.34 (t, 3 H, $^3J = 7.1$, C$H_3$$CH_2$), 3.83 (s, 3 H, OCH_3), 4.34 (q, 2 H, $^3J = 7.1$, CH_3CH_2), 4.35 (q, 2 H, $^3J = 7.1$, CH_3CH_2), 4.69 (d, 1 H, $^2J = 14.4$, CH_2N), 5.18 (d, 1 H, $^2J = 14.4$, CH_2N), 7.44–7.61 (m, 4 H, aromatic H), 7.71 (d, 1 H, $^3J = 7.71$ Hz, aromatic H), 7.88–7.98 (m, 2 H, aromatic H). ^{19}F NMR ($CDCl_3$, 282.408 MHz): δ −72.51 (s, 3 F, CF_3). ^{13}C NMR ($CDCl_3$, 50.329 MHz): δ 14.04 (*C*$H_3$$CH_2$), 14.12 (*C*$H_3$$CH_2$), 53.78 ($OCH_3$), 54.48 ($CH_2N$), 62.20 ($CH_3$*C*$H_2$), 62.32 ($CH_3$*C*$H_2$), 72.95 (*C*$CF_3$), 126.02, 127.47, 129.23, 133.32, 133.50 (aromatic C), 128.6, 134.77 (quat. aromatic C, *C*C=O), 132.7 (q, $^1J_{CF} = 283.0$ Hz, CF_3), 128.60, 136.60, 138.53, 139.22 (quat. aromatic C), 165.44, 165.72, 166.61 (C=O).

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