New Routes to Lipophilic Amino Acids: Synthesis of Alkynyl and Fluoro-Containing Alanine Derivatives

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Abstract: Branched α-amino acids incorporating an alkynyl group have been prepared by copper-catalysed reaction of a serine-derived organozinc reagent with bromoallenes. Substantial improvements to our previously reported Negishi cross-coupling of the serine-derived organozinc reagent with cycloalkenyl triflates are possible using a combination of LiCl and SPhos as ligand. Finally, we report a preliminary example of addition of HF to cycloalkenyl alanine derivatives, leading to the corresponding tertiary fluoride.

Key words: amino acids, alkynes, cross-coupling, fluorine, zinc

α-Amino acids with lipophilic side chains are useful components of enzyme inhibitors. We have previously reported that enantiomerically pure cycloalkenyl alanine derivatives may be prepared either by copper-catalysed reaction of the serine-derived organozinc reagent **1** with cycloalk-1-en-3-yl phosphates **2**, or by Negishi cross-coupling of the same organozinc reagent **1** with cycloalkenyl triflates **3**.[1] Subsequent hydrogenation gave the corresponding saturated derivatives. These cycloalkyl alanine derivatives continue to be of interest as components of enzyme inhibitors, and recent methods for their preparation rely on resolution by diastereoisomer separation, highlighting the need for stereoselective routes to these compounds.[2] In order to improve both the activity and the metabolic stability of pseudopeptides containing such highly lipophilic residues, efficient routes to new classes of α-amino acid incorporating either an alkynyl group, **4**, or a tertiary fluoride **5** were desirable (Figure 1).

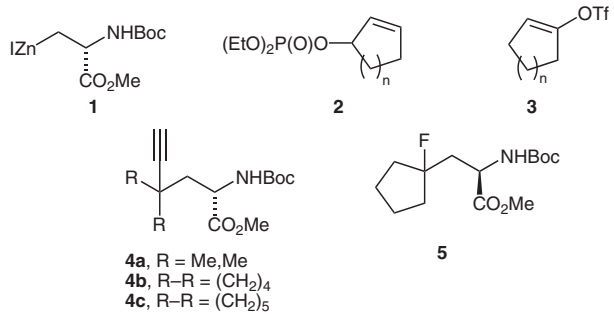

Figure 1

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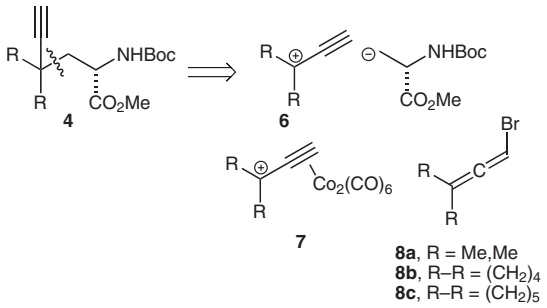
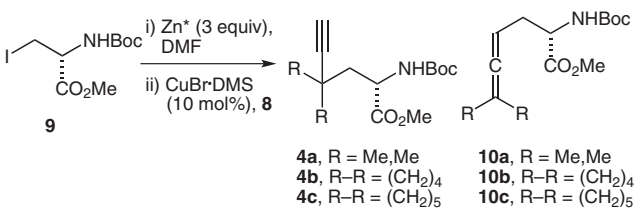
The proposed route to alkynes **4** involved disconnection at the branch point, and is illustrated in Scheme 1. The two obvious synthetic equivalents for the propargylic cation **6** were the dicobalt hexacarbonyl cation **7**[3] and the allenic bromide **8**. The latter was selected for initial investigation, since reactions of the zinc reagent **1** with allylic electrophiles generally proceed selectively in an S_N2' manner.[4]



Scheme 1 Retrosynthetic route to terminal alkynes **4**

The allenic bromides **8a–c** were prepared by the Landor method,[5] as applied by Eaton[6] and Backvall.[7] Initial optimisation of the copper(I)-catalysed reaction of the organozinc reagent **1**, prepared from iodide **9** in DMF, with allenic bromide **8a** established that the reaction was best conducted at 0 °C for an extended period, giving the desired alkyne **4a**, along with small amounts of the allene **10a**. Copper(I)-catalysed reaction of the organozinc reagent **1** with allenic bromides **8b** and **8c** was optimally carried out at –10 °C, giving satisfactory yields of the desired products **4b** and **4c** (Scheme 2, Table 1), along with the corresponding allenes **10b** and **10c**. The terminal alkyne in products **4** provides a site for further functionalisation, so a range of more complex compounds is potentially accessible.

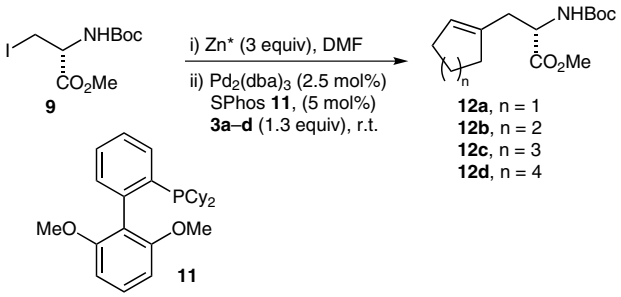


Scheme 2 Synthesis of alkynes **4**; for yields and conditions, see Table 1

Table 1 Synthesis of Alkynes **4** via Copper(I)-Catalysed Reaction of the Organozinc Reagent **1** with Allenic Bromides **8**

Allenyl bromide	Temp (°C)	Time	Alkyne, yield (%)[a]	Allene, yield (%)[a]
8a	0	22 h	**4a**, 51	**10a**, 8
8b	–10	91 h	**4b**, 43	**10b**, 8
8c	–10	68 h	**4c**, 50	**10c**, 7

[a] All yields are based on protected iodoalanine **9**, and refer to isolated material.



Scheme 3 Improved Negishi cross-coupling with cycloalkenyl triflates

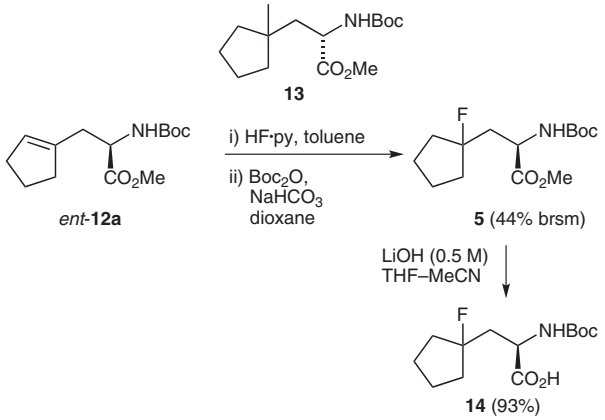
Table 2 Formation of the Cycloalkenyl Alanine Derivatives **12a–d**

Triflate	Additive	Product	Yield (%)[a]
3a	none	**12a**	70
3b	none	**12b**	70
3c	none	**12c**	54
3c	LiCl (1.8 equiv)	**12c**	62
3d	none	**12d**	58
3d	LiCl (1.8 equiv)	**12d**	63

[a] All yields are based on protected iodoalanine **9**.

It has recently been established that the yields in Negishi cross-coupling reactions can often be improved by the use of biarylphosphine ligands.[8] Although most reports have concentrated on the use of aryl halides as cross-coupling partners,[9] there are a number of reports in which the use of biarylphosphine ligands has also been shown to be effective in Negishi cross-coupling with vinyl halides and triflates.[10] In our previously published method for the Negishi coupling of cycloalkenyl triflates with organozinc reagent **1**,[1] we had employed $(Ph_3P)_2PdCl_2$ as the catalyst, obtaining yields in the range 41–46% (and 58% in a larger scale coupling with cycloheptenyl triflate). Given these modest yields, we have therefore investigated the use of the biarylphosphine ligand SPhos **11** in cross-coupling of organozinc reagent **1** with cycloalkenyl triflates. Application of the standard conditions that we had previously reported for the coupling of the organozinc reagent **1** with aryl iodides, namely $Pd_2(dba)_3$ (2.5 mol%) and SPhos **11** (5 mol%) at room temperature,[11] but using cyclopentenyl triflate,[12] resulted in a significantly improved yield of the desired adduct **12a** (70%). These conditions were also effective for coupling with cyclohexenyl triflate, but the yields for coupling with cycloheptenyl and cyclooctenyl triflate were lower (Scheme 3, Table 2). It has been known for some time that addition of lithium halides improves yields in Stille cross-coupling of aryl triflates,[13] and also that the addition of LiCl can increase the reactivity of alkylzinc halides by the proposed formation of higher order organozincate intermediates.[14,15] We were pleased to observe that addition of LiCl (1.8 equiv) to the cross-coupling of zinc reagent **1** with both cycloheptenyl and cyclooctenyl triflate resulted in a consistent increase in isolated yield of the desired products **12c** and **12d**. In contrast, the use of either tetrabutylammonium chloride or tetrabutylammonium bromide reduced the isolated yields substantially. It is not possible to be sure whether the increase in yield using LiCl is due to stabilisation of the catalyst, or to an increase in the reactivity of the alkylzinc iodide **1**, or to a combination of both factors. Nevertheless, it is clear that the combined use of SPhos as ligand, and the addition of LiCl, has allowed a significant improvement in the efficiency of the formation of the cycloalkenyl alanine derivatives **12a–d** (and therefore, the corresponding cycloalkyl alanine derivatives formed by subsequent hydrogenation[1]).

In earlier work, we have reported the synthesis of the methylated cyclopentylalanine derivative **13**,[1] for use as a component of an enzyme inhibitor. Subsequent work established that incorporation of the analogous fluorinated derivative **5** rendered the inhibitor less susceptible to metabolic degradation, but synthetic access to this compound was inefficient and required resolution.[16] It has been reported that simple tertiary fluorides can be prepared by addition of HF to cyclic alkenes using HF·pyridine,[17] which suggested that a very simple route to enantiomerically pure **5** might be possible through HF addition to the alkene *ent*-**12a**; the compatibility of this reagent with protected amino acid functionality was an obvious concern. A preliminary trial was conducted on *ent*-**12a**, prepared in an analogous way to **12a**, but using protected iodoalanine *ent*-**9** derived from D-serine. In the event, after screening a variety of solvents, use of toluene gave the best results for HF addition. Rapid removal of the Boc group was observed, to give the HF salt of the deprotected amine. This salt was evidently sufficiently soluble to allow HF addition, although the reaction did not proceed to completion. Boc-reprotection allowed the isolation of the desired product **5** (30%, 44% based on recovered *ent*-**12a**), along with recovered starting material *ent*-**12a** (32%). Although the overall yield was not high, the route is short and simple. Hydrolysis of methyl ester **5** proceeded uneventfully to give the free acid **14** (93%), illustrating the stability of the tertiary fluoride to these basic conditions (Scheme 4). While this process has yet to be optimised, it provides a very simple and direct route to the fluorocyclopentylalanine derivative **14**.



Scheme 4 Addition of HF to cyclopentenylalanine derivative *ent*-**12a**

In conclusion, we have reported simple methods[18] for the synthesis of a range of new α-amino acids with lipophilic side chains.

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(18) **General Method for the Preparation of Alkynes 4**: The organozinc reagent **1** was prepared from protected iodoalanine **9** (329 mg, 1 mmol) as a ca. 1 M solution in DMF according to our previously reported method.[11] CuBr·DMS (20.6 mg, 0.1 mmol) was gently heated under vacuum in a dry flask until the powder turned light green, and was then allowed to cool under nitrogen. DMF (0.6 mL) and the bromoallene **8** (1.1 mmol) were added. The reaction mixture was cooled to –10 °C. After 2 min stirring at –10 °C, a solution of the organozinc reagent **1** (1 mL of a 1 M solution in DMF, 1 mmol) was added dropwise via syringe over 10 min. The reaction mixture was stirred for the time indicated at either –10 °C or 0 °C. The reaction mixture was applied directly to a silica gel column, which was eluted (5% Et_2O in toluene) to give the alkynes **4**[19–21] and the allenes **10** as light yellow oils.
General Method for the Preparation of Alkenes 12: The cycloalken-1-yl triflate **3** (1.3 mmol, 1.3 equiv), $Pd_2(dba)_3$ (22 mg, 2.5 mol%), SPhos (21 mg, 5 mol%) and LiCl (1.8 mmol, 1.8 equiv), if required, were added at r.t. to the organozinc reagent **1** (1 mL of a ca. 1 M solution in DMF). The reaction mixture was stirred at r.t. overnight under a positive pressure of nitrogen, and then applied directly to a silica gel column, which was eluted (10% EtOAc in petroleum ether) to give the cross-coupled product **12**.
(*R*)-2-Amino-3-(1-fluorocyclopentyl)propionic Acid Methyl Ester (5): Alkene *ent*-**12a** (492 mg, 1.83 mmol) was dissolved in toluene (4 mL) in a Teflon bottle, cooled to 0 °C and stirred vigorously. HF–pyridine (70% HF, 3.2 mL, **CAUTION**: very toxic) was added and the bottle was sealed. After 2 h, the reaction mixture was carefully transferred into a slurry of $CaCO_3$ (12.8 g) in H_2O (50 mL) and CH_2Cl_2 (35 mL) cooled to 0 °C. The mixture was stirred while the pH was adjusted to ca. 10 by addition of sat. aq Na_2CO_3, followed by stirring for a further 30 min. Celite (6.4 g) was washed with Na_2CO_3 solution, H_2O, EtOH, EtOAc and CH_2Cl_2 in sequence and added to the slurry. The suspension was filtered and the filter cake was washed with CH_2Cl_2 (50 mL in portions) and H_2O (25 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with sat. aq $NaHCO_3$ (20 mL) and evaporated. The crude mixture of amino esters (0.253 g) was dissolved in 1,4-dioxane (4 mL), aq sat. $NaHCO_3$ (6 mL) was added and the mixture was cooled to 0 °C with stirring. Boc_2O (0.323 g, 1.48 mmol) in 1,4-dioxane (4 mL) was added to the reaction mixture. The reaction mixture was allowed to reach r.t. and stirred for 1 h. The reaction mixture was diluted with Et_2O (10 mL) and H_2O (10 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with H_2O and brine (10 mL each) and evaporated. The product was purified by gradient column chromatography [Column 40 mm i.d. × 82 mm, loaded with 50 g Biotage KP-Sil (silica gel) 2–17% EtOAc in *iso*-hexane] to give **5**[22] (158 mg, 30% over two steps) and recovered *ent*-**12a** (160 mg, 32%).

(19) Characterisation data for alkyne **4a**: $[\alpha]_D^{21}$ +9.8 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.26 (s, 3 H), 1.27 (s, 3 H), 1.42 (s, 9 H), 1.74 (dd, *J* = 9.1, 14.0 Hz, 1 H), 1.90 (dd, *J* = 4.3, 14.2 Hz, 1 H), 2.15 (s, 1 H), 3.71 (s, 3 H), 4.43–4.48 (m, 1 H), 5.17 (d, *J* = 7.7 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.4, 28.9, 29.8, 29.8, 44.3, 51.8, 52.2, 69.2, 79.9, 90.5, 155.2, 173.5. IR (ATR): 3293, 2973, 1744, 1705, 1508, 1436, 1391, 1366, 1279, 1246, 1209, 1160, 1048, 1028, 868, 779, 629 cm^{-1}. HRMS (ES): *m*/*z* [M + H^+] calcd for $C_{14}H_{24}NO_4$: 270.1705; found: 270.1716.

(20) Characterisation data for alkyne **4b**: $[\alpha]_D^{21}$ +2.9 (*c* = 10.2, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 1.45–1.54 (m, 2 H), 1.55–1.72 (m, 2 H), 1.73–1.89 (m, 3 H), 1.90–2.00 (m, 2 H), 2.04 (dd, *J* = 4.3, 14.2 Hz, 1 H), 2.18 (s, 1 H), 3.71 (s, 3 H), 4.43–4.56 (m, 1 H), 5.18 (d, *J* = 7.7 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.4, 23.8, 28.4, 40.2, 40.5, 41.1, 41.9, 52.2, 52.5, 70.1, 79.8, 89.8, 155.2, 173.5. IR (ATR): 3294, 2954, 2874, 1709, 1507, 1437, 1391, 1366, 1248, 1214, 1162, 1049, 1019, 868, 778, 630 cm^{-1}. HRMS (ES): *m*/*z* [M + H^+] calcd for $C_{16}H_{26}NO_4$: 296.1862; found: 296.1864.

(21) Characterisation data for alkyne **4c**: mp 56–57 °C; $[\alpha]_D^{21}$ +2.0 (*c* = 7.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.04–1.27 (m, 3 H), 1.42 (s, 9 H), 1.56–1.70 (m, 5 H), 1.70–1.85 (m, 3 H), 1.89 (dd, *J* = 4.1, 14.1 Hz, 1 H), 2.33 (s, 1 H), 3.70 (s, 3 H), 4.45–4.51 (m, 1 H), 5.21 (d, *J* = 7.6 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5, 22.6, 25.8, 28.4, 35.2, 37.0, 38.0, 44.3, 51.2, 52.2, 71.9, 79.8, 88.5, 155.2, 173.7. IR (ATR): 3306, 2930, 2857, 2360, 1744, 1712, 1506, 1449, 1391, 1366, 1252, 1206, 1165, 1048, 1023, 866, 776, 632 cm^{-1}. HRMS (ES): *m*/*z* [M + H^+] calcd for $C_{17}H_{28}NO_4$: 310.2018; found: 310.2017.

(22) Characterisation data for **5**: mp 47–51 °C; $[\alpha]_D^{21}$ –5.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 1.50–1.70 (m, 4 H), 1.73–1.85 (m, 2 H), 1.93–2.07 (m, 2 H), 2.10–2.32 (m, 2 H), 3.72 (s, 3 H), 4.40–4.50 (m, 1 H), 5.21 (br d, *J* = 7.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.5, 23.6, 28.3, 37.65 (d, *J* = 13 Hz), 37.8 (d, *J* = 13 Hz), 39.9 (d, *J* = 23 Hz), 51.3, 52.3, 79.9, 105.9 (d, *J* = 172 Hz), 155.2, 173.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –142.7. IR (ATR): 3364, 2974, 1750, 1718, 1508, 1367, 1167 cm^{-1}. HRMS (ES): *m*/*z* [M + H^+] calcd for $C_{14}H_{25}NO_4F$: 290.1768 (base peak is 579 [M_2H^+]); found: 290.1769.

