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Enantioselective and diastereoselective synthesis of fluorinated dipeptides by late electrophilic fluorination

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Abstract—A series of optically enriched monofluorinated dipeptides incorporating an α-fluoro-α-amino acid were prepared by enantio- and diastereoselective electrophilic fluorination. This previously unsuccessful approach to fluorinated dipeptides can now be achieved with up to 73:27 enantiomeric ratio and high >98:2 diastereomeric ratio.

Selective incorporation of unnatural amino acids into proteins is an area of major interest in peptidomimetic chemistry. In particular, fluorinated amino acids have emerged as valuable building blocks for designing peptide analogues.[1] All known fluoro amino acids are synthetic molecules.[2] Interestingly, they can be incorporated into peptides for protein engineering, leading to positive effects on protein stability, on the interactions with host molecules, and providing opportunities to study protein conformations and metabolic processes by ^{19}F NMR. Within the important class of fluorinated amino acids, free α-fluoro-α-amino acids are unstable as rapid dehydrofluorination at ambient temperature occurs.[3,4] Although several fluorinated amino acids have been synthesised and methods for the incorporation of unnatural amino acids into proteins have advanced significantly over recent years,[5] the lack of availability of free α-fluoro-α-amino acids has precluded the incorporation of this structure into peptides. In 1998, Takeuchi et al. reported the first preparation of fully protected dipeptides containing an α-fluoroglycine moiety exploiting the Gabriel reaction in the key step.[6] When starting from chiral amido derivatives, they obtained equimolar mixtures of diastereomers. Noteworthy, the direct fluorination of dipeptides using fluorinating agents was unsuccessful.[6] Carbonyl-bridged peptides containing an α-fluoroglycine residue were also prepared via a Gabriel reaction.[7]

We have recently developed a new class of efficient enantioselective electrophilic fluorinating agents derived from cinchona alkaloids which have demonstrated high performances in the fluorination of various substrates.[8] In particular, we succeeded in the enantioselective synthesis of *N*-phthaloyl protected α-fluoro-α-phenylglycine derivatives.[9] Our next goal was to investigate the direct asymmetric electrophilic fluorination of dipeptides. We chose a peptide with *N*-methylated peptidic bond in order to prevent dehydrofluorination. Interestingly, *N*-methyl amino acids are present in natural products and give rise to important therapeutic compounds.[10] Elongation of such dipeptides can be realised by activation either at the C-terminal of the fluorinated residue or at the N-terminal residue (Fig. 1).

We report in this letter the first asymmetric synthesis of a series of dipeptides containing an α-fluoro-α-amino acid as the C-terminal residue by late enantioselective and diastereoselective electrophilic fluorination.

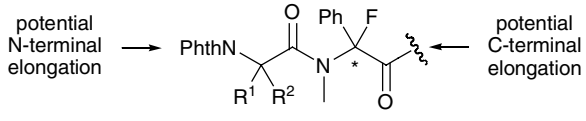

Figure 1.

Keywords: Electrophilic fluorination; Dipeptide; Enantioselective synthesis; Fluorine chemistry; Amino acid.
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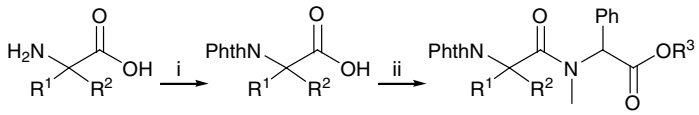

Scheme 1. Synthesis of dipeptides. Reagents and conditions: (i) phthalic anhydride, 180 °C, 30 min; (ii) $(COCl)_2$, CH_2Cl_2, rt, 2 h, then 0 °C, (+/−)-*N*-Me–Phg–OR^3·HCl, DPEA, 24 h, rt.

Starting dipeptides were prepared in a two-step sequence which involves a protection of the amino group of the N-terminal amino acid[11] [1-aminocyclopentanecarboxylic acid (Ac5c), 2-aminoisobutyric acid (Aib) and 2-amino-2-(4-bromophenyl)-propionic acid ((*S*)-MPBrG)[12]] followed by the coupling with *N*-methyl-phenylglycine methyl ester or *N*-methyl-phenylglycine benzyl ester (Scheme 1).

Dipeptides of achiral amino acids (Aib, Ac5c) and racemic *N*-methyl-phenylglycine were selected first for enantioselective electrophilic fluorination under the previously optimised conditions for *N*-phthaloyl phenylglycine methyl ester.[9] Thus, deprotonation of the dipeptide with LiHMDS at −78 °C in THF gave the ester enolate, which was subsequently fluorinated with *N*-fluoro cinchona alkaloid derivatives (Scheme 2).[13] In the case of Phth–Ac5c–(*N*-Me–Phg)–OBn, fluorination with *O*-(*p*-chlorobenzoyl)-*N*-fluoroquininium tetrafluoroborate (F–*p*ClBzQN–BF_4) resulted in 73:27 enantiomeric ratio (Table 1, entry 5).

Evaluation of various *N*-fluoro cinchona alkaloids indicated that F–*p*ClBzQN–BF_4 and F–*p*ClBzCD–BF_4 give better enantioselectivities than their corresponding pseudoenantiomers F–*p*ClBzQD–BF_4 and F–*p*ClBzCN–BF_4, respectively, which yielded the fluorinated dipeptides with opposite configuration (Table 1, entries 1–4). In addition, enantioselectivity was higher using F–*p*ClBzQN–BF_4 than with F–*p*ClBzCD–BF_4. In all cases, the conversion was higher than 95% and the products were isolated in 86–92% yields in analytically pure form after column chromatography.

Next, we examined the diastereoselective fluorination of dipeptides of a C^{α} quaternary chiral amino acid ((*S*)-MPBrG) and racemic *N*-methyl-phenylglycine (Table 1, entries 8 and 9). In this case, the electrophilic fluorination was conducted with the aid of *N*-fluorobenzenesulfonimide (NFSI), and the stereoselectivity is directed intramolecularly by the enantiomerically pure substrate Phth–(*S*)-MPBrG–(*N*-Me–Phg)–OR^3. Diastereoselectivity of 91:9 was obtained with *N*-methyl-phenylglycine methyl ester derived dipeptide, and diastereoselectivity of >98:2 was obtained with *N*-methyl-phenylglycine benzyl ester analogue. Interestingly, this approach gives access to a dipeptide possessing two consecutive enantiopure quaternary amino acids, which could be incorporated into a longer peptide.

In summary, we succeeded in stereocontrolled electrophilic fluorination of dipeptides with moderate to high stereoselectivities. Our approach allows to incorporate a fluorine atom at a late stage of a dipeptide synthesis. The full scope of this work is currently being investigated.

Acknowledgements

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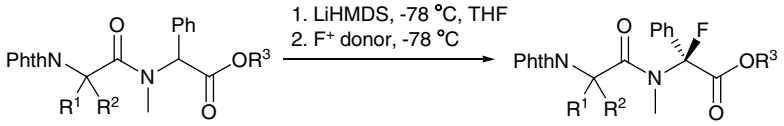

Scheme 2. Electrophilic fluorination of dipeptides.

Table 1. Enantioselective and diastereoselective fluorination of dipeptides

Entry	R^1	R^2	R^3	Fluorinating reagent	Conv%[a]	Er or dr[b]
1		$-(CH_2)_4-$	Me	F–*p*ClBzQN–BF_4	>98	67:33
2		$-(CH_2)_4-$	Me	F–*p*ClBzQD–BF_4	>98	36:64
3		$-(CH_2)_4-$	Me	F–*p*ClBzCN–BF_4	95	47:53
4		$-(CH_2)_4-$	Me	F–*p*ClBzCD–BF_4	95	58:42
5		$-(CH_2)_4-$	Bn	F–*p*ClBzQN–BF_4	>98 (92)	73:27
6	Me	Me	Me	F–*p*ClBzQN–BF_4	>98	66:34
7	Me	Me	Bn	F–*p*ClBzQN–BF_4	95 (88)	72:28
8	Me	4-BrC_6H_4	Me	NFSI	>98	91:9
9	Me	4-BrC_6H_4	Bn	NFSI	>98 (86)	>98:2

[a] Conversion was determined by HPLC. In brackets are isolated yields.
[b] Ers were determined by HPLC using Chiralcel OD-H or AD-H columns (hexane–^{i}PrOH). Drs were determined by ^{19}F NMR.

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13. *Typical procedure for asymmetric electrophilic fluorination of a dipeptide*. To a solution of Phth–Aib–(*N*-Me–Phg)–OBn (0.15 mmol, 70.6 mg) at −78 °C in THF (1 mL), LiHMDS (1 M in THF, 0.3 mmol) was added dropwise. After 30 min the fluorinating reagent (F–*p*ClBzQN–BF_4, 0.165 mmol, 96.8 mg) was added in portions. The mixture was stirred at −78 °C for 3 h and then hydrolyzed with a saturated solution of NH_4Cl. THF was evaporated and the product extracted in CH_2Cl_2, then washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography over silica gel to afford the fluorinated dipeptide in 88% yield; HPLC: Chiralcel OD-H, hexane–^{i}PrOH 80:20, 1 mL/min, t_1 = 14.3 min, t_2 = 16.5 min. ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -138.4$; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.86 (s, 3H), 1.88 (s, 3H), 2.67 (d, 3H, J = 1.2 Hz), 5.19 (d, 1H, J = 12.3 Hz), 5.30 (d, 1H, J = 12.3 Hz), 7.25–7.38 (m, 8H), 7.58–7.61 (m, 2H), 7.74–7.77 (m, 2H), 7.85–7.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 25.2, 32.9, 61.4, 67.7, 100.7 (d, J = 220.7 Hz), 123.5, 126.6, 127.0, 128.5, 128.6, 128.7, 129.6, 131.5, 134.2 (d, J = 27.3 Hz), 134.5, 135.5, 166.3 (d, J = 26 Hz), 167.8, 174.4 (d, J = 1.3 Hz); HRMS Calcd for $C_{28}H_{25}FN_2O_5$ [M] 488.1748. Found 488.1750.