Access to Fluorine-Containing Asparagine and Glutamine Analogues via Palladium-Catalyzed Formate Reduction

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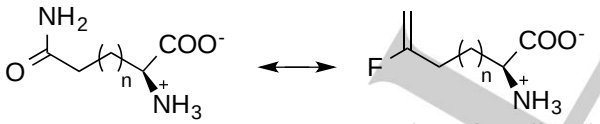
A New Access to Fluorine-containing Asparagine and Glutamine Analogues via Pd-catalyzed Formate Reduction

Yoshinosuke Usuki,* Yosuke Wakamatsu, Minoru Yabu, and Hideo Iio[a]

Abstract: A new synthesis of fluorine-containg asparagine and glutamine analogues (**1** and **2**) via palladium-catalized formate reduction of fluorinated carbonate esters is described. Primary amide moieties at side-chain of asparagine and glutamine were successfully replaced with fluoroolefin, which are proposed to be aprotic mimic for amides due to their electronic properties.

The ability of fluorine to impart unique properties to organic molecules has been exploited in the design of fluorine-containing bioactive compounds.[1] Functionalized fluoroolefins are particularly important, with current applications in the synthesis of biologically active materials such as peptide isosteres.[2,3] Asparagine and glutamine residues play important structural roles in proteins because their side-chain amide groups could act as both hydrogen bond acceptors and donors.[4] In addition, chemical modification such as deamidation, which is conjected to be one of the factors that limit the useful lifetime of proteins, occurs at these residues.[5] In our continuing studies on synthetic organofluorine chemistry towards fluorinated biomimetics,[6] we have been interested in replacement of side-chain amide moieties of asparagine and glutamine with fluoroolefins, which are proposed to be aprotic mimic for amides due to their electronic properties.[3a] Recent studies on fluorine-containing π-allyl palladium complex encouraged us to investigate Pd-catalyzed formate reduction of fluoro-allyl carbonate.[6a,6b,7] This report describes a new synthesis of fluorine-containg asparagine and glutamine analogues (**1** and **2**) via formate reduction.[8]



Asparagine analogue (**1**; n=0)
Glutamine analogue (**2**; n=1)

Figure 1. Replacement of side-chain amide moiety with fluoroolefin.

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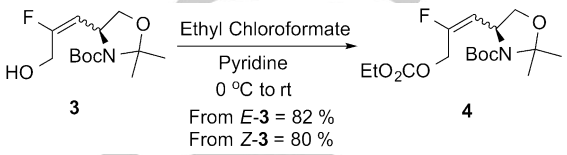
Our synthesis of **1** commences with fluorinated allyl alcohol ***E*-3** and ***Z*-3**.[9] Acylation of ***E*-3** and ***Z*-3** were achieved with ethyl chloroformate in pyridine to give the desired allyl carbonate ***E*-4** and ***Z*-4** respectively in good yields.

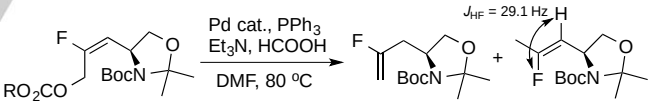


3 **4**

Scheme 1. Preparation of carbonate **4**.

Pd-catalyzed formate reduction of ***E*-4** was examined. Treatment of ***E*-4** with $HCO_2^-NEt_3H^+$ (1.2 equiv) in the presence of $Pd_2(dba)_3$•$CHCl_3$ in DMF at 80 ºC for 4 h afforded a 8:1 mixture of the desired γ-product **5** and the α-product **6** (Table 1, entry 1). The *Z* configurations of internal fluoroolefin **6** was established by the large coupling constant between the vinylic proton and fluorine ($^3J_{HF}$=29.1 Hz) on the ^{19}F NMR spectrum. Interestingly, the use of $Pd_2(dba)_3$ led to optimum regioselectivity (**5**:**6** = 21:1) as shown in entry 2. Addition of 2.5 mol% $CHCl_3$ to $Pd_2(dba)_3$ decreased the regioselectivity significantly (entry 3), although the role of $CHCl_3$ is still obscure. Under the optimized reaction conditions, reactions of ***Z*-4** and phenyl carbonate ***E*-4'** proceeded smoothly the desired terminal fluoroolefin **5** in good regioselectivity (entry 4, 5).

Table 1. Pd-catalyzed formate reduction of carbonate **4**.



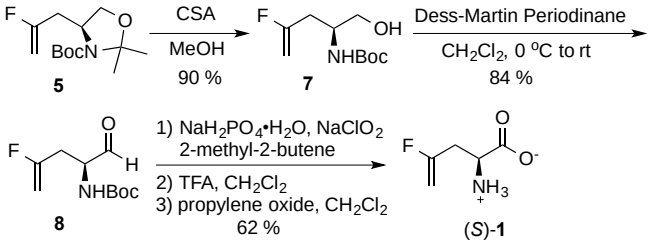
4 **5** **6**

Entry	R	Pd Catalyst	Yields[%] **5**	**5**:**6**[a]
1	Et (***E*-4**)	$Pd_2(dba)_3$•$CHCl_3$	69	8:1
2	Et (***E*-4**)	$Pd_2(dba)_3$	72	21:1
3	Et (***E*-4**)	$Pd_2(dba)_3$ + 2.5 mol% $CHCl_3$	65	11:1
4	Et (***Z*-4**)	$Pd_2(dba)_3$	74	19:1
5	Ph (***E*-4'**)	$Pd_2(dba)_3$	67	19:1

[a] Determined by ^{19}F NMR spectroscopy.

Treatment of **5** with CSA in MeOH resulted in removal of acetonide moiety to afford **7** in 90% yield. Dess–Martin oxidation of **7** proceeded to give the corresponding aldehyde **8** in 84% yield. Pinnick oxidation of **8** followed by acidic removal of Boc group afforded the desired L-asparagine analogue (*S*)-**1** in 62%

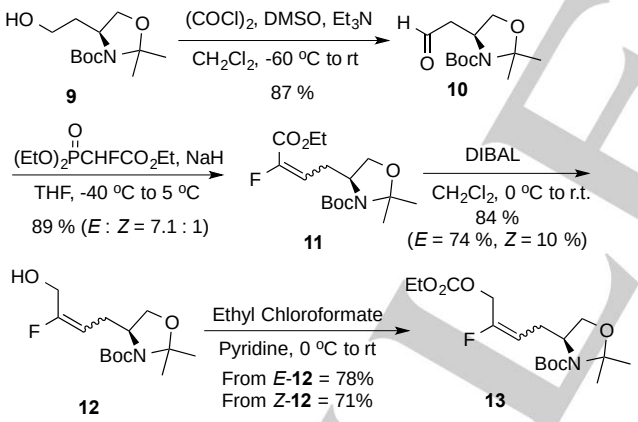
yield for 2 steps.[10] The optical rotation of (*S*)-**1**, $[\alpha]_D$ -20.0 (c 0.52, H_2O), was in close agreement with the value reported in the literature, $[\alpha]_D$ -18.0 (c 1.0, H_2O).[11]



5 **7** **8** (*S*)-**1**

Scheme 2. Synthesis of (*S*)-**1**.

Attention was next directed to the synthesis of L-glutamine analogue (*S*)-**2**. *N*, *O*-Acetal **9**, prepared from L-aspartic acid by the literature procedure,[12] was oxidized to afford the desired aldehyde **10** in 87% yield. Treatment of triethyl α-fluorophosphonoacetate with NaH (1 eq.) in THF at −40 ºC and the following addition of **10** afforded the corresponding α-fluoro-α,β-unsaturated ester **11** as a 7:1 mixture of *E*/*Z* isomers in 89% yield. Reduction of **11** with DIBAL-H afforded allyl alcohols ***E*-12** and ***Z*-12**, which were easily separated by flash column chromatography. Acylation of ***E*-12** and ***Z*-12** were achieved with ethyl chloroformate in pyridine to give the desired allyl carbonate ***E*-13** and ***Z*-13** respectively in good yields.

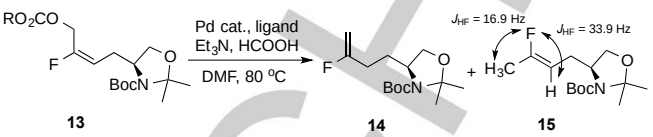


9 **10** **11** **12** **13**

Scheme 3. Preparation of carbonate **13**.

***E*-13** was treated with $HCO_2^-NEt_3H^+$ (1.2 equiv) in the presence of $Pd_2(dba)_3$ in DMF at 80 ºC for 4 h. However a 6.3:1 mixture of the desired γ-product **14** / the α-product ***Z*-15** was obtained (Table 2, entry 1). The *Z* configurations of internal fluoroolefin **15** was established by the large coupling constant between the vinylic proton and fluorine ($^3J_{HF}$=33.9 Hz) on the ^{19}F NMR spectrum. Interestingly, $CHCl_3$ did not have any effect on the regioselectivity (entries 1 and 2). Although the use of phenyl carbonate ***E*-13'** or $P(OPh)_3$ did not increase the regioselectivity (entries 3 and 4), the reaction in the presence of P(n-Bu)$_3$ proceeded nicely to afford the desired terminal fluoroolefin **14** in good regioselectivity (entry 5). Electron-donating ability of P(*n*-Bu)$_3$ makes the cathionic intermediate π-allyl palladium complex more stable, which would increase regioselectivity.[8]

Table 2. Pd-catalyzed formate reduction of carbonate **13**.

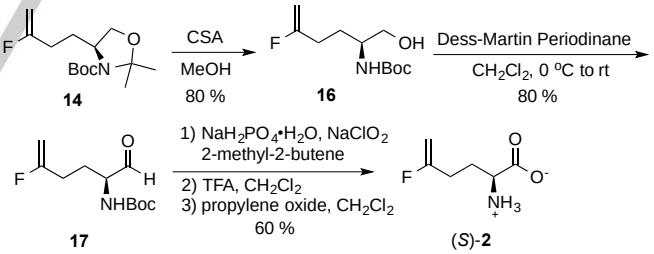


13 **14** **15**

Entry	R	Pd Catalyst	Ligand	Yields[%] **14**	**14**:**15**[a]
1	Et (***E*-13**)	$Pd_2(dba)_3•CHCl_3$	PPh_3	66	5.9:1
2	Et (***E*-13**)	$Pd_2(dba)_3$	PPh_3	70	6.3:1
3	Ph (***E*-13'**)	$Pd_2(dba)_3$	PPh_3	65	6.1:1
4	Et (***E*-13**)	$Pd_2(dba)_3$	$P(OPh)_3$	62	3.1:1
5	Et (***E*-13**)	$Pd_2(dba)_3$	P(*n*-Bu)$_3$	77	16:1
6	Et (***Z*-13**)	$Pd_2(dba)_3$	P(*n*-Bu)$_3$	76	16:1

[a] Determined by ^{19}F NMR spectroscopy.

Conversion of **14** into the desired L-glutamine analogue (*S*)-**2** was achieved as shown in Scheme 4.[13] To evaluate enantiopurity of (*S*)-**2**, derivatization with L- or D-FDLA was carried out and the resulting mixtures were analyzed by ESI–LC/MS.[14] These analyses revealed that (*S*)-**2** had >99% ee.



14 **16** **17** (*S*)-**2**

Scheme 4. Synthesis of (*S*)-**2**.

In summary, we have developed a new approach for the synthesis of fluorine-containing asparagine and glutamine analogues, where side-chain amide moieties are replaced with fluoroolefin. Investigations into the application of the developed protocol to other fluorinated biomimetics are currently underway in our laboratory.

Experimental Section

General procedure of Tsuji-Trost reaction.

To a mixture of Pd catalyst (0.025 mmol) and phosphine ligand (0.2 mmol) in DMF (0.5 mL) was added a solution of oxazolidine (1.0 mmol) in DMF (0.5 mL) at 0 °C. After stirring for 10 min at that temperature, a solution of triethylammonium formate in DMF (0.5 mL), prepared from formic acid (1.4 mmol) and triethylamine (1.4 mmol), was added to the reaction mixture. The resulting mixture was stirred at 80 °C for 4 h. before the reaction was quenched with aq. NH_4Cl. The resulting mixture was filtered through a short pad of Celite and then extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. Filtration and concentration in vacuo afforded the crude product, which was purified by silica gel column chromatography with hexane-EtOAc (49:1) as an eluent to give pure terminal olefin.

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Acknowledgements

We thank Dr Naoko Mizuhara, Graduate School of Science, Osaka City University, for ESI-LC/MS experiments.

Keywords: Fluorinated amino acid • mimic • Fluoroolefin isostere • Formate reduction • Pd-catalyzed reaction

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[10] **1**: $[\alpha]_D$ -20.0º (c 0.52, H_2O); ^{1}H NMR (400 MHz, D_2O) δ□2.66-2.81 (m, 2H), 3.80 (br s, 1H), 4.47 (dd, 1H, J_{HH} = 3.2 Hz, J_{HF} = 50.8 Hz), 4.67 (dd, 1H, J_{HH} = 3.2 Hz, J_{HF} = 18.0 Hz); ^{13}C NMR (150 MHz, D_2O/CD_3OD) δ 34.1 (d, J_{CF} = 27.9 Hz), 53.0, 95.6 (d, J_{CF} = 18.0 Hz), 161.6 (d, J_{CF} = 254.1 Hz), 174.1; ^{19}F NMR (283 MHz, D_2O) δ□□-98.4 (ddt, J_{HF} = 18.0, 22.3, 50.8 Hz); HRMS *m/z* calcd. for $C_5H_9FNO_2$ $[M+H]^+$ 134.0617, found 134.0613.

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[13] **2**: $[\alpha]_D$ -11.3º (c 0.3, H_2O); ^{1}H NMR (600 MHz, D_2O/CD_3OD) δ 2.01-2.13 (m, 2H), 2.36 (ddt, 2H, J_{HH} = 7.2 Hz, J_{HH} = 8.4 Hz, J_{HF} = 15.3 Hz), 3.77 (t, 1H, J_{HH} = 6.2 Hz), 4.44 (dd, 1H, J_{HH} = 3.1 Hz, J_{HF} = 51.8 Hz), 4.64 (dd, 1H, J_{HH} = 3.1 Hz, J_{HF} = 18.6 Hz); ^{13}C NMR (150 MHz, D_2O/CD_3OD) δ 28.0 (d, J_{CF} = 27.5 Hz), 28.1, 54.9, 91.7 (d, J_{CF} = 19.1 Hz), 165.8 (d, J_{CF} = 253.7 Hz), 175.1; ^{19}F NMR (283 MHz, D_2O) δ□□-97.2 (ddt, J_{HF} = 15.3, 18.6, 51.8 Hz). HRMS *m/z* calcd. for $C_6H_{11}FNO_2$ $[M+H]^+$ 148.0774, found 148.0774.

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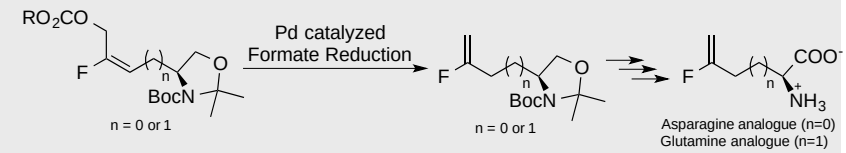

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