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Synthesis and applications of the first polyfluorous proline derivative

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Abstract—Starting from *trans*-4-hydroxy-L-proline, a polyfluorinated proline derivative having a fluorine content of 54% has been prepared. It has been tested as a catalyst in the aldol reaction between *p*-nitrobenzaldehyde and acetone with 73% ee in BTF and in copper(I)-catalyzed allylic oxidation of cyclohexene with 20% ee in HFIP.

1. Introduction

Proline is a well known α-amino acid used in numerous reactions.[1] It can act as a ligand in asymmetric transition-metal catalysis such as allylic oxidation of olefins[2] or reduction by transfer hydrogenation of ketones.[3] It can also be an effective organocatalyst[4,5] for aldol and Michael reactions.[6] Even if the first reported use of proline in asymmetric catalysis was made by Hajos and Parrish[7] in the early 1970s for intramolecular aldol reactions, proline is still a chiral compound of current interest as is proven by the large number of articles, from letters to reviews, which have been published on the subject this year.[1,4,5,8,9]

At the same time, there is growing interest for non-standard solvents such as fluorinated ones in asymmetric catalysis.[10] These media were selected to ensure good separation between the catalyst and the products and to allow recycling of the catalytic system. The common strategy was to prepare polyfluorous ligands and therefore numerous well known chiral ligands such as BINOL,[11] BINAP,[12] quinine[13] or MOP[14] derivatives have been synthesized and used in fluorous biphase media (FBS).

We want to report here the first synthesis of a proline derivative bearing a polyfluorinated ether chain and the results of its first tests in asymmetric catalysis.

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2. Results and discussion

We first had to choose an anchoring site for the perfluorinated alkyl chain we wished to graft on the proline skeleton. As both the nitrogen atom and the carboxylic function have to remain untouched we decided to start from 4-hydroxy-L-proline and to introduce a perfluorinated chain via radical addition of a perfluoroalkyl group to an allyl ether funtionality. The overall synthesis is depicted in Scheme 1.

Before the introduction of the allyl group, the amino group has to be protected. The *t*-butoxycarbonyl group (*t*-Boc) was first tried but at the end of the synthesis, after deprotection with trifluoroacetic acid, it was difficult to recover the free polyfluoroamino acid. We finally chose the benzyloxycarbonyl group (Cbz), which was cleaved at the end of the synthesis by hydrogenolysis during the reduction of the double bond by catalytic hydrogenation.

Thus, 4-hydroxy-L-proline was derivatized using benzyl chloroformate in the presence of aq. $NaHCO_3$. Compound **1** was isolated quantitatively and could be used in the following step without further purification. Allylation of **1** gave **2** using NaH and allyl bromide and after saponification the free acid **3** was isolated with 51% isolated yield. The double bond thus introduced allowed now the introduction of the fluorinated chain. Several methods were tested. With sodium dithionite,[15] only traces amounts of the desired product were iso-

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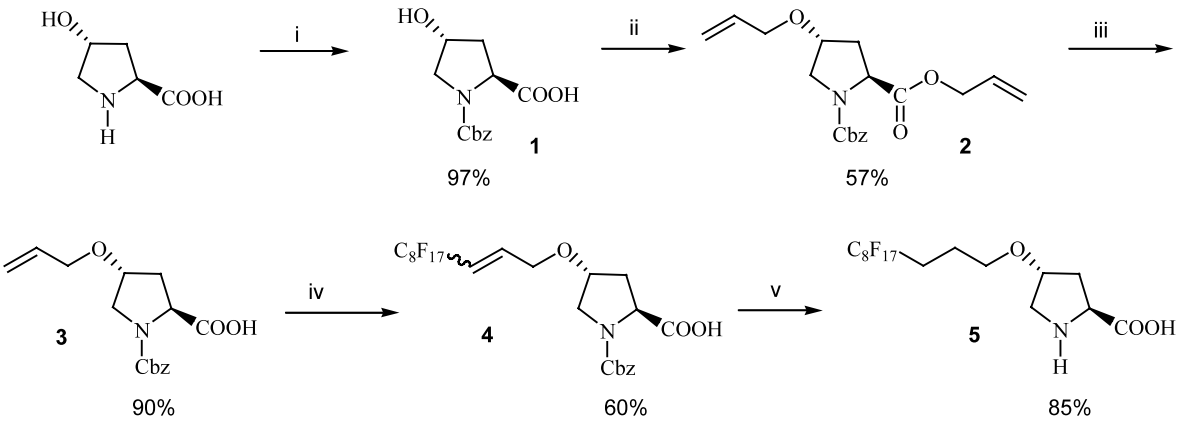


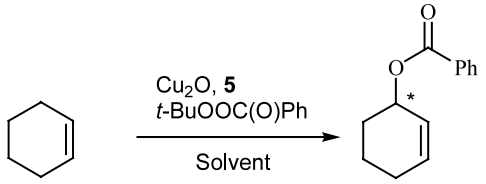
Scheme 1. *Reagents and conditions*: (i) $Cl(CO)OCH_2Ph$, $NaHCO_3$; (ii) NaH, DMF, $BrCH_2CH{:}CH_2$; (iii) NaOH, H_2O; (iv) $C_8F_{17}I$, CuCl, $NH_2CH_2CH_2OH$; (v) H_2, Pd/C.

lated and BEt_3/O_2[16] was totally inefficient. Finally, the method described by Riess et al.[17] using CuCl, $C_8F_{17}I$ and ethanolamine gave **4** in 60% isolated yield. Only the elimination product **4** was detected, with no traces of the iodinated product. The *E* isomer was the most abundant (*E*/*Z* ratio: 80/20). We did not try to separate them as the double bond has to be reduced under H_2 pressure using Pd/C to give **5** in 85% yield, with an overall fluorine content of 54%.

Proline has been successfully used in allylic oxidation[2,18] of olefins with copper derivatives. We decided therefore to investigate the performance of our new polyfluorinated proline derivative **5** in this reaction (Scheme 2).

Numerous chiral ligands have been described for such a reaction and ees of up to 80%[19] have been achieved with cyclohexene. More specifically, with proline in benzene, ee of 45% was obtained by Muzart et al.[2] with 59% isolated yield. Under the same conditions with Cu_2O (10% Cu) and **5** similar activity was obtained (53% yield, Table 1, entry 1) but the enantioselectivity was much lower (10%). We therefore searched for a more suitable solvent and tested different systems. Preliminary results are summarized in Table 1.

To take advantage of the fluorotail of **5**, we decided to work in a biphasic system. We chose the $ClCH_2CH_2Cl$/FC-72 mixture for our first test and were surprised to see no reaction (Table 1, entry 3) whereas $ClCH_2CH_2Cl$ or FC-72 alone led respectively to 37% and 58% isolated yield with 3% and 17% ee. In the course of our study, Muzart et al.[20] published an interesting study



Scheme 2. Allylic oxidation of cyclohexene.

where allylic oxidation was performed with success in benzenetrifluoride (BTF). In this solvent, the reactivity of our system was high but again the enantioselectivity was very poor (Table 1, entry 5). Finally, we tested HFIP (hexafluoroisopropanol) as solvent, and with **5** 77% isolated yield and 20% ee were obtained on cyclohexene. We have very recently shown[21] that Cu_2O combined with a perfluoroacid $C_{11}F_{23}COOH$ allowed the allylic oxidation of olefins in HFIP and that our system was recyclable. In the absence of acid no reaction occurred in this solvent and we proposed that the acid is necessary to ensure good solubility of the catalytic species in HFIP. In this asymmetric version of our system, the acid was useless, probably because the polyfluoroproline derivative **5** plays the same role and ensures the solubilization of copper in HFIP. Moreover, the catalytic system could be recovered very easily (see experimental part) and reused without additional copper and ligand (Table 1, entry 7). Unfortunately, both activity and selectivity diminished (54% isolated yield and 13% ee).

Our polyfluorous proline derivative **5** was also used in the aldol reaction between *p*-nitrobenzaldehyde and acetone (Scheme 3).

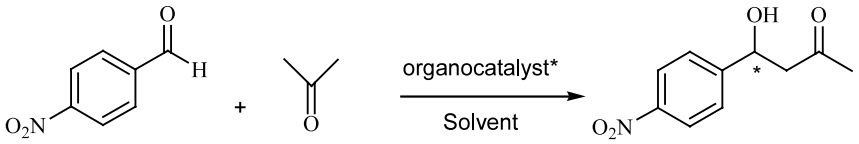
It has been shown that the intermolecular asymmetric reaction between a ketone and an aldehyde was possible in the presence of proline if a large excess of the ketone donor was used. Thus, in DMSO, 76% ee and 68% isolated yield were obtained in 5 h for the reaction depicted in Scheme 3, with 30% proline.[5] Extraction of the crude product was necessary to get rid of the excess DMSO. We decided to take advantage of the fluorous tail of **5** and to use benzenetrifluoride (BTF) as solvent (Table 2).

The results with **5** were similar to those obtained with proline in DMSO under standard conditions (Table 2, entry 2), that is to say, with excess acetone and 25% of organocatalyst. Nevertheless, there was no need for extraction and the crude mixture was purified directly by chromatography without evaporation of the reaction solvent (BTF). In the same solvent, proline itself was

Table 1. Influence of the solvent on the rate and enantioselectivity of the allylic oxidation of cyclohexene in presence of **5**

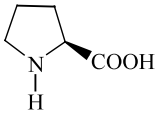
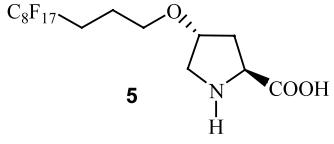
Entry	Solvent	Time (h)	Isolated yield (%)	ee* (%) (abs. conf.)
1	Benzene	5	53	10 (*S*)
2	$ClCH_2CH_2Cl$	5	37	3 (*S*)
3	$ClCH_2CH_2Cl$+FC-72	5	0	–
4	FC-72	5	58	17 (*S*)
5	BTF	5	61	4 (*S*)
6	HFIP[a]	2	77	20 (*S*)
7		4	54	13 (*S*)

Standard conditions: see experimental part; a: without benzoic acid; * ee determined by polarimetry.



Scheme 3. Aldolization reaction.

Table 2. Influence of the reaction conditions on the rate and enantioselectivity of the reaction between *p*-nitrobenzaldehyde and acetone in benzenetrifluoride

Entry	Organocatalyst	Experimental conditions		
		Standard*	1eq acetone/ aldehyde	7% catalyst
1	 Proline	58% yield 63% ee (*R*) (2 days)	6% yield -[a] (4 days)	30% yield 40% ee (*R*) (4 days)
2	 **5**	72% yield 73% ee (*R*) (1 day)	40% yield 40% ee (*R*) (4 days)	27% yield 60% ee (*R*) (4 days)

* see experimental part; the enantiomeric excess were measured by 1H NMR after esterification with a enantiomerically pure acid; a: not measured.

slightly less efficient in terms of enantioselectivity, but the reaction took 2 days as compared to only 1 day for **5**. This may be due to the solubility of proline, which may not be high enough in BTF at the concentration used. More interestingly, when we worked with a ketone/aldehyde ratio of 1:1, proline was inactive, whereas **5** was still efficient. As proline is insoluble in BTF, we can assume that it is the proline solubilized in acetone that is active and with only an equimolar quantity of acetone and aldehyde a very small quantity of proline is available for reaction. When we used only 7% of the organocatalyst, both the activities and selectivities were similar for proline and its polyfluorous derivative **5**.

3. Conclusion

We have synthesized the first polyfluorous analogue of proline. The same activity and selectivity were observed in the aldol reaction between acetone and *p*-nitrobenzaldehyde with our compound in benzenetrifluoride than with proline itself in DMSO but in a more volatile solvent and with no need for extraction before chromatography. For allylic oxidation, the reaction occurred but with low enantioselectivity. Considering the numerous reactions using proline, work is in progress to widen the scope of the applications of our polyfluoroproline derivative in asymmetric reactions.

4. Experimental

4.1. General

All commercially available reagents were used as received. Cyclohexene and all the solvents except HFIP have been distillated from CaH_2 before use. All reactions were monitored by TLC (GF254 Merck). Column chromatography was performed on silica gel 60 (230–240 mesh, Merck). Optical rotations were recorded on a Perkin–Elmer 343 polarimeter. NMR spectra were recorded with a Bruker AMX 300 spectrometer and referenced as following: ^{1}H (300 MHz), internal $SiMe_4$ at δ 0.00 ppm, ^{13}C (75 MHz), internal $CDCl_3$ at δ 77.23 ppm and ^{19}F (282 MHz) external $CFCl_3$ at δ 0.00 ppm.

4.2. *N*-Benzyloxy-*trans*-4-hydroxy-L-proline 1

A solution of *trans*-4-hydroxy-L-proline (4 g, 30.4 mmol) in THF (46 mL) and satd aq. $NaHCO_3$ solution (80 mL) at 0°C was treated by dropwise addition of benzoyl chloride (8.56 mL, 60 mmol). The solution was stirred overnight at room temperature. The pH was maintained at 1 by addition of 2N aq. HCl and the reaction mixture was extracted with AcOEt and dried over $MgSO_4$. After evaporation of the solvent and flash-chromatography on silica gel, pure **1** was isolated (7.8 g, 29.4 mmol, 97%). Oil; R_f=0.5 (CH_2Cl_2/MeOH: 95/5); $[\alpha]_D^{25}=-92.2$ (*c* 0.8, $CHCl_3$), lit.[22] $[\alpha]_D^{24}=-94.1$ (*c* 0.76, $CHCl_3$) ^{1}H NMR ($CDCl_3$): δ 2.2 (m, 2H, CH_2), 3.60 (m, 3H, CH_2+CH-OH), 4.22 (m, 1H, CH), 5.09 (m, 2H, CH_2), 6.38 (OH), 7.29 (m, 5H, H Ar); ^{13}C NMR ($CDCl_3$) (2 conformational isomers): δ 38.0 and 38.9, 54.5 and 54.9, 57.7 and 58.0, 67.6 and 67.7, 69.2 and 69.8, 127.6–128.6 C Ar, 136.0 and 136.1 Cq Ar, 155.1 and 155.9 N-C=O, 175.1 and 176.2 C=O.

4.3. *N*-Benzyloxy-*trans*-4-(allyloxy)allyl-L-prolinate, 2

A solution of **1** (1.98 g, 7.5 mmol) in dry DMF (18 mL) at 0°C under nitrogen was treated with NaH (60% dispersion in oil, 470 mg, 19.5 mmol). After stirring for 30 min, allyl bromide (1.6 mL, 18.7 mmol) was added with a syringe and the solution was stirred at room temperature overnight. After addition of water (13 mL), 5N HCl was added until the pH value reached 2. The solution was then extracted with Et_2O (3×40 mL) and dried over $MgSO_4$. After evaporation of the solvent and flash-chromatography on silica gel, pure **2** were isolated (1.47 g, 4.3 mmol, 57%). Oil; R_f=0.57 (petroleum ether/AcOEt: 3/1); $[\alpha]_D^{25}=-41.1$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.15 (m, 1H, CH_2), 2.39 (m, 2H, CH_2), 3.74 (m; 2H, CH_2), 3.99 (m, 2H, CH_2-O-CH), 4.16 (m, 1H, CH-C=O), 4.46 (m, 1H, CH_2-O-C=O), 4.55 (m, 1H, CH-O), 4.67 (d, 1H, J=5.4 Hz, CH_2-O-C=O), 5.22 (m, 6H, CH_2=CH+CH-Ar), 5.75 (m, 1H, CH=), 5.90 (m, 1H, CH=), 7.33 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 36.0, 37.2, 52.4 and 52.1, 58.5, 66.1, 67.6, 70.6, 75.1, 75.2, 117.8, 119.0 and 118.9, 128.2, 128.3, 128.4, 128.7, 128.8, 132.2 and 131.9, 134.6, 136.9 and 136.7 Cq Ar, 155.3 and 154.8 N-C=O, 172.8 C=O.

4.4. *N*-Benzyloxy-*trans*-4-allyloxy-L-proline, 3

A solution of **2** (2.3 g, 6.67 mmol) in MeOH (8 mL) was treated with a solution of NaOH (8 g, 20 mmol) in water (6 mL) were added and the reaction mixture was allowed to stir at room temperature for 24 h. After addition of water (5 mL), the pH was adjusted at 10 by addition of 5N aq. HCl and the reaction mixture was extracted with Et_2O (2×10 mL). The pH was then adjusted to 4 and the solution extracted with AcOEt (3×40 mL). These organic phases were dried over $MgSO_4$ and after evaporation of the solvent and purification by flash-chromatography, pure **3** was obtained (1.83 g, 90%). Oil; R_f=0.65 (CH_2Cl_2/MeOH: 90/10); ^{1}H NMR ($CDCl_3$): δ 2.13–2.45 (m, 2H), 3.64 (m, 2H), 3.98 (m, 2H), 4.15 (m, 1H), 4.51 (m, 1H), 5.22, 4H, CH_2=+CH_2-Ar), 5.87 (m, 1H, CH=), 7.31 (m, 5H, Ar-H), 8.25 (m, 1H, COOH); ^{13}C NMR ($CDCl_3$): δ 35.0 and 36.8, 51.9, 60.5, 67.3 and 67.8 CH_2-Ar, 70.2 CH_2=, 75.9 and 76.4, 117.5, 127.6, 128.0, 128.2, 128.4, 128.6 C Ar, 134.2 CH=, 136.1 and 136.4 Cq Ar, 154.5, 156.2.

4.5. *N*-Benzyloxy-*trans*-4-(perfluorooctyl)allyloxy-L-proline, 4

A mixture of ethanolamine (1.33 mL, 22 mmol), **3** (1.35 g, 4.43 mmol), *t*-BuOH (6.6 mL), CuCl (133 mg, 1.34 mmol) and $C_8F_{17}I$ (12 g, 22.15 mmol) was stirred at 80°C for 3 days. After extraction with AcOEt, and flash-chromatography on silica gel, pure **4** was isolated (1.92 g, 60%). Oil; R_f=0.65 (CH_2Cl_2/MeOH: 90/10); ^{1}H NMR ($CDCl_3$): δ 2.1–2.6 (m, 2H), 3.68 (m, 2H), 4.14–4.55 (m, 2H), 5.2 (m, 2H, CH_2-Ar), 5.6 (m, 1H, CH= *Z*), 5.89 (m, 1H, CH= *E*), 6.23 (m, 1H, CF_2-CH *Z*), 6.44 (m, 1H, CF_2-CH *E*), *Z*/*E* ratio: 20/80, 7.35 (m, 5H Ar); ^{19}F NMR ($CDCl_3$): δ −126.5 (s, 2F, CF_2), −124.2 (s, 2F, CF_2), −123.6 (s, 2F, CF_2), −123.1 (s, 4F, CF_2), −121.9 (s, 2F, CF_2), −112.2 (s, 2F, CF_2CH *E*), −108.4 (s, 2F, CF_2CH *Z*), −81.2 (s, 3F, CF_3).

4.6. *trans*-4-(Perfluorooctyl)propyloxy-L-proline, 5

A suspension of **4** (1.8 g, 2.49 mmol) and Pd/C (500 mg, 10%) in EtOH (35 mL) was stirred at rt under 12 bar H_2 pressure for 24 h. After filtration on celite and evaporation of the solvent, pure **5** (1.25 g, 2.1 mmol, 85%) was isolated. Oil; $[\alpha]_D^{25}=-11.7$ (*c* 0.47, EtOH); ^{1}H NMR ($CDCl_3$): δ 1.85 (m, 1H), 2.12 (m, 2H), 2.48 (m, 1H), 2.92 (m, 4H), 3.50 (m, 5H), 4.16 (m, 1H); ^{19}F NMR ($CDCl_3$): δ −126.7 (s, 2F, CF_2), −123.9 (s, 2F, CF_2), −123.3 (s, 2F, CF_2), −122.5 (s, 6F, CF_2), −114.9 (s, 2F, CF_2-CH_2), −81.4 (s, 3F, CF_3); MH^+ calculated for $C_{16}H_{15}F_{17}NO_3$: 592.07804, found 592.07887.

4.7. Allylic oxidation reaction

Cyclohexene (0.5 mL, 5 mmol), Cu_2O (7 mg, 0.049 mmol), benzoic acid (183 mg, 1.5 mmol), **5** (80 mg, 0.13 mmol) and *t*-butyl peroxybenzoate (190 μL, 1 mmol) were mixed in a solvent (1.5 mL) under reflux. Evaporation of the liquid phase and flash-chromatography on silica gel led to the pure product. For recycling experiment, after evaporation of the solvent, the crude mix-

ture was rinsed with petroleum ether and the catalyst (blue precipitate) was recovered by simple decantation of the supernatant liquid.[21] The solid catalyst could be re-used without further addition of copper or ligand. Ee were measured by polarimetry $[\alpha]_D^{25} = -71$ (c 2.74, $CHCl_3$).[2]

4.8. Aldol reaction

p-Nitrobenzaldehyde (75.5 mg, 0.5 mmol) was dissolved in benzenetrifluoride (4 mL) under argon. Excess acetone (1 mL) were added and then the catalyst (proline or **5**). After 48 h stirring the product was purified by flash-chromatography on silica gel without extraction and without evaporation of the solvent of reaction (BTF and acetone). The aldolization product was esterified with pure (*S*)-(+)-2-phenylpropionic acid and the enantiomeric excess of the reaction was measured by ^1H NMR (300 MHz). In the aldolization product, δ CH_3: 2.19 ppm. After esterification: δ: 2.05 ppm (major product), 2.25 (minor product).

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