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First catalytic asymmetric synthesis of β-amino-β-polyfluoroalkyl ketones *via* proline-catalysed direct asymmetric carbon–carbon bond formation reaction of polyfluoroalkylated aldimines

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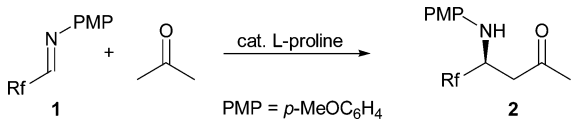
Proline-catalysed direct asymmetric carbon–carbon bond formation reaction of polyfluoroalkylated aldimines with acetone afforded the corresponding β-(*p*-methoxyphenyl)amino-β-polyfluoroalkyl ketones in high enantioselectivities (up to 98% ee).

Catalytic asymmetric syntheses of trifluoromethylated or fluorinated molecules are one of the most important challenging topics in the pharmaceutical and material chemistries.[1] Particularly, enantiomerically pure amines or amino carbonyl compounds carrying a trifluoromethyl group on the chiral centre are expected to play a significant role based on the special electronic properties of the trifluoromethyl group in bioactive natural products as well as pharmaceutically important compounds. Although auxiliary-based asymmetric syntheses of these compounds have been reported, to the best of our knowledge, reports dealing with the catalytic asymmetric syntheses of α-trifluoromethylated amino derivatives are quite rare, and all of them involve reduction.[2]

We disclose here, for the first time, the L-proline-catalysed direct asymmetric carbon–carbon bond formation reaction of polyfluoroalkylated aldimines with acetone producing α-polyfluoroalkylated amines carrying a keto-carbonyl group at the β-position[3,4] which is accomplished with high levels of asymmetric induction.

Treatment of trifluoroacetaldehyde *N*-(*p*-methoxyphenyl)imine **1a** in the presence of 50 mol% of L-proline in a mixed solvent of dimethyl sulfoxide (DMSO)–dry acetone (Kanto Chemical Co., Inc.) (4 : 1) at room temperature for 1 day gave β-(*p*-methoxyphenyl)amino-β-trifluoromethyl ketone **2a** in 44% yield with 75.0% *ee*, along with the recovery (17%) of **1a** and a trace amount of 1-hydroxy-(*N*-*p*-methoxyphenyl)-2,2,2-trifluoroethylamine (**3a**) as well as 4-hydroxy-5,5,5-trifluoropentan-1-one (**4a**)[5] in 16% yield (Scheme 1, Table 1, entry 4). The results of the survey of an amount of L-proline are shown in entries 1–4. When the imine **1a** was treated in the absence of L-proline, no β-amino-β-trifluoromethyl ketone **2a** was obtained and the starting imine **1a** was recovered in 84% yield (entry 1). The reaction in the presence of 10–30 mol% of L-proline proceeded smoothly to give the ketone **2a** in 33–40% yields (entries 2 and 3). For a solvent, the reaction in a mixed solvent of *N*,*N*-dimethylformamide (DMF)–acetone (4 : 1) increased the enantioselectivities of **2**, but the yields of **2a** were decreased severely (entry 5). The best enantioselectivity (94.0% ee) was obtained when the reaction was carried out in only acetone (entry 6). The influences of ratios of DMSO *vs.* acetone are shown in entries 4, 6–10. Increasing the portion of acetone from 20% to 100 vol% led to a decrease in the yields with higher enantioselectivity. These results apparently demonstrate that the solvent polarity is very crucial for the yields of **2a** as well as the enantioselectivites. Thus, a less polar solvent is more suitable for increasing the



Scheme 1 Asymmetric synthesis of β-amino-β-polyfluoroalkyl ketones *via* catalytic asymmetric Mannich reaction.

Table 1 Asymmetric synthesis of β-*p*-(methoxyphenylamino)-β-polyfluoroalkyl ketones **2** *via* proline-catalysed carbon–carbon bond formation reaction

			Conditions				Yields (%)[a] of					
Entry	Rf	Solvent	L-Proline/ mol%	Molar	Temp.	Time/ d	**2**	**3**	**4**	**1**	Er[b] of **2** (*R* : *S*)	Ee[b] (%) of **2**
1	CF_3	DMSO–acetone (4 : 1)	none	0.1	rt	1	0	0	0	84	—	—
2	CF_3	DMSO–acetone (4 : 1)	10	0.1	rt	1	33 (32)	tr	6	44	(12.2 : 87.8)	75.6
3	CF_3	DMSO–acetone (4 : 1)	30	0.1	rt	1	40 (32)	tr	12	22	(10.6 : 89.4)	78.8
4	CF_3	DMSO–acetone (4 : 1)	50	0.1	rt	1	44 (36)	tr	16	17	(12.5 : 87.5)	75.0
5	CF_3	DMF–acetone (4 : 1)	50	0.1	rt	1	13 (12)	tr	tr	37	(6.0 : 94.0)	88.0
6	CF_3	Acetone	50	0.1	rt	1	9 (6)	0	0	88	(3.0 : 97.0)	94.0
7	CF_3	DMSO–acetone (3 : 2)	50	0.1	rt	1	38 (34)	tr	13	33	(9.7 : 90.3)	80.6
8	CF_3	DMSO–acetone (1 : 1)	50	0.1	rt	1	39 (34)	tr	8	41	(8.8 : 91.2)	82.4
9	CF_3	DMSO-acetone (2 : 3)	50	0.1	rt	1	32 (29)	tr	tr	49	(7.6 : 94.3)	84.8
10	CF_3	DMSO–acetone (1 : 4)	50	0.1	rt	1	22 (18)	0	tr	65	(5.7 : 94.3)	88.6
11	CF_3	DMSO–acetone (4 : 1)	50	0.1	rt	4	49 (42)	tr	31	tr	(13.1 : 86.9)	73.8
12	CF_3	Acetone	50	0.1	rt	4	14 (13)	0	0	74	(1.9 : 98.1)	96.2
13	CF_3	Acetone	50	0.1	rt	7	24 (20)	0	0	49	(3.1 : 96.9)	93.8
14	CF_3	DMSO–acetone (1 : 1)	50	0.1	0 °C	4	16 (11)	0	tr	69	(6.4 : 93.6)	87.2
15	CF_3	Acetone	50	0.1	reflux	1	83 (71)	0	0	0	(39.8 : 60.2)	20.4
16	CF_3	Acetone	50	0.05	rt	4	22 (16)	0	6	65	(4.0 : 96.0)	92.0
17	CF_3	Acetone	50	0.02	rt	4	38 (29)	0	tr	54	(3.7 : 96.3)	92.6
18	CF_3	Acetone	50	0.02	rt	7	41 (37)	0	0	47	(4.6 : 95.4)	90.8
19	CHF_2	Acetone	50	0.02	rt	7	71 (55)	10	0	0	(1.0 : 99.0)	98.0
20	CF_3CF_2	Acetone	50	0.02	rt	7	22 (20)	0	0	78	(5.6 : 94.4)	88.9

[a] Measured by ^{19}F NMR using benzotrifluoride. Values in parentheses stand for the yields of the isolated **2**. [b] Determined by chiral HPLC analysis with DAICEL CHIRALCEL OD–H (hexane–*i*-PrOH = 95 : 5).

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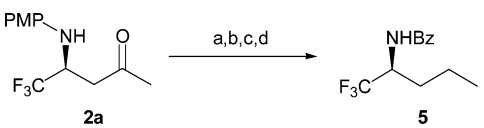
enantioselectivity *via* hydrogen bonding, and polar solvents are quite useful for producing good yields of **2a**. Next, in order to improve the yield, elongation of the reaction time was examined (entries 11–13). Longer reaction time (4 days) in a mixed solvent of DMSO–acetone (4 : 1) afforded **2a** with slightly higher yield (entry 11). The reaction in acetone for 4 or 7 days also provided the ketone **2a** with higher yields (entries 12 and 13). Screening of the reaction temperatures in various solvents is shown in entries 14 and 15. Lowering reaction temperature (0 °C) in DMSO–acetone (1 : 1) for 4 days did not have a significant effect on the increase in the enantioselectivity, but decreased the yields of the product (entry 14). Elevated reaction temperature (reflux) in only acetone produced an 83% yield of **2a** in an even shorter reaction time (1 day). However, the selectivity decreased dramatically (entry 15). The influence of the concentration of **1a** on the yields as well as the enantioselectivities are shown in entries 16–18. Performing the reaction at 0.02 or 0.05 M (mmol ml^{-1}) of **1a** in acetone for 4 or 7 days resulted in an increase in the yields with similar enantioselectivities (entries 16 and 17). The reaction of **1a** (0.02 M) for 7 days gave **2a** in the best yield with 90.8% *ee* (entry 18).†

Unfortunately, the reaction of trifluoroacetaldehyde *N*-(*p*-methoxyphenyl)imine **1a** in the presence of 50 mol% of L-proline in various ketones such as cyclohexanone, ethyl methyl ketone, diethyl ketone and acetophenone, did not proceed at all, along with quantitative recovery of imine **1a**.

The present protocol can be applied to difluoroacetaldehyde *N*-(*p*-methoxyphenyl)imines **1b** as well as pentafluoropropionaldehyde *N*-(*p*-methoxyphenyl)imines **1c**. Compared with trifluoromethylated aldimine **1a**, the reaction of **1b** with the difluoromethyl substituent under the same conditions provided the higher yield (71%) as well as an excellent enantioselectivity (98.0% *ee*) of **2b** (entry 19). In contrast, treatment of the imine **1c** with the pentafluoroethyl substituent in the presence of 50 mol% of L-proline in acetone gave the corresponding β-amino ketone **2c** in only 22% yield with a slight decrease in *ee* (entry 20).

The absolute configuration for β-amino-β-trifluoromethyl ketone **2a** was determined as *S* as follows (Scheme 2). Reduction of ketone **2a** (80.8% *ee*) produced the corresponding β-amino-β-trifluoromethyated alcohol, followed by dithiocarbonylation, methylation, reduction with tributyltin hydride,[6] deprotection with CAN, and reprotection with benzoyl chloride leading to *N*-benzoyl-1-trifluoromethyl-1-butylamine **5** (77.4% *ee*). In these reactions, the processes were not optimized. The absolute configuration of thus obtained amine **5** was assigned as *S* by comparison of the retention time in HPLC of the racemic as well as enantiopure product (*R*)-**5** produced by the other method.[7] This result clearly suggests that the absolute configuration at the 4-position of β-amino-β-trifluoromethyl ketone **2a** is also established unambiguously as *S*.

According to the result, the reaction proceeds *via* the same transition state proposed by Barbas III or List,[4] where not only hydrogen bonding between the nitrogen atom of the imine **1** and the carboxyl group but also the steric repulsion between the pyrrolidine and aromatic ring are quite crucial. However, in the case of trifluoromethylated or pentafluoroethylated aldimines, the trifluoromethyl or pentafluoroethyl group also appears to affect the reaction: that is, they interfere with the coordination of the carboxyl group toward the nitrogen atom due to steric hindrance[8] as well as reduction of the polarisation, which is supported by the ^{13}C NMR chemical shift of the C1 carbon of the aldimines (**1a**; 144.20 ppm, **1b**; 150.86 ppm, **1c**; 144.35 ppm).[9] Consequently, a decrease in *ee* occurred in DMSO–acetone and a longer reaction time is required in only acetone.



Scheme 2 *Reagents and conditions:* (a) LAH, THF, −78 to 0 °C (58%), (b) CS_2, MeI, DMF, 0 °C to rt (56%) (c) cat. Et_3B, Bu_3SnH, benzene, rt (67%) (d) CAN, MeCN, rt, then cat. DMAP, Et_3N, PhCOCl, rt (11%).

In summary, we have elaborated that the first L-proline-catalysed asymmetric carbon–carbon bond formation reaction of polyfluoroalkylaldehyde *N*-(*p*-methoxyphenyl)imine **1** with acetone proceeds to give the corresponding β-amino-β-polyfluoroalkyl ketone (*S*)-**2** in good yields with high enantioselectivities (up to 98% *ee*).

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Notes and references

† A typical procedure: to a suspension of a catalytic amount of L-proline (0.029 g, 0.25 mmol) in dry acetone (25 ml) was added *N*-(2,2,2-trifluoroethylidene)-*p*-methoxyphenylamine (**1a**) (0.102 g, 0.5 mmol) at room temperature under an inert atmosphere. After being stirred at room temperature for 7 d, the reaction mixture was quenched with brine (50 ml), followed by extraction with Et_2O (30 ml × 3). The organic layer was dried over Na_2SO_4 and the solvents were removed by distillation under reduced pressure. After the measurement of the residue by ^{19}F NMR using benzotrifluoride, purification by flash chromatography on silica gel (hexane–Et_2O = 5 : 1) gave (*S*)-**2a** (37%, 0.049 g). *Rf* 0.10 (hexane–Et_2O = 5 : 1); $[\alpha]_D^{23}$ + 15.41 (*c* = 1.03, $CHCl_3$; 90.8% *ee*); Chiral HPLC (Daicel, CHIRALCEL OD–H, *n*-hexane–*i*-PrOH = 95 : 5, 0.8 ml min^{-1}, 254 nm, t_R = 22.1 min (*R*), 55.8 (*S*)); IR ν_{max}(KBr)/cm^{-1} 3377.4 (NH), 1716.9 (C=O); δ_H (400 MHz, $CDCl_3$) 2.12 (3H, s, CH_3), 2.66 (1H, dd, $^2J_{H-H}$ 17.08, $^3J_{H-H}$ 8.29, C*H*$_A$CH$_B$), 2.76 (1H, dd, $^2J_{H-H}$ 17.08, $^3J_{H-H}$ 4.39, CH$_A$C*H*$_B$), 3.48 (1H, br s, NH), 3.69 (3H, s, OCH_3), 4.37 (1H, br s, CF_3CH), 6.63 and 6.70 (4H, AB q, *J* 9.03, Aryl H); δ_C (100 MHz, $CDCl_3$) 30.69, 42.90, 53.53 (q, *J* 29.77), 114.82, 115.98, 125.93 (q, *J* 283.40), 139.55, 153.49, 203.90; δ_F (376 MHz, $CDCl_3$, TFA) 2.11 (d, *J* 7.62); HRMS (EI) 261.0977 (M^+, 100%, $C_{12}H_{14}O_2NF_3$ requires 261.0977).

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