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Reactions of fluorinated silanes with 2-nitrocinnamates

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ABSTRACT

The interaction of 2-nitrocinnamates with silicon reagents Me_3SiR_f (R_f = CF_3, C_2F_5, and C_6F_5) promoted either by sodium acetate in DMF or by tetrabutylammonium acetate in dichloromethane has been described. The reactions proceed as conjugate addition of fluorinated carbanion at the C=C bond and afford 3-aryl-2-nitrobutanoates bearing a fluorinated substituent in good yields as diastereomeric mixtures in ratio from 1:1 to 1.6:1.

1. Introduction

Silicon reagents bearing a fluorinated group have become valuable reagents as synthetic equivalents of fluorinated carbanions [1]. While the major attention has been devoted to trifluoromethylation reactions using Me_3SiCF_3 (the Ruppert–Prakash reagent), silanes with other fluorinated or fluorine-containing fragments have also been exploited due to convenience of their handling and mild reaction conditions [2,3].

The reactions are typically carried out in the presence of Lewis basic activator which interacts with the silane to generate five-coordinate species followed by transfer of the fluorinated carbanion from silicon to electrophile. The interaction of silanes with C=O and C=N bonds is very well developed [1], whereas addition of fluorinated group to C=C bond still has a limited scope [4–8].

Thus, recently we have demonstrated that highly electrophilic Michael acceptors such as arylidenemalononitriles [6] and arylidene Meldrum's acids [7], which bear two electron-withdrawing substituents, serve as suitable substrates for the coupling with Me_3SiCF_3. We also showed that α,β-unsaturated nitriles, esters and ketones containing additional activating acetoxy group (acylated Baylis–Hillman adducts) can be pentafluorophenylated with the use of complicated silanes $Me_nSi(C_6F_5)_{4-n}$ [8]. In continuation of these studies, herein we report the reactions of trimethylsilicon reagents Me_3SiR_f with 2-nitrocinnamates. The products of this reaction can be considered as precursors to α-amino acids bearing a fluorinated group in β-position [9].

2. Results and discussion

2-Nitrocinnamates **1** were obtained from aldehydes or their *N*-phenylimines and methyl nitro acetate by Knoevenagel condensation [10] (Scheme 1). Compounds **1** were isolated as mixtures of geometrical isomers.

Nitrocinnamate **1a** (mixture of isomers 1.6:1) was selected as a model substrate and its reaction with the Ruppert–Prakash reagent was investigated (Table 1).

Performing the reaction in DMF with stoichiometric amount of sodium acetate as basic activator provides desired product **2a** in reasonable yields as a 1:1 mixture of diastereoisomers (entries 1–3). The variation of temperature and time had no effect on the product yield. We also tested analogous substrate with the *tert*-butyl instead of methyl ester group, that gave identical result (68% yield). When the amount of Lewis base was decreased to 10 mol%, virtually no product was formed, suggesting that the nitronate anion, which is produced after the addition of CF_3-carbanion at C=C bond, cannot activate the silicon reagent. For the variation of solvent, we used tetrabutylammonium acetate, which was reported to be effective activator of the Ruppert–Prakash reagent in different media [11]. Thus, we observed that the reaction of **1a** with Me_3SiCF_3 in tetrahydrofuran or toluene promoted by Bu_4NOAc (1.2 equiv.) occurs rapidly and exothermically, but affords the product **2a** in only 70% yield. However, decreasing the reaction temperature significantly slowed down the process (entries 8–11). Finally, the best result was obtained when reaction was performed in dichloromethane at −20 °C furnishing **2a** in 82% isolated yield (entry 12).

Based on the optimization studies, two procedures were selected for further investigation: method A involving NaOAc in DMF, and method B involving Bu_4NOAc in dichloromethane. The

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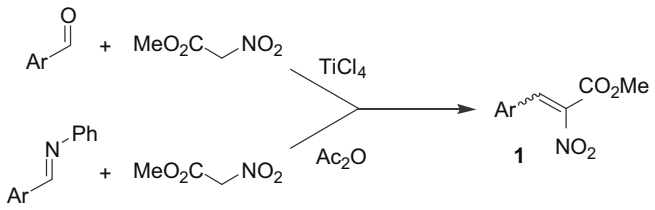
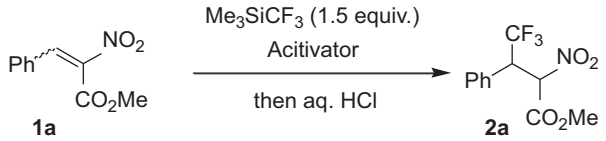


Scheme 1.

Table 1
Trifluoromethylation of nitrocinnamate **1a**.



Entry	Activator	Equiv.	Solv.	*t*, °C	Time, h	Yield,[a,b] %
1	NaOAc	1.5	DMF	50	3	(67)
2	NaOAc	1.5	DMF	r.t.	18	(62)
3	**NaOAc**	**1.2**	**DMF**	**r.t.**	**3**	**67**
4	NaOAc	0.1	DMF	50	3	n.r.
5	LiOAc	1.2	DMF	r.t.	16	(57)
6	NaOBz	1.2	DMF	50	2	(50)
7	NaOAc	1.5	MeCN	r.t.	18	0
8	NBu_4OAc	1.25	THF	−20	0.3	(66)
9	NBu_4OAc	1.25	THF	−50	1	(8)[c]
10	NBu_4OAc	1.1	THF	0	0.2	68
11	NBu_4OAc	1.2	Toluene	−20	0.2	(72)
12	**NBu_4OAc**	**1.2**	**CH_2Cl_2**	**−20**	**3**	**82**

[a] In all cases product **2a** is formed as isomeric mixture, dr 1:1.
[b] In parenthesis – yield by NMR standard, without parenthesis – isolated yield.
[c] Conversion of **1a** is 18%.

former procedure is more practical, while the latter gives higher yields.

A variety of nitrocinnamates **1** were reacted with fluorinated silanes (Table 2). As a rule, good yields of trifluoromethylated products **2a–d** can be achieved. Only substrate with the furyl substituent gave decreased yields, despite complete conversion of starting material. Silanes with pentafluoroethyl and pentafluorophenyl groups also were successfully employed smoothly leading to the desired products **2g** and **h** in high yields. All products **2** were obtained as mixtures of diastereoisomers in ratio from 1:1 to 1.6:1. This ratio does not depend on the isomeric composition of starting nitrocinnamate as clearly demonstrated for substrate **1c**, for which the sample of **1c** enriched with one geometrical isomer (dr 25:1) gave product **2c** with virtually no selectivity (dr 1.2:1, entry 3). However, as evidenced from the reaction of substrate **1d** (entries 4 and 5) the isomeric composition of the product can depend on reaction conditions. The latter phenomenon may be associated with the subtle change of reactivity of nitronate anion coupled with either sodium counterion in DMF or tetrabutylammonium counterion in dichloromethane.

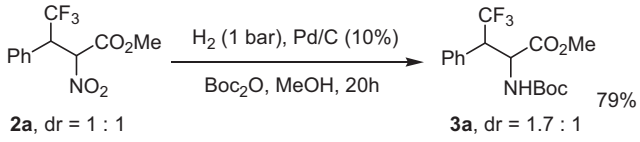
The opportunity to transform compounds **2** to derivatives of fluorine-containing amino acids was examplified by the reduction of compound **2a** under mild conditions (Scheme 2). The hydrogenation was performed over palladium on carbon under atmospheric pressure in the presence of acylating reagent furnishing *N*-Boc protected product **3a**. Interestingly, the isomeric ratio of the product was different from that of starting compound thereby suggesting the rapid epimerization of the C–H acidic chiral center prior to the reduction.

In summary, a method for the conjugate addition of fluorinated carbanions (CF_3, C_2F_5, and C_6F_5) to alkenes bearing nitro and ester groups using readily available silicon reagents has been described. The reactions proceed under mild conditions and provide facile access to fluorinated α-nitro propionates, which can be transformed to amino acid derivatives.

3. Experimental

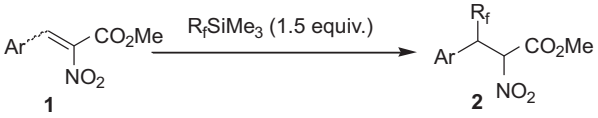
3.1. General experimental procedures

All reactions were performed under an argon atmosphere. DMF was distilled under vacuum from P_2O_5 and stored over MS 4 Å;



Scheme 2.

Table 2
Reactions of nitrocinnamates **1** with silanes.



Method A: NaOAc (1.2 equiv.), DMF, r.t., 3h
Method B: Bu_4NOAc (1.2 equiv.), CH_2Cl_2, –20 °C, 3h

Entry	Ar	Starting	dr of **1**	R_f	Product	Method	Yield (B),[a] %	dr of **2**[b]
1	4-$MeOC_6H_4$	**1b**	1.1:1	CF_3	**2b**	A	67	1:1
2						B	82	1:1
3	4-ClC_6H_4	**1c**	25:1	CF_3	**2c**	B	84	1.2:1
4	2-Thienyl	**1d**	1.3:1	CF_3	**2d**	A	32	1.6:1
5						B	68	1:1.2
6	2-Furyl	**1e**	1.2:1	CF_3	**2e**	A	<1	
7						B	37	1.2:1
8	1-Naphthyl	**1f**	1.7:1	CF_3	**2f**	B	70	1:1
9	Ph	**1a**	1.6:1	C_2F_5	**2g**	A	88	1.4:1
10	Ph	**1a**	1.6:1	C_6F_5	**2h**	A	99	1.2:1

[a] Isolated yield.
[b] Determined by NMR spectroscopy of crude product.

CH_2Cl_2 was freshly distilled from CaH_2. Column chromatography was carried out employing Merck silica gel (Kieselgel60, 230–400 mesh). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography visualizing with UV and/or acidic aq. $KMnO_4$ solution. NMR spectra were recorded on a Bruker AM-300 instrument. Microanalyses were performed on KarloErba 1106 instrument. Me_3SiCF_3 and $Me_3SiC_2F_5$ were purchased from P&M. Nitrocinnamates **1a–d** [10a] and **1e** and **f** [10b], as well as $Me_3SiC_6F_5$ [12], were obtained according to the literature procedures.

3.2. General procedures for perfluoroalkylation

3.2.1. Method A

Sodium acetate (98 mg, 1.2 mmol) was added to a solution of nitrocinnamate **1** (1.0 mmol) and Me_3SiR_f (1.5 mmol) in DMF (2 mL) at room temperature. The resulting suspension was stirred for 3 h and quenched with aq. HCl (4 mL, 0.5 M). The aqueous phase was extracted with Et_2O (3 × 5 mL), the combined organic layer was filtered through Na_2SO_4, concentrated under reduced pressure, and the residue was purified by column chromatography.

3.2.2. Method B

Tetrabutylammonium acetate (361 mg, 1.2 mmol) was added to a stirred solution of nitrocinnamate **1** (1.0 mmol) and Me_3SiCF_3 (0.22 mL, 1.5 mmol) in CH_2Cl_2 (2 mL) at −20 °C. The resulting homogeneous solution was kept at −20 °C for 3 h, then warmed to room temperature and quenched with aq. HCl (4 mL, 0.5 M), and worked-up similar to the method A.

*3.2.2.1. Methyl 4,4,4-trifluoro-2-nitro-3-phenylbutanoate (**2a**).* Mixture of isomers 1:1. Mp 77–79 °C. R_f 0.23 (hexane/EtOAc, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.49 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 4.54 (dq, 1H, J = 10.6, 8.4, CHCF$_3$), 4.64 (dq, 1H, J = 10.6, 8.4, CHCF$_3$), 5.75 (d, 2H, J = 10.6, $CHNO_2$ of both isomers), 7.30–7.45 (m, 10H, 2Ph). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 50.6 (q, J = 20.8), 51.0 (q, J = 28.2), 53.8, 54.4, 86.5, 87.0, 124.4 (q, J = 280.4), 124.9 (q, J = 280.8), 129.2, 129.3, 129.8 (q, J = 0.8), 129.87, 129.90, 161.7, 162.7. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −67.1 (d, 3F, J = 8.4, CF_3), −68.9 (d, 3F, J = 8.4, CF_3). Anal. Calcd for $C_{11}H_{10}F_3NO_4$ (277.20): C, 47.66; H, 3.64; N, 5.05. Found: C, 47.61; H, 3.59; N 5.11.

*3.2.2.2. Methyl 4,4,4-trifluoro-3-(4-methoxyphenyl)-2-nitrobutanoate (**2b**). Mixture of isomers 1:1.* Oil. R_f 0.22 (hexane/EtOAc, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.52 (s, 3H, CO_2Me), 3.80 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.92 (s, 3H, CO_2Me), 4.48 (dq, 1H, *J* = 10.5, 8.6, $CHCF_3$), 4.58 (dq, 1H, *J* = 10.5, 8.6, $CHCF_3$), 5.69 (d, 1H, *J* = 11.0, $CHNO_2$), 5.70 (d, 1H, *J* = 10.5, $CHNO_2$), 6.90 (d, 4H, *J* = 8.7, $2CH_{Ar}$ of both isomers), 7.25 (d, 2H, *J* = 8.7, $2CH_{Ar}$), 7.29 (d, 2H, *J* = 8.7, $2CH_{Ar}$). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 49.9 (q, *J* = 29.0), 50.3 (q, *J* = 28.4), 53.8, 54.4, 55.4, 86.5, 87.2, 114.6, 114.7, 120.1, 120.8, 124.5 (q, *J* = 280.4), 124.8 (q, *J* = 280.6), 130.5, 131.1, 160.6, 160.7, 161.8, 162.8. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −67.5 (d, 3F, *J* = 8.6, CF_3), −69.3 (d, 3F, *J* = 8.6, CF_3). Anal. Calcd for $C_{12}H_{12}F_3NO_5$ (307.22): C, 46.91; H, 3.94; N, 4.56. Found: C, 46.77; H, 3.98; N, 4.54.

*3.2.2.3. Methyl 3-(4-chlorophenyl)-4,4,4-trifluoro-2-nitrobutanoate (**2c**). Mixture of isomers 1.2:1.* Mp 89–90 °C. R_f 0.21 (hexane/EtOAc, 12:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: major isomer: 3.93 (s, 3H, CH_3), 4.53 (dq, 1H, *J* = 10.5, 8.3, $CHCF_3$), 5.70 (d, 1H, *J* = 10.5, $CHNO_2$), 7.25–7.42 (m, 4H, $2CH_{Ar}$ of both isomers); minor isomer: 3.55 (s, 3H, CH_3), 4.63 (dq, 1H, *J* = 10.5, 8.3, $CHCF_3$), 5.72 (d, 1H, *J* = 10.5, $CHNO_2$), 7.25–7.42 (m, 4H, $2CH_{Ar}$ of both isomers). ^{13}C NMR (75 MHz, $CDCl_3$), δ: major isomer: 50.4 (q, *J* = 28.2), 54.6, 86.8, 124.1 (q, *J* = 280.8), 127.5 (q, *J* = 1.5), 129.6, 130.6 (q, *J* = 1.3), 136.3, 162.4; minor isomer: 50.0 (q, *J* = 29.2), 54.0, 86.2, 124.4 (q, *J* = 280.8), 127.0 (q, *J* = 1.4), 129.5, 131.1 (q, *J* = 1.4), 136.3, 161.5. ^{19}F NMR (282 MHz, $CDCl_3$), δ: major isomer: −67.2 (d, 3F, *J* = 8.3, CF_3); minor isomer: −69.0 (d, 3F, *J* = 8.3, CF_3). Anal. Calcd for $C_{11}H_9ClF_3NO_4$ (311.64): C, 42.39; H, 2.91; N, 4.49. Found: C, 42.30; H, 2.78; N, 4.32.

*3.2.2.4. Methyl 4,4,4-trifluoro-2-nitro-3-(thiophen-2-yl)butanoate (**2d**). Mixture of isomers 1.6:1.* Mp 80–81 °C. R_f 0.20 (hexane/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: major isomer: 3.92 (s, 3H, CH_3), 4.86 (dq, 1H, *J* = 10.1, 8.4, $CHCF_3$), 5.66 (d, 1H, *J* = 10.1, $CHNO_2$), 7.05 (dd, 1H, *J* = 5.0, 4.1, S–CH=C*H*), 7.16 (d, 1H, *J* = 4.1, S–CH), 7.38 (d, 1H, *J* = 5.0, S–C=CH); minor isomer: 3.59 (s, 3H, CH_3), 4.98 (dq, 1H, *J* = 10.1, 8.3, $CHCF_3$), 5.66 (d, 1H, *J* = 10.1, $CHNO_2$), 7.03 (dd, 1H, *J* = 5.0, 4.1, S–CH=C*H*), 7.14 (d, 1H, *J* = 4.1, S–CH), 7.40 (d, 1H, *J* = 5.0, S–C=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ: major isomer: 46.4 (q, *J* = 29.9), 54.5, 87.5, 123.8 (q, *J* = 280.8), 127.4, 128.0, 129.3 (q, *J* = 1.7), 129.8, 162.3; minor isomer: 45.9 (q, *J* = 30.3), 54.0, 86.4, 124.2 (q, *J* = 281.0), 127.8, 128.3 (q, *J* = 1.7), 130.1, 130.1, 161.5. ^{19}F NMR (282 MHz, $CDCl_3$), δ: major isomer: −68.2 (d, 3F, *J* = 8.4, CF_3); minor isomer: −69.9 (d, 3F, *J* = 8.3, CF_3). Anal. Calcd for $C_9H_8F_3NO_4S$ (283.22): C, 38.17; H, 2.85; N, 4.95. Found: C, 38.14; H, 2.91; N 4.87.

*3.2.2.5. Methyl 4,4,4-trifluoro-3-(furan-2-yl)-2-nitrobutanoate (**2e**). Mixture of isomers 1.2:1.* Oil. R_f 0.23 (hexane/EtOAc, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: major isomer: 3.66 (s, 3H, CH_3), 4.86 (dq, 1H, *J* = 10.1, 8.3, $CHCF_3$), 5.73 (d, 1H, *J* = 10.1, $CHNO_2$), 6.41 (dd, 1H, *J* = 3.7, 1.6, O–CH=C*H*), 6.49 (d, 1H, *J* = 3.7, O–CH), 7.45 (d, 1H, *J* = 1.6, O–C=CH); minor isomer: 3.92 (s, 3H, CH_3), 4.75 (dq, 1H, *J* = 10.1, 8.3, $CHCF_3$), 5.70 (d, 1H, *J* = 10.1, $CHNO_2$), 6.40 (dd, 1H, *J* = 3.7, 1.6, O–CH=C*H*), 6.50 (d, 1H, *J* = 3.7, O–CH), 7.44 (d, 1H, *J* = 1.6, O–C=CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ: major isomer: 44.8 (q, *J* = 30.7), 54.2, 84.7, 111.1, 112.3, 123.6 (q, *J* = 281.2), 141.8 (q, *J* = 2.0), 144.3, 162.3; minor isomer: 45.2 (q, *J* = 30.3), 54.5, 85.0, 111.1, 112.0, 123.3 (q, *J* = 281.0), 142.3 (q, *J* = 2.1), 144.2, 161.6. ^{19}F NMR (282 MHz, $CDCl_3$), δ: major isomer: −69.3 (d, 3F, *J* = 8.3, CF_3); minor isomer: −67.8 (d, 3F, *J* = 8.3, CF_3). Anal. Calcd for $C_9H_8F_3NO_5$ (267.16): C, 40.46; H, 3.02; N, 5.24. Found: C, 40.27; H, 2.94; N, 5.07.

*3.2.2.6. Methyl 4,4,4-trifluoro-3-(naphthalen-1-yl)-2-nitrobutanoate (**2f**). Mixture of isomers 1:1.* Mp 62–94 °C. R_f 0.22 (hexane/EtOAc, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.31 (s, 3H, CH_3), 3.99 (s, 3H, CH_3), 5.60 (dq, 1H, *J* = 11.1, 8.3, CHCF$_3$), 5.69 (dq, 1H, *J* = 11.0, 8.3, $CHCF_3$), 5.98 (d, 1H, *J* = 11.1, $CHNO_2$), 5.99 (d, 1H, *J* = 11.0, $CHNO_2$), 7.42–7.75 (m, 8H, $4CH_{Naph}$ of both isomers), 7.92 (d, 4H, *J* = 7.7, $2CH_{Naph}$ of both isomers), 8.24 (d, 2H, *J* = 8.5, CH_{Naph} of both isomers). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 44.0 (q, *J* = 29.0), 44.4 (q, *J* = 28.4), 53.8, 54.6, 87.3, 87.4, 122.5, 122.7, 124.5 (q, *J* = 280.3), 124.8, 124.9 (q, *J* = 281.0), 125.0, 125.4 (q, *J* = 1.4), 125.6, 126.5, 126.6, 126.7, 127.7, 127.8, 129.3, 130.7, 132.0, 132.3, 134.1, 134.2, 161.5, 163.1. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −68.6 (d, 3F, *J* = 8.3, CF_3), −66.9 (d, 3F, *J* = 8.3, CF_3). Anal. Calcd for $C_{15}H_{12}F_3NO_4$ (327.26): C, 55.05; H, 3.70; N, 4.28. Found: C, 55.09; H, 3.64; N, 4.17.

*3.2.2.7. Methyl 4,4,5,5,5-pentafluoro-2-nitro-3-phenylpentanoate (**2g**). Mixture of isomers 1.4:1.* Oil. R_f 0.22 (hexane/EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: major isomer: 3.41 (s, 3H, CH_3), 4.75 (ddd, 1H, *J* = 25.8, 10.1, 3.5, $CHCF_3$), 5.84 (d, 1H, *J* = 10.1, $CHNO_2$), 7.30–7.44 (m, 5H, CH_{Ar}); minor isomer: 3.92 (s, 3H, CH_3), 4.62 (ddd, 1H, *J* = 26.8, 10.5, 3.5, $CHCF_3$), 5.83 (d, 1H, *J* = 10.5, $CHNO_2$), 7.30–7.44 (m, 5H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$), δ: major isomer: 48.3 (t, *J* = 19.3), 53.7, 85.7, 161.9; minor-isomer: 48.7 (q, *J* = 18.7), 54.4, 87.0, 162.8; both isomers: 127.8 (d, *J* = 6.3), 128.2 (d, *J* = 6.9), 129.1, 129.2, 129.8 (br), 130.0 (d, *J* = 2.3), 130.4 (d, *J* = 2.3). ^{19}F NMR

(282 MHz, $CDCl_3$), δ: major isomer: −82.4 (s, 3F, CF_3), −113.8 (dd, 1F, J = 273.4, 3.5, CF_AF_B), −122.9 (dd, 1F, J = 273.4, 25.8, CF_AF_B); minor isomer: −82.2 (s, 3F, CF_3), −111.0 (dd, 1F, J = 271.3, 3.5, CF_AF_B), −122.1 (dd, 1F, J = 271.3, 26.8, CF_AF_B). Anal. Calcd for $C_{12}H_{10}F_5NO_4$ (327.20): C, 44.05; H, 3.08; N, 4.28. Found: C, 44.04; H, 2.97; N, 4.19.

*3.2.2.8. Methyl 2-nitro-3-(perfluorophenyl)-3-phenylpropanoate (**2h**). Mixture of isomers 1.2:1.* Oil. R_f 0.24 (hexane/EtOAc, 12:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: major isomer: 3.67 (s, 3H, CH_3), 5.43 (d, 1H, J = 12.1, $CHCF_3$), 6.23 (d, 1H, J = 12.1, $CHNO_2$), 7.28–7.42 (m, 5H, CH_{Ar}); minor isomer: 3.79 (s, 3H, CH_3), 5.41 (d, 1H, J = 12.5, $CHCF_3$), 6.30 (d, 1H, J = 12.5, $CHNO_2$), 7.28–7.42 (m, 5H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$), δ: major isomer: 42.6, 53.9, 88.0 (t, J = 4.0), minor isomer: 42.2, 54.2, 88.3 (t, J = 4.3); both isomers: 127.6 (t, J = 1.7), 128.2 (t, J = 1.7), 128.97, 129.01, 129.6, 134.6, 135.2, 163.1, 163.2. ^{19}F NMR (282 MHz, $CDCl_3$), δ: major isomer: −142.4 (ddd, 2F, J = 21.2, 21.2, 8.5, *meta*), −154.4 (t, F, J = 21.2, *para*), −161.2 (dd, J = 21.2, 8.5, *ortho*); minor isomer: −141.5 (ddd, 2F, J = 21.2, 21.2, 8.1, *meta*), −154.5 (t, F, J = 21.2, *para*), −161.0 (dd, J = 21.2, 8.5, *ortho*). Anal. Calcd for $C_{16}H_{10}F_5NO_4$ (375.25): C, 51.21; H, 2.69; N, 3.73. Found: C, 51.19; H, 2.69; N, 3.64.

3.2.2.9. tert-Butyl 4,4,4-trifluoro-2-nitro-3-phenylbutanoate. Mixture of isomers 2.2:1. Obtained according to method A using tert-butyl 2-nitro-3-phenylacrylate (mixture of isomers 1.3:1). Yield 68%. Mp 100–102 °C. R_f 0.20 (hexane/EtOAc, 20:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: major isomer: 1.11 (s, 9H, t-Bu), 4.60 (dq, 1H, J = 10.5, 8.3, $CHCF_3$), 5.65 (d, 1H, J = 10.5, $CHNO_2$), 7.30–7.45 (m, 5H, Ph); minor isomer: 1.54 (s, 9H, t-Bu), 4.49 (dq, 1H, J = 11.0, 8.5, $CHCF_3$), 5.65 (d, 1H, J = 11.0, $CHNO_2$), 7.30–7.45 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$), δ: major isomer: 27.1, 50.6 (q, J = 28.6), 85.6, 87.4, 124.8 (q, J = 280.8), 129.0, 129.8, 130.3, 159.9; minor isomer: 27.5, 50.7 (q, J = 28.2), 86.1, 88.3, 124.5 (q, J = 280.6), 129.2, 129.3, 129.7, 160.9. ^{19}F NMR (282 MHz, $CDCl_3$), δ: major isomer: −69.3 (d, 3F, J = 8.3, CF_3); minor isomer: −66.7 (d, 3F, J = 8.5, CF_3). Anal. Calcd for $C_{14}H_{16}F_3NO_4$ (319.28): C, 52.67; H, 5.05; N, 4.39. Found: C, 52.71; H, 5.11; N, 4.31.

3.3. Reduction of 2a

Palladium on carbon (35 mg, 10% of Pd) and Boc_2O (3.0 mmol, 655 mg) were added to a solution of compound **2a** (1.0 mmol) in methanol (2 mL), and the mixture was vigorously stirred for 20 h under the hydrogen atmosphere (1 bar). After the complete conversion of starting material was determined by TLC, the stirring was discontinued, the liquid phase was decanted and the palladium black was washed with excess of methanol, and combined methanol solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL), washed with H_2O (3 × 5 mL), filtered through Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography in hexane/EtOAc (6:1) to give 275 mg (79% yield) of **3a**.

*3.3.1. Methyl 2-((tert-butoxycarbonyl)amino)-4,4,4-trifluoro-3-phenylbutanoate (**3a**)*

Mixture of isomers 1.7:1. Mp 54–56 °C. R_f 0.18 (hexane/EtOAc, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: major isomer: 3.73 (s, 3H, CO_2Me), minor isomer: 3.63 (s, 3H, CO_2Me); both isomers: 1.41 (s, 9H, *t*-Bu), 3.85–4.04 (m, 1H, $CHCF_3$), 4.80–4.95 (m) and 5.18–5.26 (m) (2H, NH + $CHNO_2$), 7.26–7.42 (m, 5H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$), δ: both isomers: 28.3, 51.6 (q, J = 26.3), 51.9 (q, J = 26.3), 52.6, 52.9, 54.4, 80.5–80.7 (m), 125.7 (q, J = 280.5), 125.8 (q, J = 281.2), 128.9, 129.0, 129.1, 129.4, 129.5, 130.4 (q, J = 1.8), 131.6 (q, J = 1.8), 154.7–155.0 (m), 170.4, 170.6. ^{19}F NMR (282 MHz, $CDCl_3$), δ: major isomer: −67.0 (br), −67.3 (d, 3F, J = 8.5, CF_3); minor isomer: −64.9 (br), −65.1 (d, 3F, J = 8.5, CF_3). Anal. Calcd for $C_{16}H_{20}F_3NO_4$ (347.33): C, 55.33; H, 5.80; N, 4.03. Found: C, 55.31; H, 5.87; N, 3.95.

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