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Title	Effective Synthesis of Optically Active Trifluoromethyldiazirinyl Homophenylalanine and Aroylalanine Derivatives with the Friedel-Crafts Reaction in Triflic Acid
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1	Full paper
2	Running title :
3	Effective Synthesis of Photoreactive Homophenylalanine and Aroylalanine
4	
5	Effective Synthesis of Optically Active Trifluoromethyldiazirinyl
6	Homophenylalanine and Aroylalanine Derivatives with Friedel-Crafts
7	Reactions in Triflic Acid.
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- 2 Effective Friedel-Crafts reactions with
- 3 3-(3-methoxyphenyl)-3-(trifluoromethyl)-3*H*-diazirine and optically active
- 4 N-TFA-Asp(Cl)-OMe in triflic acid afforded homophenylalanine derivatives
- 5 effectively without loss of the optical purity.
- 6
- 7
- 8 Key words:
- 9 diazirine; photoaffinity labeling; Friedel-Crafts reaction; triflic acid;
- 10
- 11

1 Introduction

 $\mathbf{2}$ Photoaffinity labeling is a useful biochemical method in the 3 investigations of structural and functional relationships between small 4 biologically active compounds and biomolecules, such as enzymes, RNA, and DNA.¹⁾ Various photophores, such as phenyldiazirine, arylazide and $\mathbf{5}$ 6 benzophenone, have been developed as the photophores. It would be ideal 7 because we can furnish photolabeling groups with minimum structural 8 alteration. It has been also established that 9 (3-trifluoromethyl)phenyldiazirinyl function can be selectively activated 10 without giving damages to peptides and proteins by irradiating at 350nm.²⁾ 11 But it usually requires not only steps of manipulations to introduce 12photophores into the target molecules, but also independent construction of 13the (3-trifluoromethyl)phenyldiazirinyl groups. These encouraged us in 14establishing effective protocol to furnish the 15(3-trifluoromethyl)phenyldiazirinyl photophore.³⁾ It was expected that amino acid derivatives carrying photolabeling group would become powerful tool in 1617the mechanistic investigations of biologically active peptides, and in 18 studying their metabolic pathways.

19We focused on developping the (3-trifluoromethyl)diazirinyl photophore 20into homophenylalanine (hPhe), since interesting biological behaviors have 21been discovered by replacing a phenylalanine in biological peptides with 22hPhe^{4,5)} and also reported as a starting material for pharmaceutical 23products such as benazepril and enarapril, both of which inhibit angiotensin $\mathbf{24}$ converting enzyme (ACE) ^{6, 7)} Efficient synthesis of photoactivatable optically 25pure hPhe is important. Although several synthetic protocols for optically 26active hPhe have been reported with various methodologies including 27enzymatic resolution,⁸⁾ Suzuki-coupling,⁹⁾ diastereoselective Michael 28addition¹⁰⁾ and catalytic asymmetric hydrogenation¹¹⁾, these required the

1 special reagents or precursors. It might not be sutable to apply those for 2 preparation of diazirinylated hPhe because some conditions might decline 3 the diazirine function. In this paper, we would like to report an effective 4 method providing optically active diazirinyl hPhe with featuring 5 Friedel-Crafts (F-C) reactions with 6 3-(3-methoxyphenyl)-3-(trifluoromethyl)-3*H*-diazirin 1¹²⁾ and β -acid chloride 7 of aspartic acid 2¹³⁾ as key steps.

8

9 Results and Discussion

10 We chose β -acid chloride form of *N*-trifluoromethyl (*S*)-aspartic acid 11 α -methyl ester **2** as the electrophilic precursor. When we first attempted the 12reaction between 1 and 2 at room temperature employing aluminium 13chloride as the activator, however, the desired reaction did not proceed and 14both 1 and 2 were recovered in CH_2Cl_2 or CH_3NO_2 . (Fig.1, Run 1 and 2) The 15reflux conditions led decomposition of **2**. (Fig.1, Run 3 and 4) Although F-C reactions between N- aspartic anhydride derivatives and aromatics have 16been reported,¹⁴⁻¹⁹⁾ the aromatics had to be employed excess amounts as the 1718 solvents. It would be preferable if we could use stoichiometric amounts of 19aromatics in the process by taking account of not only operational feasibility 20as well as economic matters. The reaction did not proceed by employing 21titanium chloride, which had been effective for formylation²⁰⁾ as the activator 22in CH₂Cl₂ or neat conditions. (Fig.1, Run 5 and 6) It was found that the 23desired reaction smoothly proceeded at 0 °C to give the adduct 3 and 4 in 24over 87% by employing stoichiometric amounts of 1, when 25trifluoromethanesulfonic acid (TfOH) was employed as the solvent. The 26suspension at the initial stage became clear solution upon the onset of the 27reaction. The regioisomer **3** and **4** were readily separated by silica gel column 28chromatography. The NOESY spectrum of major product 3 gave the

1	correlation signals between $C_{2'}$ OCH $_3$ and $C_{3'}$ H, which disclosed the
2	substitution pattern. In the case of mainor product 4, NOESY correlation
3	was obtained $C_{4'}$ OCH ₃ and both $C_{3'}$ and $C_{5'}$ H. (<i>R</i>)-2 was also reacted with 1
4	in the same condition to afford (<i>R</i>)- 3 and 4 in good yield. (Fig.1, Run 7)
5	Notably the higher temperature afforded complexed mixture because the
6	decomposition of 1 and 2 . (Fig.1, Run 8) These results were consistent with
7	the report that diazirinyl N - N double bond was easily decomposed in the
8	presence of Lewis acid over 25 °C. $^{21)}$ Unfortunately,
9	3-phenyl- 3 -(3 -trifluoromethyl)- $3H$ -diazirine, which has no activating
10	methoxy substituent on benzene ring, did not react with (S)- or (R)- 2 in
11	TfOH at 0°C. Higher temperature decomposed the diazirinyl ring at higher
12	temperatures. We have already reported that the
13	3-phenyl- 3 -(3 -trifluoromethyl)- $3H$ -diazirine easily reacted with
14	dichloromethyl methyl ether to give formylation product in TfOH. $^{22)}$ These
15	results indicated that the reactivity of both acyl donor and acyl acceptor also
16	plays a critical role. Furthermore, trifluoromethyldiazirinyl moiety plays
17	slightly as the electron withdrawing group for nucleophilic substitution of
18	aromatic compounds. ²³⁾
19	

21

Figure.1

As the adduct 3 and 4 in hand, the newly introduced carbonyl group was then reduced to a hPhe derivative. It has already been reported that the diazirinyl *N*-*N* double bond was labiel under H₂-Pd/C conditions.²⁴⁾ We found selective reduction of benzylic carbonyl to methylene could be performed with triethylsilane / TFA system to give **5** in good yield.²⁵⁾ No decomposition of the diazirinyl ring was observed during the reduction. Finally deprotections of (*S*)- and (*R*)- **5** were performed using an alkaline condition to

 $\mathbf{5}$

1	afford diazirinyl hPhe 6 in good yield (90%). However, the conditions						
2	decomposed to result complex mixture when aroyl derivative 3 was employed.						
3	Deprotection of 3 could be achieved by treating with 6N HCl in acetic acid at						
4	80 °C, affording 7 (Scheme 1).						
5							
6	Scheme 1						
7							
8	The enantiopurities of compounds 6 and 7 were determined with chiral						
9	HPLC (CHIROBIOTIC T, Astec) ²⁶⁾ which revealed these were >98% ee to						
10	prove no racemization during the synthesis. (Fig. 2)						
11							
12	Figure 2						
13							
14	Photolysise properties of diazirinyl compounds were examined with						
15	black light (15W). We have already demonstrated that the concentration of						
16	diazirinyl compound was to be set less than 1 mM to minimize the						
17	isomerization to the diazo compound. $^{\rm 27)}$ Maximum absorptions at 360 nm for						
18	${f 6}$ and ${f 7}$ were decreased upon irradiation times (Fig.3). The half-life of ${f 6}$ and ${f 7}$						
19	was determined to be 8.5 and 3.2 min, respectively based on the intensity at						
20	360 nm. We concluded the values are fast enough for photoaffinity labeling.						
21							
22	Figure 3						
23							
24	In these studies we have developed effective synthesis of photoreactive						
25	and enantiomerically pure hPhe and 2-methoxybenzoylalanine from						
26	3-(3-methoxyphenyl)-3-(trifluoromethyl)-3H-diazirin and (S)- and (R)-						
27	aspartic acid derivative as the effective photolabeling probe without						
28	racemization. The key F-C reaction proceeded by employing						

1 trifluoromethanesulfonic acid as the solvent. The following silane promoted

2 reduction took place the transformation the benzylic carbonyl to methylene.

3 The results will be contributed to the studies in structure-activity

4 relationships for the side chain of aromatic α -amino acids.

 $\mathbf{5}$

6 Experimental

7 General methods. Optical rotation values were measured by a JASCO 8 DIP-370 polarimeter. IR spectra were measured by a JASCO FTIR-4100. ¹H-, 9 ¹³C- and ¹⁹F- NMR spectra were measured by a JEOL ECA 500 spectrometer. 10In the ¹H-NMR spectra, the chemical shifts are expressed in ppm downfield 11 from the signal for tetramethylsilane used as an internal standard. Splitting 12patterns are designated as s (singlet), d (doublet), t (triplet), and m 13(multiplet). In the ¹³C-NMR spectra, the ¹³C chemical shifts of the solvents 14were used as the internal standard (¹³CDCl₃ 77.0ppm; or ¹³CD₃OD, 49.5ppm). In the 19F-NMR spectra, the chemical shifts are reported with default 15values without correction. MS spectra were obtained with a Hitachi 1617NanoFrontier LD mass spectrometer. Chiral HPLCs were performed with 18 CHIROBIOTIC T (Astec) 4.6 x 250 mm, eluted with 10% EtOH – H_2O ; flow rate 1.0 ml/min; UV detection at 210 nm. 19

20

21 (S)-Methyl 4-(2-methoxy-4-(3-(trifluoromethyl)-3H-diazirin-3-yl)

22 phenyl)-4-oxo-2-(2,2,2-trifluoroacetamido)butanoate ((S)-3) and (S)-methyl

23 4-(4-methoxy-2-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-4-oxo-

24 2-(2,2,2-trifluoroacetamido)butanoate ((S)-4)

Compound 1¹² (24.7 mg, 0.11 mmol) and (S)- 2¹³ (29.0 mg, 0.11 mmol)
were dissolved in TfOH (0.25 ml, 2.9 mmol) at 0 °C. The yellow reaction
mixture was stirred for two hours at the same temperature, then poured into
cold water and AcOEt (30 : 30 ml). The organic layer was washed with

1 aqueous 1M HCl, saturated NaHCO₃, 1N HCl and saturated NaCl, then $\mathbf{2}$ dried over MgSO₄, and filtered. The filtrate was concentrated, the residue was subjected to silica chromatography (AcOEt : n-hexane = 1 : 5) to afford 3 pure (S)-3 (34.4 mg, 71%) and (S)-4 (13.6 mg, 28%) as a pale yellow oil. 4 $\mathbf{5}$ (*S*)- **3**: $[\alpha]_D$ +77° (c 1.0, CHCl₃); IR (film) cm⁻¹ : 3330, 1720, 1675, 1610; 6 ¹H-NMR (CDCl₃) δ : 7.79 (1H, d, J = 8.0 Hz), 7.54 (1H, brd, J = 8.0 Hz), 6.80 (1H, d, J = 8.0 Hz), 6.66 (1H, s), 4.89-4.86 (1H, m), 3.91 (3H, s), 3.78 (1H, dd, 7 8 J = 19.2, 4.3 Hz), 3.73 (3H, s), 3.57 (1H, dd, J = 18.9, 4.0 Hz); ¹³C-NMR (CDCl₃) δ : 197.34, 170.12, 159.47, 156.91 (q, ² J_{CF} = 37.6 Hz), 136.06, 131.46, 9 126.42, 121.77 (q, ${}^{1}J_{CF}$ = 274.7 Hz), 118.80, 115.63 (q, ${}^{1}J_{CF}$ = 287.9 Hz), 109.63, 10 11 55.85, 53.15, 48.92, 45.29, 28.45 (q, $^2J_{CF}$ = 40.4 Hz); ¹⁹F-NMR (CDCl₃) δ: 12-63.18, -74.34; ESI-MS *m/z*: 442 (M+H)+, ESI-HRMS: calcd. for C₁₆H₁₄F₆N₄O₅ 13(M+H)+, 442.0832; found, *m/z* 442.0826. 14(*S*)- 4: $[\alpha]_D$ +57° (c 1.0, CHCl₃); IR (film) cm⁻¹ : 3330, 1725, 1690, 1610; ¹H-NMR (CDCl₃) δ : 7.82 (1H, d, J = 8.6 Hz), 7.63 (1H, brd, J = 7.4 Hz), 7.19 15(1H, s), 7.02 (1H, d, J = 8.6 Hz), 4.97-4.94 (1H, m), 3.91 (3H, s), 3.86-3.82 (4H, m)1617m), 3.56 (1H, dd, J = 18.3, 3.4 Hz); ¹³C-NMR (CDCl₃) δ : 196.22, 169.70, 163.71, 157.05 (q, ${}^{2}J_{CF}$ = 38.0 Hz), 132.51, 130.09, 129.53, 121.62 (q, ${}^{1}J_{CF}$ = 18275.1 Hz), 117.60, 115.56 (q, ${}^{1}J_{CF}$ = 287.5 Hz), 115.20, 55.87, 53.25, 48.71, 1940.81, 29.22 (q, ${}^{2}J_{CF}$ = 40.0 Hz); ¹⁹F-NMR (CDCl₃) δ : -66.75, -72.86; ESI-MS 2021m/z: 442 (M+H)+, ESI-HRMS: calcd. for C₁₆H₁₄F₆N₄O₅ (M+H)+, 442.0832; 22found, *m/z* 442.0828. 2324(*R*)-Methyl 4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl) 25phenyl)-4-oxo-2-(2,2,2-trifluoroacetamido)butanoate ((R)-3) and (R)-methyl 264-(4-methoxy-2-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-4-oxo-272-(2,2,2-trifluoroacetamido)butanoate ((R)-4)

28

8

The same treatment of **1** (24.7 mg, 0.11 mmol) and (*R*)-**2** (29.0 mg, 0.11

1	mmol) as described in above gave (<i>R</i>)- 3 (33.0 mg, 68%) and (<i>R</i>)- 4 (9.2 mg,
2	19%) as yellow oil. The $^1\mathrm{H}\text{-},^{13}\mathrm{C}\text{-}$ NMR and IR of these samples were identical
3	to these record for (S) -3 and 4.
4	(<i>R</i>)-3 $[\alpha]_{\rm D}$ -76° (c 1.0, CHCl ₃); (<i>R</i>)-4: $[\alpha]_{\rm D}$ -58° (c 1.0, CHCl ₃)
5	
6	(S)-Methyl 4-(2-methoxy-4-(3-(trifluoromethyl)-3H-diazirin-3-yl)
7	phenyl)-2-(2,2,2-trifluoroacetamido)butanoate ((S)-5)
8	To a solution of (<i>S</i>)- 3 (169 mg, 0.38 mmol) in TFA (1.5 ml, 20 mmol),
9	Et_3SiH (0.30 ml, 1.9 mmol) was added dropwise. The reaction mixture was
10	stirred for two hours, and partitioned with AcOEt (80 ml). The organic layer
11	was washed with saturated NaHCO ₃ , 1N HCl and saturated NaCl, then
12	dried over $MgSO_4$ and filtered. After the filtrate was concentrated, the
13	residue was subjected to silica chromatography (AcOEt : n-hexane = $1 : 10$) to
14	afford a colorless amorphous mass (115 mg, 76%).
15	$[\alpha]_{\rm D}$ +65° (c 1.0, CHCl ₃); IR (film) cm ⁻¹ : 3320, 1720, 1610; ¹ H-NMR
16	(CDCl ₃) δ: 7.11 (1H, d, J= 7.4 Hz), 7.04 (1H, d, J= 7.4 Hz), 6.74 (1H, brd, J=
17	6.9 Hz), 6.57 (1H, s), 4.64-4.62 (1H, m), 3.81 (1H, s), 3.68 (1H, s), 2.64 (2H, t,
18	J = 7.7 Hz), 2.25-2.22 (1H, m), 2.10-2.03 (1H, m); ¹³ C-NMR (CDCl ₃) δ : 171.00,
19	157.40, 156.74 (q, ${}^{2}J_{CF}$ = 37.2 Hz), 130.41, 130.21, 128.69, 122.07 (q, ${}^{1}J_{CF}$ =
20	274.3 Hz), 118.90 , 115.63 (q , ${}^{1}\!J_{CF}\!=\!287.5$ Hz), 108.12 , 55.24, 52.65, 52.18,
21	31.03, 28.37 (q, ${}^{2}J_{CF}$ = 40.0 Hz), 25.32; 19 F-NMR (CDCl ₃) δ : -66.54, -75.28.
22	ESI-MS m/z : 400 (M-N ₂ +H)+, ESI-HRMS: calcd. for C ₁₆ H ₁₆ F ₆ NO ₄ (M-N ₂ +H)+,
23	400.0978; found, <i>m/z</i> 400.0989.
24	
25	(R)- Methyl 4-(2-methoxy-4-(3-(trifluoromethyl)-3H-diazirin-3-yl)
26	phenyl)-2-(2,2,2-trifluoroacetamido)butanoate ((<i>R</i>)- 5)
27	The same treatment of (<i>R</i>)- 3 (168 mg, 0.38 mmol) as described in above
28	gave (R)-5 (121 mg, 80%) as yellow oil. The ¹ H-, ¹³ C- NMR and IR of these

1 samples were identical to these record for (S)-5.

- 2 $[\alpha]_{\rm D}$ -65° (c 1.0, CHCl₃).
- 3

4 (S)-2-amino-4-(2-methoxy-4-(3-(trifluoromethyl)-3H-diazirin-3-yl)
5 phenyl)butanoic acid ((S)-6)

To a solution of (S)-4 (26.4 mg, 60 μmol) in MeOH (6.0 ml), 1N NaOH
(0.50 ml) was added at room temperature. After stirring for 1 hour, silica gel
(2 g) was added. The resulting mixture was then evaporated. The residue
was subjected to silica chromatography (CH₂Cl₂ : MeOH : H₂O : acetic acid =
10 : 2 : 0.25 : 0.05) to afford a colorless solid (17.3 mg, 91%).
[α]_D -15° (c 2.0, MeOH); IR (film) cm⁻¹ : 2950, 1680; ¹H-NMR (CD₃OD) δ:

12 7.22 (1H, d, J = 7.4 Hz), 6.79 (1H, d, J = 7.4 Hz), 6.68 (1H, s), 4.33 (1H, q, J =13 4.8 Hz), 3.82 (3H, s), 2.73 (2H, t, J = 7.4 Hz), 2.27-2.18 (1H, m), 2.07-2.01 (1H, 14 m); ¹³C-NMR (CD₃OD) δ : 173.82, 159.24, 132.56, 131.76, 129.42, 123.65 (q, 15 ${}^{J}J_{CF} = 273.5$ Hz), 119.90, 109.14, 55.92, 53.69, 31.64, 29.57 (q, ${}^{2}J_{CF} = 40.4$ Hz), 16 27.44; ¹⁹F -NMR (CD₃OD) δ : -66.38; ESI-MS m/z: 318 (M+H)+, ESI-HRMS: 17 calcd. for C₁₃H₁₅F₃N₃O₃ (M+H)+, 318.1060; found, m/z 318.1067; chiral HPLC 18 $t_{\rm R} = 13.2$ min

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20 (R)- 2-Amino-4-(2-methoxy-4-(3-(trifluoromethyl)-3H-diazirin-3-yl)
21 phenyl)butanoic acid ((R)-6)

The same treatment of (R)-4 (26.0 mg, 60 µmol) as described in above gave (R)-6 (16.8 mg, 90%) as yellow oil. The ¹H-, ¹³C- NMR and IR of these samples were identical to these record for (S)-6

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25 [\alpha]_D +15° (c 2.0, MeOH); chiral HPLC t_R = 17.0 min
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26

27 (S)-2-Amino-4-(2-methoxy-4-(3-(trifluoromethyl)-3H-diazirin-3-yl)
28 phenyl)-4-oxobutanoic acid ((S)-7)

1 To a stirred solution of (S)-3 (31.6 mg, 72 µmol) in acetic acid (12 ml), $\mathbf{2}$ concentrated HCl (12 ml) was added. The reaction mixture was stirred for 12 hours at 50°C, then concentrated. The residue was subjected to silica 3 chromatography (CH₂Cl₂: MeOH : H₂O : acetic acid = 10 : 2 : 0.25 : 0.05) to 4 afford a colorless solid (22.3 mg, 94%). $\mathbf{5}$ 6 [α]_D -14° (c 2.0, MeOH);IR (film) cm⁻¹ : 2940, 1670, 1610; ¹H-NMR 7 (CD_3OD) δ : 7.87 (1H, d, J = 8.0 Hz), 6.95 (1H, d, J = 8.6 Hz), 6.81 (1H, s), 3.99-3.97 (4H, m), 3.72 (1H, d, J = 19.5 Hz), 3.55 (1H, d, J = 19.5 Hz); 8 9 ¹³C-NMR (CD₃OD) δ: 199.11, 179.04, 160.88, 136.24, 132.52, 128.79, 123.34 (q, ${}^{1}J_{CF}$ = 273.9 Hz), 119.74, 111.08, 56.54, 51.84, 29.54 (q, ${}^{2}J_{CF}$ = 40.4 Hz), 10 23.2; ¹⁹F -NMR (CD₃OD) δ: -66.83; ESI-MS *m/z*: 332 (M+H)+, ESI-HRMS: 11 12calcd. for C₁₃H₁₃F₃N₃O₄ (M+H)+, 332.0853; found, *m/z* 332.0866; chiral HPLC 13 $t_{\rm R} = 10.2 \text{ min.}$ 1415(R)-2-Amino-4-(2-methoxy-4-(3-(trifluoromethyl)-3H-diazirin-3-yl) phenyl)-4-oxobutanoic acid ((R)-7)1617The same treatment of (R)-4 (31.8 mg, 72 µmol) as described in above gave (R)-7 (21.0 mg, 88%) as yellow oil. The 1 H-, 13 C- NMR and IR of these 18 19samples were identical to these record for (S)-6 $[\alpha]_{\rm D}$ +14° (c 2.0, MeOH); chiral HPLC $t_{\rm R}$ = 15.0 min 202122Photolysis of the diazirinyl compounds in methanol 23Methanolic solution of (S)- 6 or 7 (0.5 mM) was placed in a quartz 24cuvette. After replacing the inner atmosphere with nitrogen, photolysis was 25carried out with 15 W black-light (UVP Inc., San Gabriel, California, USA) at 26a distance 2 cm from the surface of light source. 27

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1
     Figure legends
 \mathbf{2}
 3
     Figure 1
 4
     Friedel-Crafts reactions with diazirinyl compound 1 and optically pure
 \mathbf{5}
     aspartic acid derivative 2.
 6
 \overline{7}
 8
     Scheme 1
     Synthesis of optically pure diazirinyl homophenylalanine derivatives.
 9
10
     Reagents and conditions: (a) Triethylsilane, trifluoroacetic acid, (S)-76%,
     (R)- 80%; (b) NaOH, MeOH, (S)- 91%, (R)- 90%; (c) 6N HCl, acetic acid, 80 °C,
11
12
     (S)-94%, (R)-88%.
13
14
15
16
     Figure 2
     Chiral HPLC chromatogram of synthetic diazirinyl (S)- or (R)- 6 and (S)- or
17
     (R)-7 with chiral HPLC.
18
19
     Condition; CHIROBIOTIC T (Astec) 4.6 x 250 mm, eluted with 10% EtOH -
20
     H<sub>2</sub>O; flow rate 1.0 ml/min; UV detection at 210 nm.
21
22
23
     Figure 3
     Photolysis of the 0.5 mM of (S)-6 (a) and (S)-7 (b) in methanol with 15 W
24
25
     black light.
26
     The photolysis reaction mixture, at the times (in min), was indicated with
27
     numbers.
28
```

1 Figure 1

2	F ₃ C	N N OCH eq)	+ ₃ F₃COC⊦	COC IN * COC 2 (1 eq)	CI condition CH ₃ F_3COCH	F ₃ C N 4' N 5' 2' 6' 1' 3 0 HN * COO	OCH ₃ + $6^{-4^{1}}$ CH ₃ F ₃ COCHN CO	CH_3 CO CF_3 $COCH_3$
		entry	catalyst	solvent	temperature	time (h)	yield	
		1	AICI ₃	CH_2CI_2	rt	12h	0ª	
		2	AICI ₃	CH ₃ NO ₂	rt	12h	0ª	
		3	AICI ₃	CH ₂ Cl ₂	reflux	12h	0 ^b	
		4	AICI ₃	CH₃NO₂	reflux	12h	0 ^b	
		5	TiCl ₄	CH ₂ Cl ₂	50° C	3h	0 ^b	
		6	TiCl ₄		0° C	2h	0ª	
		7	TfOH		0° C	2h	(<i>S</i>)- 71 (3), 28 (4)	
							(<i>R</i>)- 68 (3), 19 (4)	
		8	TfOH		50°C	2h	0 ^b	

3 ^a no reaction occurred, ^b the starting material **1** was decomposed.

2 Scheme 1



1 Figure 2



- 1 Figure 3
- 2 (a)



