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Diastereoselective Alkylation of Glycinates by Assistance of Intramolecular Potassium···Fluorine Interactions

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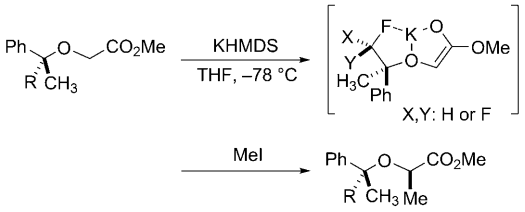
Stereoselective synthesis of α-amino acid derivatives with natural as well as unnatural structural features has constituted an important field in synthetic organic chemistry.[1] Various types of glycinates have been employed thus far as convenient key substrates for the preparation of such target molecules with exerting effective steric bias usually to esters or amides[1d] or with utilizing appropriate chiral catalysts.[2]

During our continuing study to clarify the role of fluorine atoms in organic reactions, we have reported[3] that, as shown in Scheme 1, an excellent level of diastereoselectivity

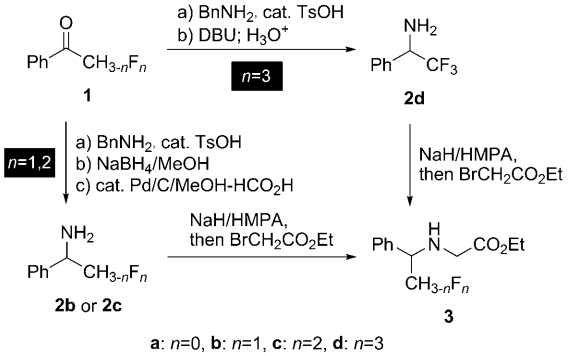


R: CH_2F: 50%, 82% *de*, CHF_2: 58%, 88% *de*
CF_3: 67%, 90% *de*, $(CH_3)_2CH$: 50%, 56% *de*

Scheme 1. Diastereoselective alkylation of CF_3-containing esters.

(up to 95:5) was attained for the alkylation of α-alkoxyesters by various types of electrophiles; in all of these reactions, the intramolecular interaction of fluorine with a metal has played a pivotal role. This process can be realized by conformationally fixing the enolate through formation of a bicyclo [3.3.0]-type structure. This would allow the appropriate electrophiles to approach exclusively from the *re*-face of the enolate as a result of preferable participation of the *pro-R* lone pair of the carbonyl α-oxygen and the auxiliary covers the opposite face. In this communication, we would like to describe our extension of this strategy to glycinates (**3**); this, like the previous α-alkoxy ester examples shown in Scheme 1, successfully demonstrated the significant importance of intramolecular metal···F chelation for attainment of excellent diastereoselectivity.

Preparation of the starting materials (**3**) was carried out from the readily available fluorinated acetophenones (**1**, Scheme 2). To this end, treatment of the benzylimine of **1d** ($n=3$)[4] with DBU efficiently catalyzed isomerization through a [1,3] proton shift as reported by Soloshonok et al.[4,5] Product **2d** was furnished upon hydrolytic workup. On the other hand, syntheses of **2b** ($n=1$) and **2c** ($n=2$) were initiated by the similar imine process from the corresponding ketones (**1b**, $n=1$ and **1c**, $n=2$, respectively)[6], and their $NaBH_4$-mediated reduction followed by regiose-



Scheme 2. Preparation of the starting materials (**3**).

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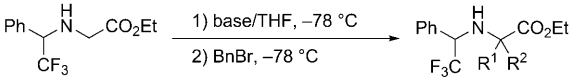
lective hydrogenolysis[7] furnished the desired products. Condensation of **2** with bromoacetate afforded the desired substrates (**3**) by the action of NaH in an HMPA solvent. It is possible that such harsh conditions were required because of the decreased nucleophilicity of the fluorinated amines **2b–d**; this was caused by attachment of the strongly electron-withdrawing fluorinated methyl groups[8] and is experimentally supported by the ready reaction of the nonfluorinated **2a** ($n=0$) with bromoacetate under the usual mild method (Et_3N/CH_2Cl_2, RT; 53% yield).[9]

With glycinates **3a–d**, which possess various numbers of fluorine atoms, in hand, our interest was focused on finding appropriate alkylation conditions after their transformation to the corresponding enolates. The representative starting material **3d** was subjected to a solution of a base in THF at −78°C to generate the enolate. After stirring for 0.5 h at the same temperature, the model electrophile, BnBr, was introduced (Table 1). Although quantitative recovery of the starting material **3d** was confirmed in cases in which 1.0 equiv of LDA was used (entry 1), complex ^{19}F NMR spectra were observed for the crude product after deprotonation with 2 equiv of LDA *without* addition of BnBr (entry 2); this indicated that an excess amount of LDA was likely to cause defluorinative decomposition of **3d**.[10] In spite of similar unfavorable results with LHMDS[10] and NaHMDS (entries 3–5), the situation was drastically altered only by changing the counter cation to potassium. Thus, as shown in entry 6, 1.0 equiv of KHMDS was found to be sufficient to furnish the desired monoalkylation product **4d** in high yield without contamination by the α,α-disubstituted compound **8a** (instead, a small amount of the substrate **3d** was recovered). To attain higher conversion, we have investigated conditions that use varying amounts of KHMDS and BnBr. Although excess KHMDS led to predominant formation of the dialkylated ester **8a**, the short reaction time after addition of BnBr successfully prevented the production of **8a** and furnished the desired product **4d** in a comparable yield to the case of entry 6 (entry 10).

At the next stage, the reaction conditions either in entries 6 or 10 in Table 1 were applied to different electrophiles; the results of this study are collected in Table 2. Use of KHMDS (1 equiv) and MeI (2 equiv) afforded **4b** with excellent product selectivity (entry 4), and by increasing of the amount of base to 2 equiv (entry 2), a much better isolated yield of **4b** was attained with a small amount of α,α-dimethylated **8b**. By employing 1 equiv of KHMDS and 2 equiv of allylBr excellent selectivity of **4c** (entry 6) was obtained, but 2 equiv of a base promoted further allylation and yielded a substantial quantity of **8c** (entry 5). The less reactive allylCl (entry 7) and the nonactivated electrophile, BuBr (entry 8), were found to be totally inappropriate for this process; this suggests that the enolate derived from **3d** is only moderately reactive.

With these good alkylation results for the trifluorinated compounds (**3d**) in hand, other enolate species with a different number of fluorine atoms were employed for similar reactions with three representative electrophiles: BnBr, MeI, and allylBr (Table 3). Good to high chemical yields and high to excellent diastereoselectivities were obtained in every instance as long as enolates possessed at least one fluorine atom, but the diastereoselectivity dropped to as low as 2% for the substrate **3a** without this special element. This tendency is identical to the one we have previously observed for the α-alkoxy esters shown in Scheme 1, and was the result of fixation of the enolate conformations. The strong

Table 1. Investigation of reaction conditions.



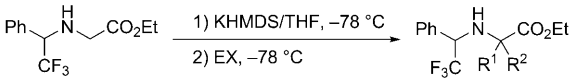
3d

4a: R^1=Bn, R^2=H
8a: R^1=R^2=Bn

Entry	Base	Amount [equiv] Base	BnBr	^{19}F NMR Yield [%] **4a**	**8a**	**3d**
1	LDA	1.0	1.0	0	0	quant
2[a]		2.0	0	0	0	0
3[a]	LHMDS	2.0	1.0	0	0	14
4	NaHMDS	2.0	1.0	20	0	61
5		2.0	2.0	7	0	65
6	KHMDS	1.0	1.0	81	0	16
7		1.5	1.5	64	21	0
8		2.0	1.0	63	0	19
9		2.0	2.0	37	56	0
10[b]		2.0	2.0	76	0	12
11[c]		2.0	2.0	26	0	39

[a] A complex mixture was obtained. [b] The reaction mixture was quenched 1 min after addition of BnBr. [c] Toluene was employed as a solvent.

Table 2. Reaction of **3d** with various electrophiles.[a]

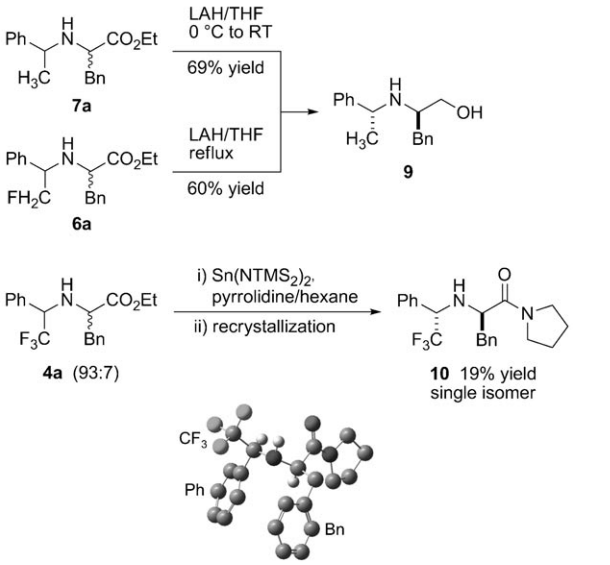


3d

4: R^1=E, R^2=H
8: R^1=R^2=E
a: E=Bn, **b**: E=Me,
c: E=Allyl

Entry	EX	Isolated yield [%] **4**	**8**	**3d**	Diastereomeric ratio[b]
1[c,d]	BnBr	70 (**a**)	0[b]	16[b]	91:9
2	MeI	91 (**b**)	8[b]	2[b]	90:10
3[d]	MeI	44	12[b]	35	87:13
4[c]	MeI	61	0	20	90:10
5	allylBr	53 (**c**)	38	6[b]	86:14
6[c]	allylBr	72	0	12[b]	83:17
7	allylCl	0	0	66	–
8	BuBr	0	0	83	–

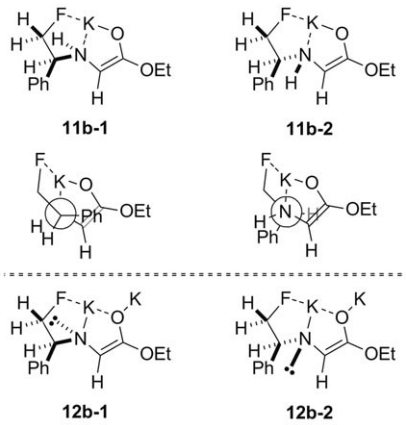
[a] Compound **3d** was added to a solution of 2.0 equiv of KHMDS in THF at −78°C. After 0.5 h, 2.0 equiv of an electrophile (EX) was introduced and the reaction was allowed to continue for 1 min unless otherwise noted. [b] Determined by ^{19}F NMR spectroscopy. [c] 1.0 equiv of KHMDS was used. [d] 1.0 equiv of an electrophile was used.



Scheme 3. Clarification of stereochemical relationship (some hydrogen atoms are omitted for clarity).

intramolecular chelation between potassium and fluorine consistently accounted for the stereoselectivity obtained.[11]

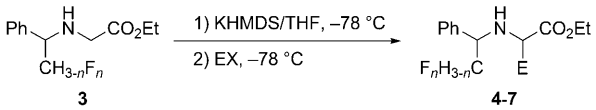
The relative stereostructure of the benzylated products was determined as follows (Scheme 3). The chromatographically separated major isomer of **7a** was treated with LAH at 0 °C to RT to furnish the already reported aminoalcohol **9**[12] in 69 % yield. The reduction in refluxing THF was also carried out on monofluorinated **6a**, and led to reductive cleavage of the C–F bond in addition to the usual ester transformation and afforded the same product, **9**, with the same (*R**,*R**)[13] stereochemical relationship, which was concluded by comparison of their ^{1}H NMR spectra. In the case of the trifluorinated material **4a**, good crystals appropriate for X-ray analysis were obtained by its direct derivatization into the corresponding pyrrolidine amide **10**.[14] It appeared that amide **10**, which was obtained from the major isomer of **4a**, possessed (*R**,*S**)[13] stereochemistry; this clearly demonstrated the unanimous diastereoisomeric preference of **4a**, **6a**, and **7a**. On the basis of these results, we assumed other alkylation products with a fluorinated auxiliary also consisted of the same (*R**,*S**)[13] diastereomers as the major components. From the crystallographic analysis data it was found that the N*H* in **10** contained the short contacts both with F and C=*O* of 231.3 and 250.6 pm, respectively; this unambiguously supported the intramolecular hydrogen bonding with 36 and 21 pm shorter atomic distances than the sum of their van der Waals radii.[15]



Scheme 4. The possible stable conformation of mono- and dianionic species, **11b** and **12b**, respectively.

This reaction was mechanistically elucidated by using the mono- and dianionic species, **11b** and **12b**, respectively, with a monofluorinated auxiliary. On the basis of our previous results with α-alkoxy-type substrates, **11b** was expected to form a *Z* enolate with an intramolecular interaction between potassium and the nitrogen lone pair. Two representative epimeric conformers on nitrogen, **11b-1** and **-2**, could be considered. If both conformers formed a bicyclo [3.3.0] system due to the additional K···F interaction, the phenyl moiety of **11b-1** would cover the enolate *re* (top) face; this would cause increased steric hindrance on this side. In **11b-2,** the 2-fluoro-1-phenylethyl moiety, which is located at the bottom *si* face, would not have such an unfavorable interaction because the phenyl group points outside. As a result, **11b-2** would be the more preferable conformation to accept electrophiles at the *re* face for the selective construction of alkylated products. This would also be the case for the dianionic **12b**. The only differences in this case would be the covalent and coordinating K–N and K–O bonds, respectively, and the presence of an additional K atom. Such close similarity (Scheme 4) allows consideration of the same mechanism as for **11b** and electrophiles predominantly approached from the same face.

Table 3. Reaction of **3** with various electrophiles.[a]



	BnBr[b] (**a**)		MeI[b] (**b**)		AllylBr[b] (**c**)	
n	Yield [%]	DS[c] [% *de*]	yield [%]	DS[c] [% *de*]	Yield [%]	DS[c] [% *de*]
3 (**4**)	70[d]	82	61	80	72	66
2 (**5**)	61	76	60	80	64	68
1 (**6**)	68	80	55	72	51	60
0 (**7**)	68	22	66	32	75	2

[a] 1.0 equiv of KHMDS and 2.0 equiv of EX were used. [b] EX employed. [c] DS determined by ^{19}F NMR spectroscopy. [d] 1.0 equiv of BnBr was employed.

As shown above, we have unambiguously demonstrated the utility of the intramolecular interaction between fluorine and potassium. Because of this interaction, a unique conformational fixation of the intermediary enolates occurred, and this led to diastereoselective alkylation in cases in which at least one fluorine atom was incorporated in the auxiliary. In

spite of some precedented studies in this field with α-heteroatom-containing carbonyl compounds,[16] only a small number of examples were found in which induction of stereochemistry was realized by a group on an α-heteroatom.[17] Thus, our result clearly and successfully emphasized the importance of this substrate system. Attainment of higher selectivity and utilization of the products thus obtained are being investigated in this laboratory.

Experimental Section

General procedure for alkylation. A solution of aminoester (1.0 mmol) in THF (0.5 mL) was added dropwise to a solution of potassium bis(trimethylsilyl)amide (2.0 mL as a 0.5 M solution in toluene, 1.0 mmol; toluene was removed under reduced pressure before use) in THF (4 mL) at −78 °C. After 10 min, an electrophile (2.0 mmol) in THF (0.5 mL) was added, and the reaction mixture was stirred for 30 min at the same temperature. The reaction was quenched by the addition of aq. HCl (3 M, ca. 0.5 mL) at −78 °C. After neutralization by sat. aq. $NaHCO_3$ at RT, the resulting solution was extracted with Et_2O three times, and the combined extracts were dried over K_2CO_3 and concentrated. The desired material was obtained after purification by silica gel chromatography (10:1 hexane/ethyl acetate).

Keywords: alkylation · enolates · fluorine · intramolecular chelation · stereoselective alkylation

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[9] No reaction occurred between a mixture of **2d** and bromoacetate in the presence of Et_3N even under reflux in $CHCl_3$, and 2 equiv of bromoacetate and NaH in refluxing THF were required for the construction of **3d** (67% yield). In cases in which the latter reaction was performed in an HMPA solvent, 90% yield was attained.
[10] Observation of the ^{19}F NMR spectrum of this crude material afforded clear peaks at around −65 and −71 ppm (from $CFCl_3$), which is the typical location for the $F_2C{=}C$ structure. It is interesting to note that defluorination was not observed in cases in which NaHMDS or KHMDS were employed. See, for example, a) R. Nadano, Y. Iwai, T. Mori, J. Ichikawa, *J. Org. Chem.* **2006**, *71*, 8748–8754; b) H. Ueki, T. Chiba, T. Yamazaki, T. Kitazume, *Tetrahedron* **2005**, *61*, 11141–11147.
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