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Simple, chemoselective, and diastereoselective Reformatsky-type synthesis of α-bromo-α-fluoro-β-lactams

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ABSTRACT

The chemoselective and diastereoselective synthesis of *syn*-α-bromo-α-fluoro-β-lactams was achieved using the diethylzinc-mediated Reformatsky-type reaction of ethyl dibromofluoroacetate with imines. The reaction led to diastereomerically pure β-lactams in good to moderate yields (up to 78% yield) with only small amounts of aziridine derivatives. Noncyclized 3-amino-2-bromo-2-fluoro carboxylic esters, usual Reformatsky adducts, were not formed. In contrast, reactions carried out under typical Reformatsky conditions using zinc metal were poorly chemoselective, leading to mixtures of β-lactams and aziridine derivatives.

Organofluorine compounds are utilized in many fields, especially in the medicinal field.[1] For example, the interesting effects were brought about by introducing a fluorine atom on a suitable position of bioactive compounds.[2] Therefore, many methods were developed for the introduction of fluorine functional groups to molecules.

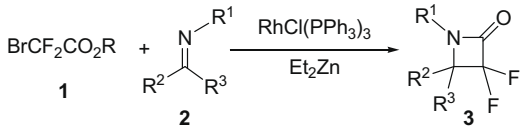
Among these methods, the Reformatsky reaction is a powerful method for the synthesis of fluorine-containing β-lactams and β-aminocarboxylic acids using fluorine-containing building blocks like ethyl bromodifluoro-acetate.[3] Frequently found in antibiotics and enzyme inhibitors, β-lactam rings can be used as synthons for the synthesis of β-amino acid derivatives via ring-opening reaction.[4] For example, Joyeau et al. reported that 3,3-difluorinated and 3-bromo-3-fluorinated β-lactams inhibited the human leukocyte elastase.[5]

Recently, we reported that the Rh-catalyzed Reformatsky reaction of bromodifluoroacetate (**1**) with imines (**2**) using Et_2Zn instead of Zn metal gave difluoro-β-lactams (**3**) in good yields.[6] Furthermore, we showed that the synthesis of **3** using a chiral ester **1** was stereoselective (Scheme 1).[6b,c] Conventional Reformatsky reaction conditions require the activation of zinc metal by acid wash or by the addition of an activating reagent such as TMSCl.[3] Our method circumvented these problems by using commercially available Et_2Zn.

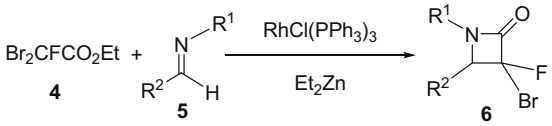
Ishihara et al. reported that the reaction of ethyl dibromofluoroacetate (**4**) with carbonyl compounds using a Zn/Et_2AlCl combination gave the Reformatsky 1,2-adducts in good to moderate yields, but the products were obtained as a nonselective diastereomixture of α-bromo-α-fluoro-β-hydroxycarboxylates.[7] Jubault and coworkers reported Et_2Zn-promoted reactions of **4** with carbonyl compounds.[8] Iseki et al. also reported that the aldol reaction of aldehydes with bromofluoroketene silyl acetals derived from **4** gave the corresponding *syn*- and *anti*-α-bromo-α-fluoro-β-hydroxycarboxylates as a *syn*/*anti* mixture of 11/89.[9]

To expand our previous results,[6] we examined the Reformatsky-type reaction of **4**, instead of **1**, with imines (**5**) in order to form α-bromo-α-fluoro-β-lactams (**6**) (Scheme 2). Herein we report our interesting results regarding the Et_2Zn-mediated chemo and stereoselective Reformatsky-type reaction.

First, we attempted the reaction of **4** with benzylidene–benzylamine (**5a**) in THF at −10 °C using the previous conditions.[6c] In the presence of $RhCl(PPh_3)_3$, the reaction gave *syn*-β-lactam (**6a**) in 63% yield as a single diastereomer, in which the relative configuration between hydrogen and fluorine atoms was *syn* (Table 1, entry 1).



Scheme 1. Rhodium-catalyzed Reformatsky reaction of **1** with imines.



Scheme 2. The Reformatsky-type reaction of **4** with imines.

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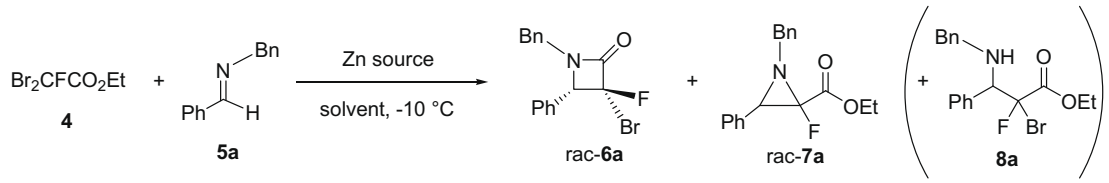
Table 1
Optimization of Et2Zn-mediated Reformatsky reaction



Entry	Zn source	Solvent	Time (h)	Yield of **6a**[a] (%)	dr of **6a**[b] (*syn*:*anti*)	^{19}F NMR yield of **7a** (%)	Dr of **7a**[b] (*syn*:*anti*)	Yield of **8a**[a] (%)
1	$RhCl(PPh_3)_3$[c] with Et_2Zn	THF	1	63	100:0	15	2 :1	N.D.
2	Activated Zn dust	THF	2	44	100:0	35	2 :1	N.D.
3	Et_2Zn	THF	1	71	100:0	10	1:1	N.D.
4	Me_2Zn	THF	24	No reaction	—	—	—	—
5	Et_2Zn	Et_2O	1	76	100:0	8	0:1	N.D.
6	Et_2Zn	Hexane	2	74	100:0	10	0:1	N.D.
7	Et_2Zn	Toluene	1	77	100:0	11	0:1	N.D.
8	Et_2Zn	DMF	18	No reaction	—	—	—	—
9	Et_2Zn	DMPU	26	No reaction	—	—	—	—

[a] Isolated yields.
[b] Determined by ^{19}F NMR.
[c] 1 mol % Rh catalyst was used.

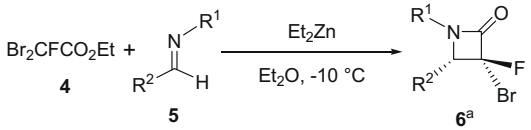
A diastereomixture of aza-Darzens-type by-products (**7a**) was also detected in 15% yield using ^{19}F NMR (dr *syn*/*anti* = 2/1).

Next, Reformatsky conditions were examined on the reaction of **4** with **5a** (entries 1–4). Under the standard Reformatsky conditions using activated Zn, the yield of **7a** increased while the yield of **6a** decreased, consistent with a decrease in chemoselectivity (entry 2). Even when Et_2Zn was used alone, without the Rh catalyst, **6a** was obtained in good yield (entry 3). In this case, a small amount of the diastereomixture of **7a** was also obtained. The use of Me_2Zn as an alkylzinc reagent was not effective at all (entry 4). In all entries, **6a** was obtained as a single diastereomer and ethyl 3-benzylamino-2-bromo-2-fluoro-3-phenyl-propionate (**8a**), the noncyclized Reformatsky adduct, was not obtained.

Changing the solvent from THF to Et_2O improved the yield to 76% and the highest chemoselectivity was achieved among these results (entry 5). Less polar solvents such as hexane and toluene showed similar yields and chemoselectivity as Et_2O. With these solvents, an aziridine by-product of *anti* configuration was formed (entries 5–7). On the other hand, highly polar solvents such as DMF and DMPU were ineffective, as no product was observed, and the imine **5a** was detected by TLC (entries 8 and 9).

In all cases, the formation of **6a** was diastereoselective in this Reformatsky-type reaction. The optimization of the reaction conditions showed that the highest yield and chemoselectivity of **6a** were attained using Et_2Zn as a promoter and Et_2O as a solvent at −10 °C, in the absence of Rh catalyst.[10,11] The reaction of various imines was examined under this optimized reaction condition and the corresponding α-bromo-α-fluoro-β-lactams (**6**) were obtained in good yields with high diastereoselectivity (Table 2). The aromatic aldimines were efficiently converted to the desired **6a**–**f** products. Imines bearing electron-donating or electron-withdrawing groups on their aromatic ring substituents gave the products in good yields, suggesting that their substituents did not affect the yields and diastereoselectivity of **6**. However, the aliphatic imine **5g**, derived from cyclohexanecarbaldehyde and *p*-anisidine, gave a mixture of products that were unstable on silica gel chromatography and could not be isolated (entry 7). ^{19}F and ^{1}H NMR spectroscopy measurements suggested that these unstable products might be lactam and aziridine.

Table 2
Scope and limitation of the optimized diethylzinc-mediated reaction



Entry	**5**			Time (h)	Yield of **6**[b] (%)	Dr of **6**[c] (*syn*:*anti*)
	R^2	R^1				
1	Ph–	Bn–	**5a**	1	76	100:0
2	Ph–	PMB–	**5b**	1	72	100:0
3	4-Cl–C_6H_4–	PMB–	**5c**	1	78	100:0
4	4-MeOCO–C_6H_4–	PMB–	**5d**	1	74	100:0
5	4-Me–CsH_4–	PMB–	**5e**	1	77	100:0
6	4-MeO–C_6H_4–	PMB–	**5f**	2	70	100:0
7[d]	Cyclohexyl	PMP–	**5g**	10 min	—	—

[a] Racemic products were obtained.
[b] Isolated yields.
[c] Determined by ^{19}F NMR.
[d] The products **6g** and **7g** decomposed rapidly.

We investigated the relative configuration of **6a** by single-crystal X-ray analysis and determined its H-F coupling constants using ^{1}H and ^{19}F NMR. X-ray analysis showed that the configuration of **6a** was *syn*, as shown in Figure 1.[12] The H–F coupling constant of **6a** was found to be 10 Hz. This value was larger than that of another diastereomer of **6a**. The H–F coupling constant of another diastereomer of **6a** was 2.5 Hz[13], which was obtained by the procedure described as follows. The reaction of *N*-benzyldibromofluoroacetamide (**9**) with benzaldehyde in the presence of Et_2Zn and $RhCl(PPh_3)_3$ gave the diastereomixture of *N*-benzyl-2-bromo-2-fluoro-3-hydroxy-propanamides (**10a**) in 86% yield (dr = 4/3). The diastereoisomers were cyclized to β-lactam (**6a**) and its isomer under Mitsunobu conditions in 57% yield (*anti*/*syn* = 7/1) (Scheme 3). All diastereomixtures of **6** and isomers were synthesized using this procedure and the diastereoratios were determined by ^{19}F NMR.

Finally, a tentative reaction mechanism for the diastereoselective formation of **6a** by the reaction of **4** with imine **5a** is shown in Figure 2. In this proposed mechanism, the reaction of **4** with Et_2Zn first gives *Z*-bromofluorozinc-enolates **11** predominantly, in which coordination of bromine onto zinc allows plausibly the formation of five-membered ring. This idea was supported by DFT calculation of *E*- and *Z*-**11**. Namely, *Z*-**11** is more stable than *E*-**11** for 5.25 kJ/mol (B88-PW91/6-31G). The stable *Z*-**11** predominantly adds to imine to give chair-like transition states, in accordance with the Zimmerman–Traxler transition-state model (**TS 1–4**). **TS-1** and **TS-2** easily lead to the desired *syn*-**6a** enantiomers via addition and intramolecular cyclization. On the other hand, **TS-3** and **TS-4**, which lead to the *anti*-**6a** isomers, are difficult to be formed due to the 1,3-diaxial repulsion between the bromine atom and the *N*-benzyl group and between the phenyl and the ethoxy groups. We believe that the difference between diastereoslectivities of our reaction of imines and Ishihara's reaction of aldehydes is attributed to the presence of the *N*-substituent. On the other hand, 2-fluoroaziridine was generated from *E*-**11** via **TS-5** and **TS-6**, in which there was no 1,3-diaxial interaction. In **TS-5** and **TS-6**, the nucleophilic nitrogen atom and bromine atom leaving groups are located in an antiperiplanar position, allowing the resulting adduct **12** to cyclize into *anti*-2-fluoroaziridine (**7a**). We suggested that the highly diastereoselective formation of **6** was explained by the predominant formation of *Z*-**11** and the rigid chair-like transition states (**TS-1**, **-2**). The study on the further mechanistic details is in progress.

In conclusion, we described a simple and diastereoselective Reformatsky-type reaction of ethyl dibromofluoroacetate with imines using commercially available Et_2Zn to yield α-bromo-α-fluoro-β-lactams. The reaction was diastereoselective, and X-ray analysis showed that these α-bromo-α-fluoro-β-lactams have a *syn* configuration.

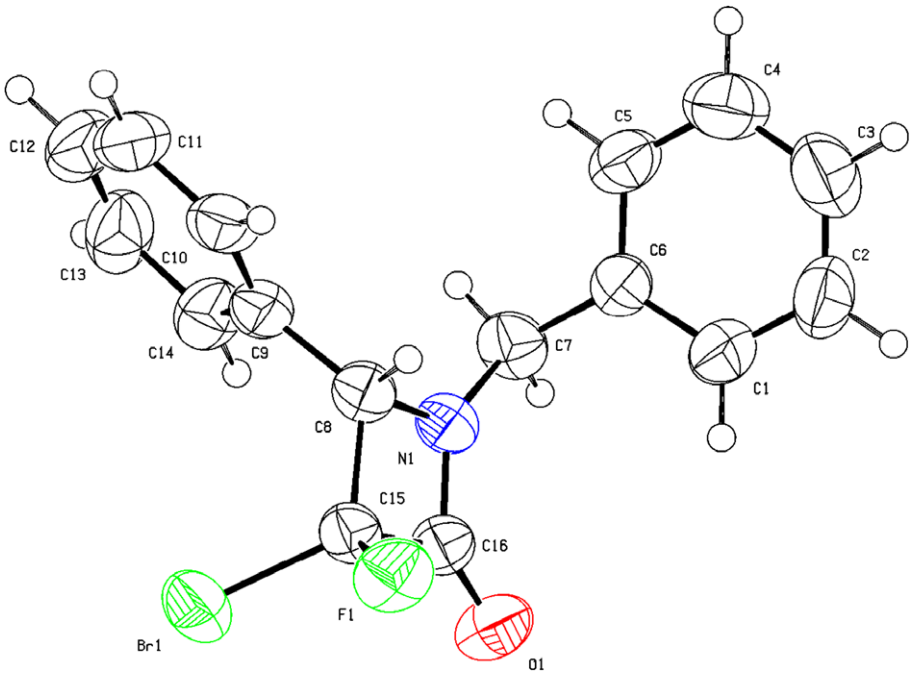
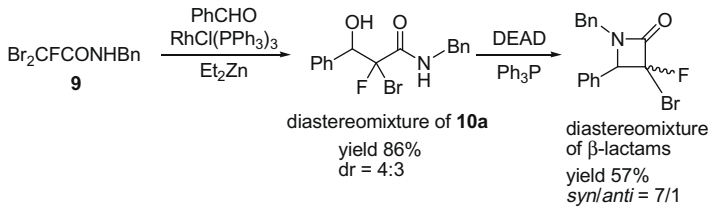


Figure 1. Single-crystal X-ray structure of **6a**.



Scheme 3. Synthesis of diastereomixture of β-lactams.

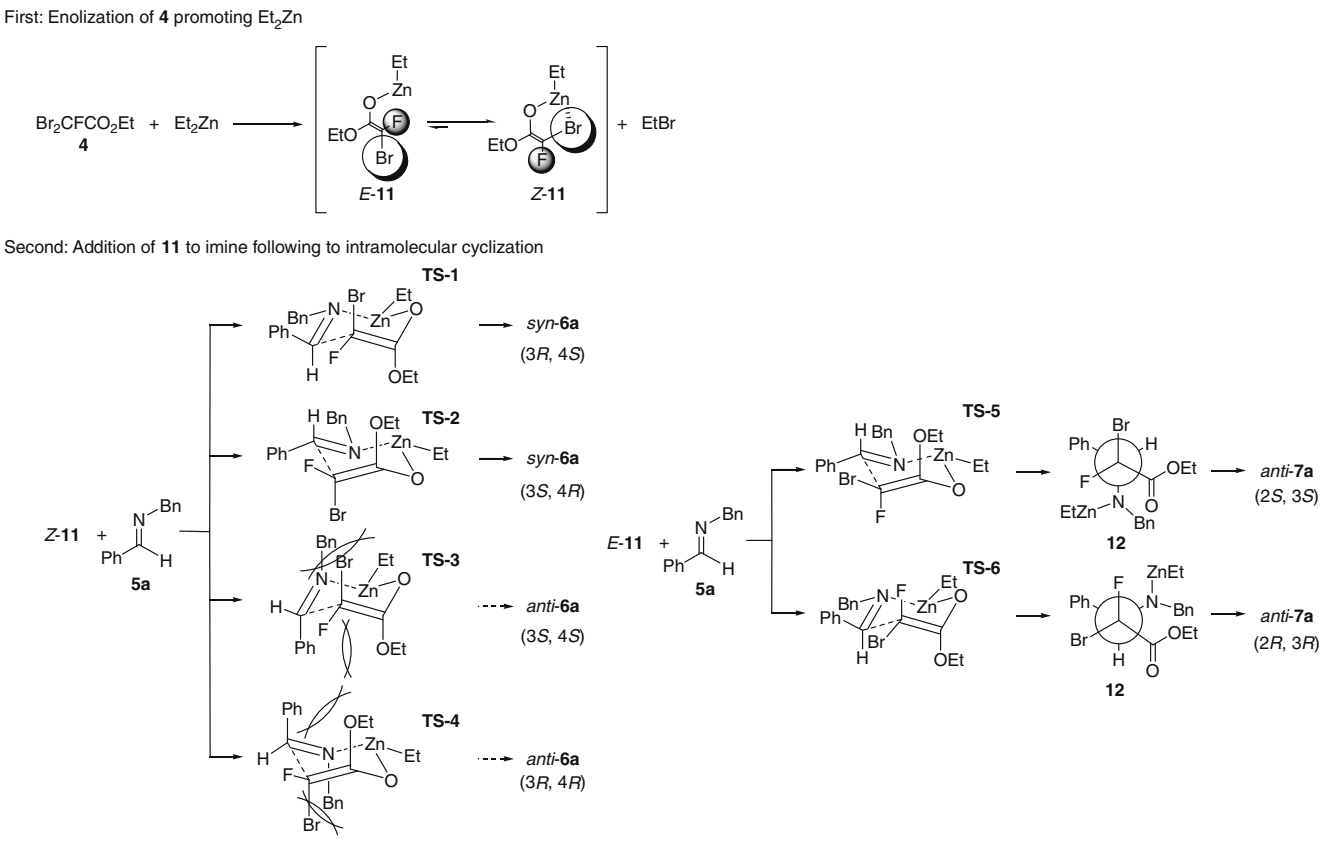


Figure 2. Proposed mechanism of the diastereoselective reactions.

Supplementary data

Supplementary data (experimental procedures and spectral date of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.023.

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10. *Preparation of α-bromo-α-fluoro-β-lactam* (**6a**): Ethyl dibromofluoroacetate (**4**; 0.41 mL, 3 mmol) was added to a solution of imine (**5a**; 0.19 mL, 1 mmol) in Et_2O (8 mL) at −10 °C. Then 1.0 M Et_2Zn in hexane (3 mL, 3 mmol) was slowly added to the mixture at −10 °C, and the resulting mixture was stirred at same temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was filtered through Celite pad. The filtrate was extracted with AcOEt, and then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, AcOEt/hexane = 1:9) to give the corresponding α-bromo-α-fluoro-β-lactam (**6a**, 254.5 mg, 76%).
11. *Spectroscopic data of* **5a**: A colorless solid; mp 81.5–82.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.93 (1H, d, J = 14.9 Hz), 4.77 (1H, d, J = 10.3 Hz), 4.97 (1H, d, J = 14.9 Hz), 7.13 (2H, m), 7.20 (2H, m), 7.32 (3H, m), 7.44 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 44.9, 69.4 (d, J = 25 Hz), 106.2 (d, J = 299 Hz), 127.8, 128.3, 128.5, 128.7, 129.0, 129.7, 132.2, 133.3, 161.0 (d, J = 26 Hz); ^{19}F NMR ($CDCl_3$, 600 MHz) δ: −54.9 (1F, d, J = 10.3 Hz); MS m/z = 333 (M^+); HRMS (pos-FAB, Gly.) Calcd for $C_{16}H_{13}BrFNO$: 333.017 (M^+), found: 334.024 (M^++H); IR (KBr) cm^{-1}: 1787, 1204.
12. CCDC 753299 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
13. The other isomer of **6a**; *anti* configuration for H–F.