HETEROCYCLES, Vol. 73, 2007, pp. 203 - 208. © The Japan Institute of Heterocyclic Chemistry
Received, 27th June, 2007, Accepted, 8th August, 2007, Published online, 10th August, 2007. COM-07-S(U)29

THE DIASTEREOSELECTIVE SYNTHESIS OF DIFLUORO-β-LACTAM USING REFORMATSKY-HONDA REACTION

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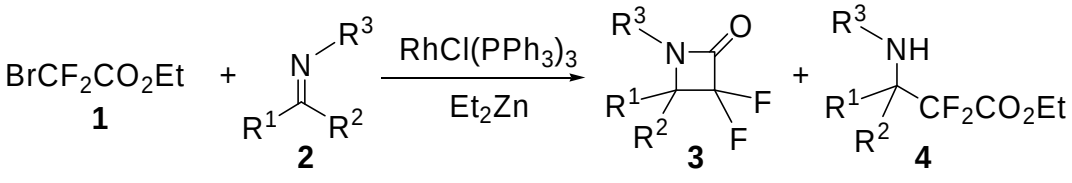
Abstract – The high diastereoselective synthesis of chiral difluoro-β-lactams (**3**) was attained by treatment of ethyl bromodifluoroacetate (**1**), 2-hydroxy-1-phenylethyl group substituted imines (**2**) and diethylzinc in the presence of rhodium-catalyst. The absolute configuration of **3** was determined by X-ray analysis of 3,5-dinitrobenzoate (**6**) derived from **3**.

Nowadays, fluorinated compounds have received a great interest of medicinal chemists due to the unique physical and biological properties imparted by fluorine.[1,2,3] A large number of therapeutic agents containing strategically placed fluorine atoms are currently widely used.[4] On the other hand, the role of amino acids in biological functions is well established, and the area of fluorine-containing amino acids is rapidly expanding, taking an important place in the family of unusual amino acids. Given the biological influence of fluorine substitution in the β-position relative to the amine and the biomedicinal and synthetic potential reported for β-amino acids,[5] the development of synthetic methodology for preparing fluorine-containing and enantiomerically pure β-amino acids is of particular interest. Since the amino acids are often interconverted to lactams, difluoro-β-lactams are source of difluoro-β-amino acids supply. Furthermore, β-lactams also are important compounds, which have an inhibition activity for bacteria's enzyme synthesizing cell walls.[6] So, we focused on importance of getting enantiopure β-lactams.

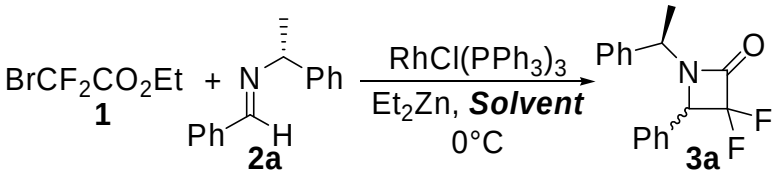


Scheme 1. Reaction of **1** with **2** in the presence of $RhCl(PPh_3)_3$

We reported Reformatsky-type addition reaction of $BrCF_2CO_2Et$ (**1**) to imines (**2**) using Et_2Zn and $RhCl(PPh_3)_3$, according to Honda's protocol,[7] to give racemic difluoro-β-lactams (**3**) and racemic 2,2-difluoro-3-aminocarboxylic ester (**4**), respectively depending on reaction condition (Scheme 1).[8] In order to expand our previous studies, we attempted the stereoselective synthsis of optically active **3**.

Recently, Honda *et al*. reported that the reaction of Reformatsky reagent, prepared by $BrCH_2CO_2Et$ and Et_2Zn, with chiral imines in the presence of $RhCl(PPh_3)_3$ gave the 3-aminocarboxylic esters diastereoselectively.[9] Thus, we applied to the diastereoselective synthesis of difluoro-β-lactams (**3**) by using chiral imines carrying chiral auxiliary on the imine-nitrogen. Among a variety of chiral auxiliaries reported in the literature, we selected commercially available phenylethylamine and phenylglycinol as amine components, respectively.[10]

The diastereoselective reaction utilizing (*R*)-benzylidene-*N*-phenethylamine (**2a**) gave a diastereo mixture of **3a** (entry 1 in Table 1). In order to improve the diastereo ratio of **3a**, we examined solvent effect. The results are summarized in Table 1.



Entry	Solvent	Time (h)	Yield of **3a** (%)[a]	Ratio[b]
1	CH_2Cl_2	1	86	3 : 2
2	toluene	4	89	1 : 1
3	hexane	1	86	1 : 1
4	Et_2O	2	62	3 : 2
5	THF	14	60	7 : 3

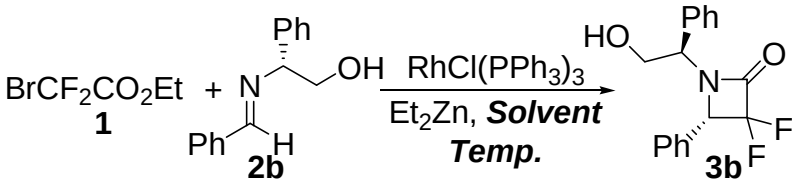
a: Isolated yield
b: Determined by ^{1}H-NMR

Table 1. Solvent effect for diastereo ratios of **3a**

Generally, non-coordinative solvents give the good results (yield and enantioselectivity) in asymmetric dialkylzinc addition, because these solvents do not contribute to the coordination to asymmetric ligand, electrophile, and dialkylzinc.[11] However, in mentioned of an asymmetric Reformatsky reaction, Jiang *et al.* have been reported that THF showed better enantioselectivity.[12] In our reaction, improvement on diastereo ratio of **3a** was achieved not by using low coordinative solvents such as CH_2Cl_2, toluene, and hexane but by using THF (entries 1-5). These results were similar to their reported.[12]

Fujii *et al*. reported that the reaction of **1** with chiral imine bearing a methyl ether of (*R*)-phenylglycinol as chiral auxiliary gave a 2,2-difluoro-3-aminocarboxylic ester as a Reformatsky adduct on the way to fluoroalkene dipeptide isosteres.[13] So we applied their methodology to the reaction of **1** with chiral imine same as them, but the main product **3** was in poor yield. Furthermore, Honda *et al*. reported the

reaction by using the benzyl ether of (*R*)-phenylglycinol as chiral auxiliary.[9] However, the removal of the auxiliary was troublesome because the deprotection was required a high pressure in hydrogenolysis, and gave a side product. To solve the problems, we used another imine (**2b**) bearing non-protected hydroxy group. Using compound **2b** prepared from (*R*)-phenylglycinol with benzaldehyde caused the high diastereoselective addition of **1,** and only one diastereomer was obtained (entry 1 in Table 2). It was obviously due to the strong coordinative effect between the hydroxy group of **2b** and zinc in the addition of zinc enolate derived from **1**. The results of searching the best reaction condition are shown in Table 2.

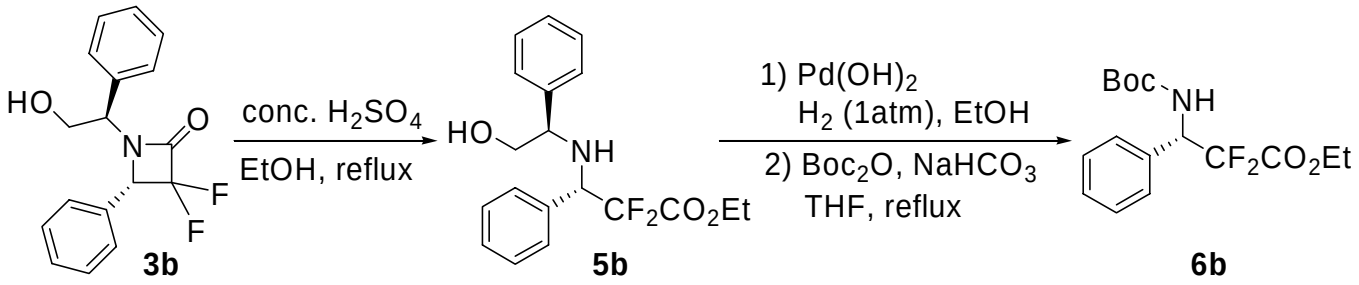


Entry	Solvent	Temp.	Time (h)	Yield of **3b** (%)[a]	de (%)
1	CH_2Cl_2	0 °C	46	46	>99
2	MeCN	0 °C	3	36	>99
3	DMF	0 °C	2	29	>99
4	toluene	0 °C ⟶ rt	9	40	>99
5	Et_2O	0 °C ⟶ rt	18	40	>99
6	DME	0 °C ⟶ rt	22	N.R.	-
7	1,4-dioxane	10 °C	3	41	>99
8	THF	0 °C	1	54	>99
9	THF	-30 °C ⟶ -10 °C	2.5	63	>99
10	THF	-10 °C	1	67	>99

a: Isolated yield

Table 2. Examination of reaction of **1** with **2b**

In examination of solvent, only one diastereomer of **3b** was obtained in all cases (entries 1-8). And, reaction temperature also affected the yield of **3b** (entries 8-10). Among them, we found the entry 10 was the best condition.

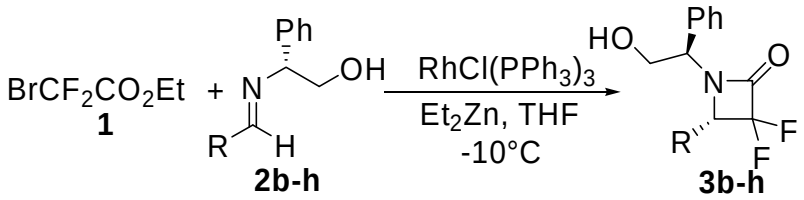


Scheme 2. Removal of chiral auxiliary from **3b**

Next, we examined the ring opening and the cleavage of the chiral auxiliary. These reactions proceeded

easily, and following *N*-Boc protection gave *N*-Boc-2,2-difluoro-3-aminocarboxylic ester (**6b**) in good yield (total yield is 65% from **3b** to **6b**: Scheme 2).

On the basis of the above results, experiments to probe the reaction generality are summarized in Table 3.[14]



Entry	Imine **2** R		Time (h)	Yield of **3** (%)[a]	de (%)
1	Ph-	**b**	1	67	>99
2	4-MeO-C_6H_4-	**c**	12	56	>99
3	4-Me-C_6H_4-	**d**	24	46	>99
4	4-Cl-C_6H_4-	**e**	1	54	>99
5	4-MeOCO-C_6H_4-	**f**	1	74	>99
6	4-CF_3-C_6H_4-	**g**	2	38	>99
7	Ph-CH_2CH_2-	**h**	1	29	>99

a: Isolated yield

Table 3. Reaction of **1** with various imines

When a wide variety of chiral aromatic aldimines with electronic properties were reacted with **1**, the desired difluoro-β-lactams were afforded in moderate to good yields. The substituents on the phenyl group did not affect the yields so much, but greatly affected the reaction rate, in which the electron withdrawing groups were much more improved it, dramatically (entries 1-6). To expand the scope of substrates, we further examined the aliphatic aldimine (entry 7). We obtained the desired product, although the yield was merely 29%. In examination of generality on substrates, only the diastereomeric pure products (**3b**-**h**) were obtained in all cases, regardless of the functional group of aldimine-carbon.

The absolute configuration of difluoro-β-lactam (**3b**) was determined by X-ray analysis of the 3,5-dinitrobenzoate (**7b**) (Figure 1).

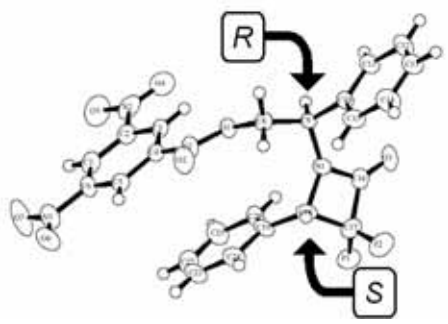


Figure 1. The result of X-ray analysis (**7b**)

On the basis of Honda's transition state,[9] this X-ray result supported that the transition state in diastereomeric addition of **1** to imine (**2b**) was as in Figure 2.

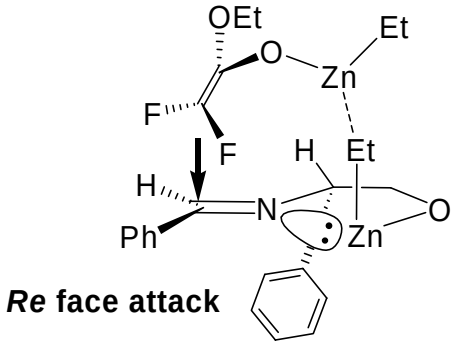


Figure 2. Proposal transition state of diastereoselective addition

This transition state well explained that the zinc enolate of **1** attacked from the sterically less hindered *re* face of the imine, avoiding the large phenyl group of the auxiliary.[9,15,16]

Unfortunately, the reaction mechanism is not obvious, but the result that the reaction stopped by addition of styrene as radical scavenger might suggested a radical process.

In conclusion, we achieved highly diastereoselective addition of **1** to the chiral imines to give difluoro-β-lactams (**3**) in good yields. The diastereoselective reaction proceeded smoothly, and this chiral auxiliary was readily cleaved from product **3** to provide *N*-Boc-2,2-difluoro-3-amiocarboxylic ester (**6**) in good yield. Compound **3** is very important synthetic intermediate in pharmacological substances such as the difluoro-β-amino acids and its peptide. We can provide a new route to the fluorine analog of optically active β-amino acid. Further applications of this methodology to the synthesis of biologically active compounds including natural products are in progress.

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14. Typical procedure is as follows: under an Ar atmosphere, **1** (0.38 mL, 3 mmol) was added to the solution of imine (**2b**, 225 mg, 1 mmol) and $RhCl(PPh_3)_3$ (9 mg, 0.01 mmol) in THF (8 mL) at -10 °C, then the mixture was stirred for 30 min. After in time, 1.0 M Et_2Zn in hexane (3 mL, 3 mmol) was gradually added to the mixture. The mixture was stirred for 1 h at the same temperature, and was quenched with saturated aqueous $NaHCO_3$. The mixture was filtered over Celite and the filterate was extract with AcOEt. The extract was washed with brine and dried over $MgSO_4$. Concentration under vacuo followed by flush chromatography over silica gel (AcOEt-hexane = 3:7) gave the corresponding product (**3b**, 204 mg, 67 %).
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