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Rhodium-catalyzed Reformatsky-type reaction for asymmetric synthesis of difluoro-β-lactams using menthyl group as a chiral auxiliary

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Abstract

We developed a new methodology for the asymmetric Reformatsky-type reaction of (−)-menthyl bromodifluoroacetate (**2**) with imine in the presence of $RhCl(PPh_3)_3$. Ester **2** with the cost-effective chiral auxiliary gave (*S*)-difluoro-β-lactams in moderate to good yields and high diastereoselectivities through spontaneous removal of the auxiliary.

Keywords: Fluorine; Rhodium; Difluoro-β-lactam; Imine; Diethylzinc; Chiral auxiliary; Reformatsky-type reaction

Fluorine compounds have attracted much attention in the field of bioactive materials as medicines. The bioactivity of the fluorine compounds is usually affected by the position or configuration of fluorine atoms or groups.[1] So, the developments of their regio- or stereoselective introduction to organic molecules have been strongly desired. On the other hand, *gem*-difluoromethylene compounds are one of the most attractive compounds among the bioactive fluorine compounds.[2] Especially, difluoromethylene analog of β-amino acids are interesting in the bioactivity, and they have been synthesized by several methods.[3] For example, enzyme inhibitors for HIV protease, α-chymotrypsin, and rennin, which have α,α-difluoro-β-amino acid unit in their molecules, were synthesized.[4]

The Reformatsky reaction have been used frequently to prepare difluoro-β-amino acids and/or difluoro-β-lactams unit of many bioactive compounds in one step.[5] One example using Reformatsky reaction is Soga's synthesis of 2′,2′-difluorinated analog of docetaxel, an anticancer taxoid, and its activity was compared with docetaxel (Fig. 1).[6]

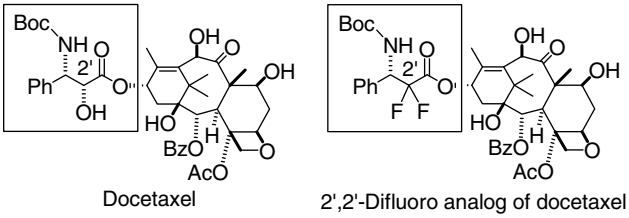

Fig. 1. Anticancer taxoid docetaxel and 2′,2′-difluoro analog of docetaxel.

Here, it was necessary to provide a chiral difluoro-β-amino acid unit to synthesize the compound, which was performed by ring-opening esterification of taxane alcohol with chiral difluoro-β-lactam.[7] However, there are only few reports on the asymmetric synthesis of difluoro-β-lactams and/or difluoro-β-amino acids.[8] The asymmetric Reformatsky reaction have been carried out mainly using diastereoselective methods. On the other hand, although asymmetric Reformatsky reactions using chiral ligands have also been reported, they were applied only to carbonyl

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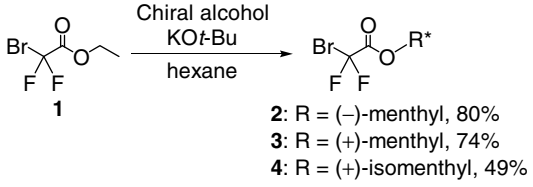
compounds and did not give high ee even by the use of the stoichiometric amount of ligand. Recently, Knochel and co-workers reported an asymmetric Reformatsky reaction using DAIB to give a high ee, but the reaction required nearly stoichiometric amount of expensive DAIB.[9] Honda and his co-workers reported a novel Reformatsky reaction of non-fluorinated bromoacetate using Wilkinson catalyst and diethylzinc (Honda's Reformatsky reaction).[10] We applied their method to the reaction of ethyl bromodifluoroacetate with imines and obtained difluoro-β-lactams in good yields.[11] Further, we have developed an asymmetric Reformatsky reaction of ethyl bromodifluoroacetate (**1**) with chiral imines to give difluoro-β-lactams in a good diastereoselectivity. On the other hand, Qurion and his co-workers reported a similar asymmetric Reformatsky reaction with imine using activated zinc,[8a,12] while we used diethylzinc.[11b] However, removal of the expensive chiral auxiliary from the product had remained as a problem. To solve this problem, we designed a new strategy for the asymmetric Reformatsky-type reaction of imine using bromodifluoroacetate of a chiral alcohol. Herein, we would like to report our new results for asymmetric synthesis of difluoro-β-lactams based on the above strategy.



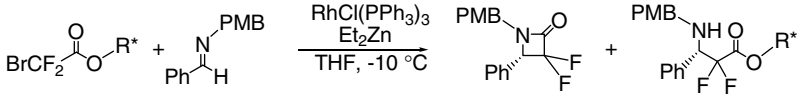
Scheme 1. Transesterification of ethyl bromodifluoroacetate with chiral alcohols.

As the chiral auxiliary, we selected natural chiral alcohols of easy availability, such as menthol. Tomioka et al. have showed high asymmetric induction of menthyl acetate on Mannich reaction.[13] However, the application of menthyl bromoacetate to Reformatsky reaction did not show high de even in the presence of amino alcohol ligands.[14] Generally, the reaction of bromodifluoroacetate with imines led to addition, followed by internal cyclization, to give difluoro-β-lactams.[5a] Based on these results, we planned asymmetric Reformatsky-type reaction using (−)-menthyl group as chiral auxiliary expecting the construction of difluoro-β-lactam skeleton through spontaneous removal of chiral auxiliary.

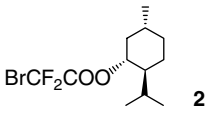
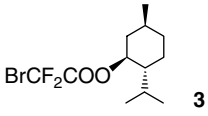
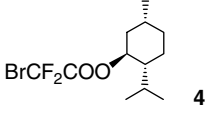
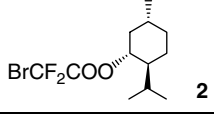
First, some bromodifluoroacetates (**2–4**) with chiral auxiliaries on the ester moiety were synthesized by transesterification of **1** with chiral natural alcohols (Scheme 1).[15]

Next, we examined the reaction of the chiral bromodifluoroacetates with imine (**5a**) by the previous reaction condition that was used on the reaction of ethyl bromodifluoroacetate with chiral imines to give chiral difluoro-β-lactams.[11b] The results are shown in Table 1.

Table 1
Effect of chiral auxiliaries on the formation of difluoro-β-lactam



2-4 5a 6a 7a

Entry	Chiral bromodifluoroacetate	Time (h)	Yield (%)		ee of **6a** (%)[16]
			6a	**7a**	
1	 **2**	2	71	0	92
2	 **3**	1	83	0	91[a]
3	 **4**	3	79	0	22[a]
4[b]	 **2**	19	58	11[c]	91

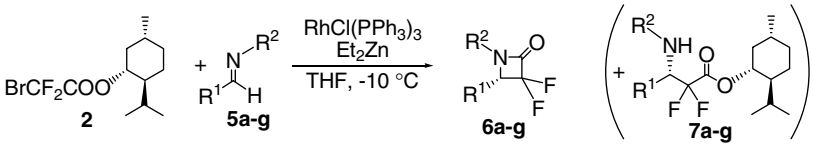
[a] Enantiomer of the product obtained by **2**.
[b] The reaction was carried out in the absence of Rh catalyst.
[c] The diastereomixture was obtained (6:1).

Interestingly, the best result on diastereoselective addition of CF_2COOR^* group was brought about by **2** that was synthesized from the most inexpensive (−)-menthol to give difluoro-β-lactam (**6a**) through spontaneous removal of the chiral auxiliary in 92% ee as shown in entry 1. Furthermore, (−)-menthol could be recovered from the reaction mixture. The product of opposite configuration was obtained using (+)-menthyl auxiliary (entry 2). On the other hand, (+)-isomenthyl group was less effective than (−)-menthyl group (entry 3). The results of entries 1–3 suggested that the configuration of the product was governed by the configuration of the alkoxy carbon moiety on the chiral auxiliary. The stereoselectivity seems to depend on the total volume of chiral auxiliary: the more widespread menthyl group works as the better auxiliary in this reaction. As shown in entry 4, the reaction of (−)-menthyl bromodifluoroacetate with **5a** in the absence of Rh catalyst for prolonged reaction time (19 h) gave **6a** in 58% yield with 91% ee and non-cyclized product (**7a**) in 11% yield, which was obtained as the diastereo mixture (6:1). In entries 1–3, **7a** was not observed in ^{19}F NMR at all. Absence of the Rh catalyst did not affect the stereoselectivity, but the chemoselectivity was decreased. So, this Rh catalyzed system provided high reactivity, chemoselectivity, and stereoselectivity for the Reformatsky-type reaction.

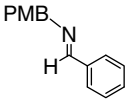
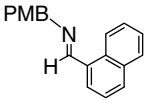
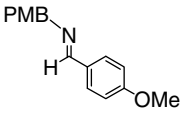
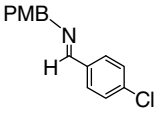
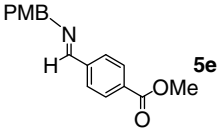
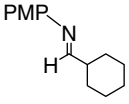
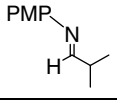
Next, the influence of the structures of various aldimines (**5a–g**) on the reactivity and diastereoselectivity was examined. The results are shown in Table 2.

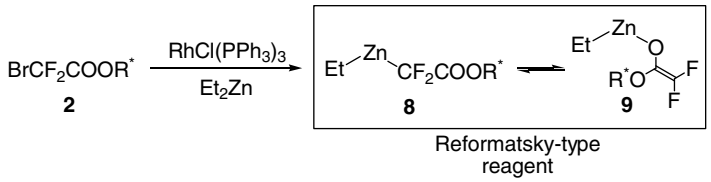
The high diastereoselectivities were achieved with aromatic imines as shown in entries 1–5. Sterically hindered 1-naphthyl group did not affect the stereoselectivity on the asymmetric Reformatsky addition, though it lowered the yield probably due to the steric hindrance (entry 2).

Table 2
Scope of the diastereoselective rhodium-catalyzed Reformatsky addition of **2** with **5a–g** using diethylzinc[17]



R^2 = PMB or PMP

Entry	Imine **5**		Time (h)	Yield of **6** (%)	ee (%)
1		**5a**	2	71	92
2		**5b**	18	45	92
3		**5c**	2	46	94
4		**5d**	2	57	87
5		**5e**	3	66	80
6		**5f**	1	41	80
7		**5g**	0.5	14	Racemic



Scheme 2. The proposed formation of chiral zinc enolate (**9**).

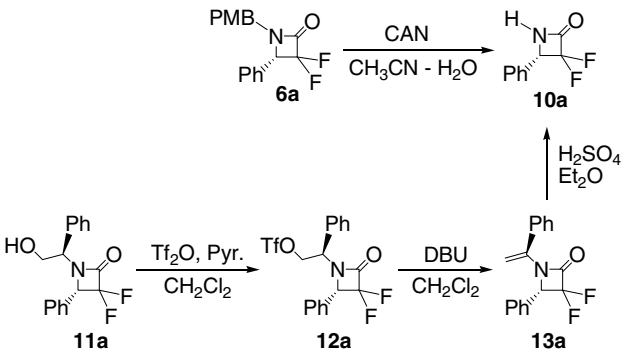
The reactions of the imines bearing electron-withdrawing group on aromatic rings showed slightly low stereoselectivities (entries 4 and 5). However, all aryl imines (**5c**–**e**) afforded the desired products in moderate yields and high ee (entries 3–5, 80–94% ee). Aliphatic imines (**5f**,**g**) also afforded the desired product in low to moderate yields. The stereoselectivity with cyclohexyl imine (**5f**) was 80% ee, but isopropyl imine (**5g**) gave racemic product (**6g**); the volume on the side chain of imines might have an influence on the stereoselectivity (entries 6 and 7). So, in order to check the influence of the volume on the side chain of imines upon the stereoselectivity, we tried to synthesize linear side chain and tertiary side chain of imines. Unfortunately, it was difficult to synthesize those imines, so we could not check these influences. In all the cases where imines could be synthesized, one diastereomer of the objective difluoro-β-lactams was obtained in high stereoselectivity (except in entry 7), and non-cyclized compounds (**7**) were not observed even in ^{19}F NMR at all.

The reaction mechanism is not clearly proved, but Honda and co-workers reported that rhodium catalyst acted as a catalyst for the formation of the Reformatsky-type reagent.[10a] In our previous work, the reaction of ethyl bromodifluoroacetate (**1**) with *N*-phenyl-imine by using diethylzinc in the absence of Rh catalyst gave the product in 60% yield, while the reaction time was much longer than that in the presence of Rh catalyst. This result supported Honda's mechanism, and the Rh catalyst would only accelerate the formation of chiral zinc enolate (**9**) (Scheme 2).

The resulting chiral zinc enolate (**9**) added to imine diastereoselectively followed by the spontaneous removal of chiral auxiliary to give chiral difluoro-β-lactams (**6**) and (−)-menthol. The study on the further mechanistic details is in progress.

Finally, the determination of the absolute configuration of difluoro-β-lactam (**6a**) is described. The N-deprotection of **6a** was performed by oxidative cleavage with CAN to give *N*-free difluoro-β-lactam (**10a**).[18] On the other hand, the (*S*)-difluoro-β-lactam (**11a**),[11b] obtained from chiral imine, was also converted to **10a** through compound **13a** via few steps (Scheme 3).[8a] Both the compounds show the same retention time on chiral HPLC analysis. Thus, the absolute configuration of **6a** was decided to be (*S*) configuration. We assume the configuration of other products would be same as **6a**.

In conclusion, we have developed a new methodology for the synthesis of chiral difluoro-β-lactams (**6**) by the reaction of (−)-menthyl bromodifluoroacetate (**2**) with imines, followed by spontaneous elimination of the chiral auxiliary in good yields and high diastereoselectivity. This highly diastereoselective Reformatsky reaction was achieved using **2,** which was derived from cost-effective and readily available (−)-menthol as a chiral source. The chiral difluoro-β-lactams themselves are expected not only to have a potentially bio-activity, but also to be the synthon for the chiral difluoroamino acids. Our new convenient route for synthesizing the chiral difluoro-β-lactams will be used in various areas.



Scheme 3. The determination of absolute configuration of **6a**.

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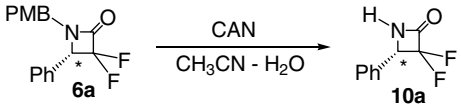
16. In order to determine the optical purity of difluoro-β-lactam (**6a**), N-deprotected difluoro-β-lactam (**10a**) was used as a standard for chiral HPLC analysis. The deprotection of **6a** was performed by oxidative cleavage with CAN to give **10a** in 70% yield, according to literature 18. Optical purities of difluoro-β-lactams (**6a–e**) obtained from aromatic imines were determined by this methodology. On the analysis of ee for **6f,g** obtained from aliphatic imines, difluoro-β-lactams were analyzed directly by chiral HPLC. Chiral HPLC: Daicel Chiralcel OD-H column (4.6 mm∅, 250 mm), isopropanol/hexane = 9:1, wavelength: 254 nm, flow rate: 0.8 mL/min, retention time: 18.9 min ((*R*)-**10a**), 38.9 min ((*S*)-**10a**).



17. Typical procedure is as follows: under an Ar atmosphere, **2** (938 mg, 3 mmol) was added to the solution of imine (**5a**, 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. Then, 1.0 M Et_2Zn in hexane (3 mL, 3 mmol) was slowly added to the mixture. The mixture was stirred for 2 h at the same temperature, and was quenched with saturated aqueous $NaHCO_3$. The mixture was filtered through Celite layer, and the filtrate was extract with AcOEt. The extract was washed with brine and dried over $MgSO_4$. Concentration of the dried layer in vacuo followed by flush chromatography on silica gel (AcOEt/hexane = 2:8) gave the corresponding product (**6a**, 214 mg, 71%).
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