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Rhodium-catalyzed Reformatsky-type reaction of ethyl bromodifluoroacetate

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Abstract—Treatment of a variety of carbonyl compounds with ethyl bromodifluoroacetate and Et_2Zn in the presence of $RhCl(PPh_3)_3$ in CH_3CN afforded Reformatsky-type products in good to excellent yields in a mild reaction condition. This is a good method to obtain a β-hydroxy-α,α-difluoro carboxylic acid ethyl ester and especially to improve the poor reactivity of ketones.

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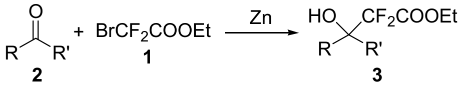
The Reformatsky reaction of ethyl bromodifluoroacetate (**1**) with various carbonyl compounds (**2**) is one of the most useful methods to give a β-hydroxy-α,α-difluoro carboxylic acid ethyl esters (**3**) (Scheme 1). This reaction was first reported by Hallinan and Fried in 1984.[1] Usually, zinc powder and **1** reacted to form an organozinc reagent, which reacted with **2** to give the corresponding esters **3**. Since this was one of the most effective methods to introduce a CF_2 group to organic compounds, many chemists have challenged to improve this reaction.[2] However, a few problems are still left for this reaction: it needs to reflux the mixture to complete the reaction, **3** are not obtained in satisfactory yields with ketones even at a high temperature, and the troublesome activation of zinc is required.

Generally, **1** reacts easily with aldehydes in good to excellent yields, but the yields from ketones are low, even if the mixture is refluxed for a long time. These problems have been solved by addition of TMS-X,[3] TDAE[4] or $CeCl_3$.[5] However, the problem of troublesome activation of zinc has not been solved yet.



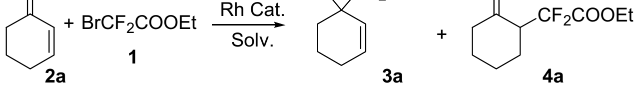
Scheme 1.

Honda et al. reported a Reformatsky-type reaction using ethyl bromoacetate and Et_2Zn catalyzed by Wilkinson's catalyst, $RhCl(PPh_3)_3$.[6] Recently, Fujii and co-workers reported that the rhodium-catalyzed Reformatsky-type reaction using ethyl bromodifluoroacetate (**1**) with imines gave α,α-difluoro-β-amino acid derivatives, independently from us.[7]

Here, we would like to report the results of this rhodium-catalyzed Reformatsky-type reaction of **1** with various carbonyl compounds.

First, we applied Honda's methodology to the reaction of **1** with 2-cyclohexen-1-one (**2a**). As we expected, the Reformatsky-type product (**3a**) was obtained, but it was a minor product. When THF was used as a solvent, an abnormal product (**4a**), where **1** was trapped at α-position of **2a**, was obtained as a main product (Scheme 2).

To improve the yield of **3a**, we examined the reaction conditions (Table 1).



Scheme 2.

Keywords: Reformatsky reaction; Fluorine; Difluoroacetate; Rhodium.

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Table 1. Examination of reaction conditions

Entry	Catalyst (mol%)	Temp (°C)	Time (h)	Et_2Zn (equiv)	Solv.	Yield[a] of **3a** (%)	Yield[a] of **4a** (%)
1	$RhCl(PPh_3)_3$ (1)	0	0.5	1.5	THF	4	71
2	$RhCl(PPh_3)_3$ (1)	0	3	1.5	Et_2O	Trace	44
3	$RhCl(PPh_3)_3$ (1)	0	3	1.5	DME	Trace	37
4	$RhCl(PPh_3)_3$ (1)	0	1	1.5	CH_3CN	80	0
5	None	0	5	1.5	CH_3CN	61	0
6	$[RhCl(cod)]_2$ (1)	0	6	1.5	CH_3CN	67	0
7	PPh_3 (100)	0	25	1.5	CH_3CN	48	0
8	$RhCl(PPh_3)_3$ (1)	0	66	0	CH_3CN	0	0

[a] Isolated yield.

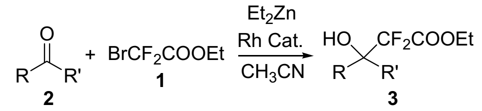
First, we examined the solvent effect (entries 1–4). When ethers were used, the main product was **4a**. We found that CH_3CN was the best solvent to obtain **3a**. The complex products were formed in toluene or DMF, although not shown in Table 1. Next, we examined the effect of catalysts. The reaction time must be prolonged and the yield of **3a** was decreased to about 60% in the absence of $RhCl(PPh_3)_3$. $RhCl(PPh_3)_3$ was very useful to shorten the reaction time and to improve the yield, but other rhodium catalysts were not effective (entries 4–6). To eliminate the possibility that triphenylphosphine (PPh_3) released from $RhCl(PPh_3)_3$ activated the zinc reagent directly, we examined the reaction only in the presence of PPh_3 (entry 7), but the reaction time was prolonged and the yield of **3a** was much decreased. Further, the Reformatsky-type product was not obtained in the absence of Et_2Zn as shown in entry 8.

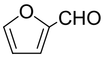
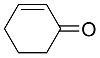
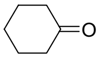
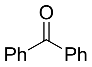
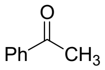
Based on the above results, we examined the Reformatsky-type reaction of various carbonyl compounds using the reaction condition in entry 4 (Table 2).[8]

With aromatic aldehydes, the reaction proceeded smoothly to give the desired products in good to excellent yields (entries 1–4). The corresponding Reformatsky-type products were also obtained in good yields from hetero aromatic aldehydes and aliphatic aldehydes (entries 5–7). With the aromatic, aliphatic or α,β-unsaturated ketones, the corresponding products were obtained in good to excellent yields, too (entries 7–11).

In conclusion, this reaction in CH_3CN could be applied to improve the yield of Reformatsky-type reaction of **1** with ketones and eliminate the troublesome activation of zinc. The reaction could be applied to the synthesis of various CF_2 compounds. Further, **4a**, where **1** was

Table 2. Reaction of **1** with various carbonyl compounds



Entry	**2**	Temp (°C)	Time (h)	Yield[a] (%)
1	Ph–CHO	0	4.5	86
2	4-MeO–C_6H_4–CHO	0	5	93
3	4-Cl–C_6H_4–CHO	0 to rt	0.5	94
4	4-MeOOC–C_6H_4–CHO	0 to rt	1	81
5		0 to rt	0.5	72
6	C_7H_{15}–CHO	0 to rt	0.5	82
7	Ph–CH_2CH_2–CHO	0 to rt	1	82
8		0	1	80
9		0 to rt	1	78
10		0 to rt	0.5	91[b]
11		0 to rt	7	85

[a] Isolated yield.

[b] **1** and Et_2Zn were used 3 equiv.

trapped at α-position of **2a**, was obtained in good yield in THF. Now the detailed mechanism and scope of this reaction giving **4a** is under investigation.

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8. The typical procedure is as follows: under an Ar atmosphere, **1** (0.19 mL, 1.5 mmol) and benzaldehyde (0.10 mL, 1 mmol) were added to the solution of $RhCl(PPh_3)_3$ (9 mg, 0.01 mmol) in CH_3CN (8 mL) at 0 °C and the mixture was stirred for 30 min. Then, 1.0 M Et_2Zn in hexane (1.5 mL, 1.5 mmol) was gradually added to the mixture, and the whole mixture was stirred at same temperature for 4.5 h. The mixture was worked-up as usual, followed by column chromatographic purification over silica gel (AcOEt–hexane = 1:4) to give the corresponding product[1] (197 mg, 86%).