

Phosphine/Lewis Acid Mediated Reformatsky-type Reaction of α -Bromoketone or -Thioester Derivatives

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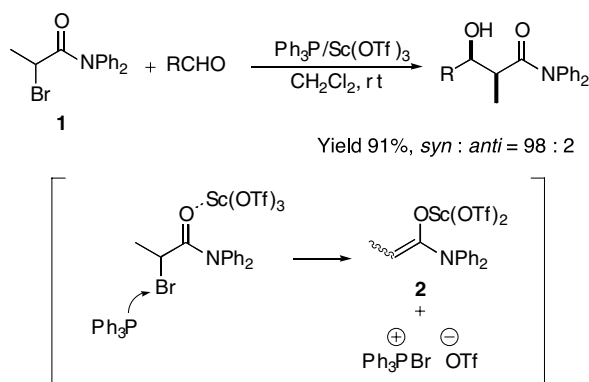
(Received October 29, 2001; CL-011066)

The combination of (*o*-tolyl)₃P/TiCl₄ effectively promoted the Reformatsky-type reaction of α -bromoketone or -thioester derivatives with various aldehydes, and the corresponding β -hydroxy carbonyl compounds were obtained in good yield with high diastereoselectivity.

In recent years, we have been focused on the study of composite reagents, combination of Lewis acid and phosphine, which showed characteristic reducing ability. We have already reported the reduction of various 2-bromocarboxylic acid derivatives proceeded in good yield under mild conditions.¹ In addition, we reported that the Reformatsky-type reaction of *N,N*-diphenyl-2-bromopropionamide was promoted by this combination in good yield with high diastereoselectivity.²

Although the Reformatsky reaction³ is one of the most useful methods for the carbon-carbon bond formation as well as aldol reaction,⁴ it has been little worth using because of low stereoselectivity. To overcome this problem, the metallic reductive species has been widely investigated,^{3b)} and we have also reported germanium metal mediated Reformatsky reaction as one of the efficient methodologies for the stereoselective and asymmetric synthesis.⁵

On the other hand, the Reformatsky-type reaction mediated by phosphine/Lewis acid combination was the first example based on the non-metallic reductive species.² The mechanism of this reaction is illustrated in Scheme 1. As can be seen from Scheme 1, it is not necessary that the center metal of enolate **2** has reducing ability. Therefore, it was expected to exhibit distinctive selectivity that was different from the conventional method. However, until now, since the substrate was limited to diphenyl amide **1**, wide applicability to the various α -bromocarbonyl compounds was strongly desired.



Scheme 1.

In this manuscript, we would like to describe the Reformatsky-type reaction of α -bromoketone or -thioester derivatives

mediated by Lewis acid and phosphine combination.

Initially, we examined the Reformatsky-type reaction of 2-bromopropiophenone by using Lewis acid/Ph₃P at room temperature. Although Lewis acid, such as MeAlCl₂, BF₃·OEt₂, Sc(OTf)₃, or TiCl₄ promoted the reaction, prolonged reaction time caused the lowering of the yield and the stereoselectivity because of the retro-aldol type reaction. It was found that this undesired degradation could be prevented when the reaction was carried out at -78°C . After reinvestigation of Lewis acids at this temperature, the combination of TiCl₄/Ph₃P was found to be the best promoter with regard to both yield and stereoselectivity (Table 1, Entry 1). Next we tried screening of phosphines, such as *n*-Bu₃P, (PhO)₃P, (mesityl)₃P, and (*o*-tolyl)₃P at -78°C using TiCl₄ as Lewis acid. Among the phosphines examined, only (*o*-tolyl)₃P gave better result than Ph₃P (Table 1, Entry 2).

Under the optimized conditions, the Reformatsky-type reaction of 2-bromoketones with various aldehydes was effectively carried out in good yield with high *syn*-diastereoselectivity (Table 1, Entries 3–6).⁶

Table 1. The Reformatsky-type reaction of α -bromoketone derivatives **3** with aldehydes **4**^a

Entry	Phosphine	3(R ¹ =)	4(R ² =)	Yield/% ^b	<i>syn</i> : <i>anti</i> ^c
1	Ph ₃ P	Ph	Ph	84	93 : 7 ^d
2	(<i>o</i> -tolyl) ₃ P	Ph	Ph	91	96 : 4
3	(<i>o</i> -tolyl) ₃ P	Ph	<i>n</i> -Pr	75	98 : 2
4	(<i>o</i> -tolyl) ₃ P	Ph	<i>i</i> -Pr	82	96 : 4
5	(<i>o</i> -tolyl) ₃ P	Ph	<i>t</i> -Bu	78	> 99 : 1
6	(<i>o</i> -tolyl) ₃ P	Et	Ph	55	90 : 10

^aMolar ratio of **3**:**4**:Phosphine:TiCl₄=1.4:1.0:1.4:1.4. ^bIsolated yield.

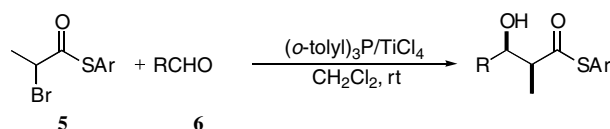
^cDetermined by HPLC,⁷ unless otherwise stated. ^dDetermined by 300 MHz ¹H NMR.

Next we applied (*o*-tolyl)₃P/TiCl₄ system to the reaction of α -bromoester or -thioester derivatives with benzaldehyde. As a result, *S*-phenyl α -bromothioester gave the best yield with moderate stereoselectivity (Table 2, Entry 1). In this case, the reaction could be performed at room temperature without any retro-aldol type reaction. In order to improve the stereoselectivity, we next examined the sulfonyl group in the thioester (Table 2, Entries 1–3). Consequently, it was found that the bulkier substituent gave better selectivity, and the corresponding β -

hydroxy thioester was obtained with high *syn*-diastereoselectivity using the newly developed thioester derived from 2,4,6-triisopropylbenzenethiol (Entry 3).⁸

Then the Reformatsky-type reaction of this bulky thioester with various aldehydes was carried out under the optimized conditions and the results were summarized in Table 2 (Entries 3–6), and the desired adduct was obtained stereoselectively in each entry.

Table 2. The Reformatsky-type reaction of α -bromothioester derivatives with aldehydes in the presence of the (*o*-tolyl)₃P/TiCl₄ combination^a



Entry	Ar	6(R=)	Time/h	Yield/% ^b	<i>syn</i> : <i>anti</i>
1	Ph	Ph	5	81	75 : 25 ^c
2	2,4,6-MeC ₆ H ₂	Ph	12	86	89 : 11 ^c
3		Ph	5	94	95 : 5
4 ^d		<i>n</i> -Pr	5	91	92 : 8 ^e
5 ^d		<i>i</i> -Pr	5	89	91 : 9
6 ^d		<i>t</i> -Bu	5	77	85 : 15

^aMolar ratio of 5:6:(*o*-tolyl)₃P:TiCl₄=1.4:1.0:1.4:1.4. ^bIsolated yield.

^cDetermined by 300 MHz ¹H NMR. ^dReaction temperature: 0 °C.

^eDetermined by GC.

In summary, the (*o*-tolyl)₃P/TiCl₄ combination was found to be an efficient mediator having a high generality for the Reformatsky-type reaction of α -bromoketone or -thioester derivatives. And the range of α -bromocarbonyl compounds was much extended as compared with that of the original Reformatsky reaction. Now the investigation of the asymmetric Reformatsky-type reaction using phosphine/Lewis acid combination is in progress.

This work was financially supported by a Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Culture,

Sports, Science and Technology, Japan.

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

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- Typical procedure for the Reformatsky-type reaction (Table 1, Entry 2): Under an argon atmosphere, to a solution of 2-bromo-1-phenyl-1-propanone (140.0 mg, 0.66 mmol) and TiCl₄ (3.3 mol/L, 0.2 mL, 0.66 mmol) in CH₂Cl₂ (3.0 mL), which was stirred for 20–30 min, was added a solution of (*o*-tolyl)₃P (198.2 mg, 0.65 mmol) in CH₂Cl₂ (1.5 mL). After cooling to –78 °C, PhCHO (50.5 mg, 0.48 mmol) was added dropwise and stirred for 24 h with keeping at –78 °C. The reaction was quenched with phosphate buffer (pH 7) and the mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined CH₂Cl₂ layers were washed with brine (1 × 10 mL) and dried over Na₂SO₄. This organic layer was filtered and evaporated under reduced pressure, and then the crude product was purified by PTLC (SiO₂, Hexane/Ethyl Acetate = 1/3) to give 3-hydroxy-2-methyl-1,3-diphenyl-1-propanone (104.8 mg, 91%, *syn* : *anti* = 96 : 4).
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- 2,4,6-Triisopropylbenzenethiol was prepared by the reduction of 2,4,6-triisopropylbenzenesulfonyl chloride with Ph₃P.⁹
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