

Triphenylphosphine/Scandium(III) Trifluoromethanesulfonate: A New Agent for the Reformatsky Reaction of α -Bromo Carboxylic Acid Derivatives with Aldehydes

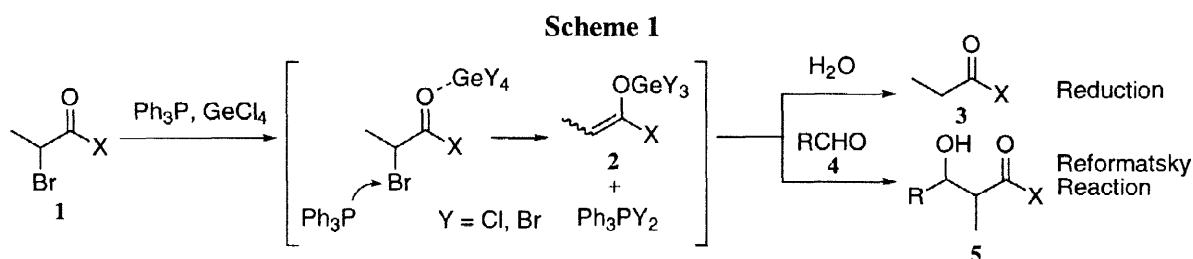
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Abstract: The $\text{Ph}_3\text{P}/\text{Sc}(\text{OTf})_3$ combination was found to be effective for the Reformatsky reaction; when α -bromo carboxylic acid derivatives were allowed to react with aldehydes in the presence of the $\text{Ph}_3\text{P}/\text{Sc}(\text{OTf})_3$ combination, the corresponding β -hydroxy carboxylic acid derivatives were obtained in good yields with excellent diastereoselectivity. © 1998 Elsevier Science Ltd. All rights reserved.

Recently, we have reported that a new reducing agent, a combination of Ph_3P and GeCl_4 , was very useful for the reduction of various α -bromo carboxylic acid derivatives **1** under mild conditions (Scheme 1).¹ The facile reduction of **1** by the $\text{Ph}_3\text{P}/\text{GeCl}_4$ combination would be attributed to the activation of the carbon-halogen bond in **1** upon coordination of GeCl_4 as a Lewis acid to their carbonyl oxygen. In this reaction, the formation of an intermediary germanium(IV) enolate **2** is plausible. Here, if **2** reacts with an aldehyde **4** instead of water as an electrophile, the Reformatsky reaction, giving β -hydroxy carboxylic acid derivatives **5**, can be achieved. This hypothesis prompted us to apply the present reduction, using the $\text{Ph}_3\text{P}/\text{Lewis acid}$ combination, to the synthetically useful Reformatsky reaction. Although a number of metals and low-valent metal compounds have been proved to promote the Reformatsky reaction until now,² there is no report on the Reformatsky reaction mediated by phosphorous(III) compounds, which act as reducing agents. Herein, we demonstrate that the $\text{Ph}_3\text{P}/\text{Sc}(\text{OTf})_3$ combination can effectively mediate the Reformatsky reaction of α -bromo carboxylic acid derivatives with aldehydes.



Our initial study was focused on the Reformatsky reaction of α -bromo amide **1a** with benzaldehyde (**4a**) using various $\text{Ph}_3\text{P}/\text{Lewis acid}$ combinations (Table 1, entries 1-5). Of the Lewis acids examined, $\text{Sc}(\text{OTf})_3$ was a quite excellent promoter with regard to both yield and diastereoselectivity (84% yield, *syn:anti* = 98:2, entry 5).⁴ Next, the Reformatsky reaction of various α -bromo carboxylic acid derivatives with aldehydes was carried out in the presence of the $\text{Ph}_3\text{P}/\text{Sc}(\text{OTf})_3$ combination (entries 5-9).⁵ The reaction of **1a** with *n*PrCHO (**4b**) in the presence of the $\text{Ph}_3\text{P}/\text{Sc}(\text{OTf})_3$ combination also proceeded smoothly to give the corresponding β -hydroxy amide **5b** in good yield with excellent *syn*-diastereoselectivity (entry 6). The substituents on the nitrogen atom in α -bromo amides strongly influenced the rate of the reduction; in contrast to the case of α -bromo amide **1a**, the reduction of α -bromo amide **1b** did not proceed in the presence of the $\text{Ph}_3\text{P}/\text{Sc}(\text{OTf})_3$ combination, and no adduct **5b** was obtained (entry 7). Although α -bromo ester **1c** was not a good Reformatsky donor (entry 8), α -bromo imide **1d** was readily reduced with the $\text{Ph}_3\text{P}/\text{Sc}(\text{OTf})_3$ combination to give the corresponding β -hydroxy imide **5e** in good yield with moderate *anti*-selectivity (entry 9).

Table 1. The Reformatsky Reaction of α -Bromo Carboxylic Acid Derivatives **1** with Aldehydes **4** in the Presence of the Ph_3P /Lewis Acid Combination

Entry	Lewis acid	1 (X =)	4 (R =)	Condition ^a	Reaction time	5	Yield ^b (%)	syn : anti ^c
1	$\text{BF}_3 \cdot \text{OEt}$	NPh_2 (1a)	Ph (4a)	A	48 h	5a	82	95 : 5
2	TiCl_4	1a	4a	A	15 min	5a	92	76 : 24
3	$\text{Yb}(\text{OTf})_3$	1a	4a	A	15 h	5a	83	83 : 17
4	$\text{Sc}(\text{OTf})_3$	1a	4a	A	15 min	5a	93	98 : 2
5	$\text{Sc}(\text{OTf})_3$	1a	4a	B	15 h	5a	84	98 : 2
6	$\text{Sc}(\text{OTf})_3$		<i>n</i> Pr (4b)	B	24 h	5b	71	97 : 3 ^d
7	$\text{Sc}(\text{OTf})_3$	(1b)	4a	B	24 h	5c	0	—
8	$\text{Sc}(\text{OTf})_3$	$\text{O}(\text{CH}_2)_3\text{Ph}$ (1c)	4a	B	24 h	5d	9	35 : 65
9	$\text{Sc}(\text{OTf})_3$	(1d)	4a	B	24 h	5e	62	11 : 89

^aA; **4**:**1**: Ph_3P :Lewis acid = 1:2:2:2. B; **4**:**1**: Ph_3P :Lewis acid = 1:1.2:1.2:1.2. ^bIsolated yields. ^cDetermined by 300 MHz ^1H NMR. ^dDetermined by GC analysis of the trimethylsilylated adducts.³

In summary, the combination of Ph_3P and $\text{Sc}(\text{OTf})_3$ was found to be a new, efficient reducing agent for the Reformatsky reaction. Further investigation on the extension of the present reaction and the mechanism is currently in progress.

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- The use of other Lewis acids, such as TMSOTf , GeCl_4 , SnCl_4 , Et_3AlCl , GaCl_3 , $\text{ZnCl}_2 \cdot \text{OEt}_2$, resulted in the formation of the corresponding adduct **5a** only in low yields (0-22%) under the condition A.
- General Procedure for the Reformatsky Reaction (Table 1, entry 5): To a suspension of $\text{Sc}(\text{OTf})_3$ (265 mg, 0.54 mmol), pre-dried at 150 °C for 6 h under reduced pressure, in CH_2Cl_2 (2 mL) were successively added dropwise **1a** (164 mg, 0.54 mmol) in CH_2Cl_2 (1 mL), Ph_3P (141 mg, 0.54 mmol) in CH_2Cl_2 (1 mL), and **4a** (48 mg, 0.45 mmol) in CH_2Cl_2 (1 mL) at room temperature. The resulting mixture was stirred for 15 h at the temperature. The reaction was quenched with water (5 mL), and the resultant mixture was extracted with CH_2Cl_2 (3×5 mL). The combined CH_2Cl_2 extracts were washed with brine (1×10 mL) and dried over MgSO_4 . The organic solution was concentrated under reduced pressure, and the residue was filtered through a silica gel short plug (hexane/AcOEt = 2/1) to remove $\text{Ph}_3\text{P}=\text{O}$. The filtrate was concentrated, and the crude product was purified by PTLC (SiO_2 , hexane/AcOEt = 5/1) to give **5a** (126 mg, 84%, syn:anti = 98:2). Syn-isomer: ^1H NMR (300 MHz, CDCl_3) δ 7.5-7.1 (m, 15H), 5.09 (d, 1H, $J = 4.4$ Hz), 3.82 (bs, 1H), 2.84 (dq, 1H, $J = 4.4$ and 7.0 Hz), 1.28 (d, 3H, $J = 7.0$ Hz); IR (neat) 3440, 1650, 1600, 1500 cm^{-1} . Anti-isomer: ^1H NMR (300 MHz, CDCl_3) δ 7.5-6.7 (m, 15H), 4.79 (d, 1H, $J = 8.4$ Hz), 4.71 (dd, 1H, $J = 4.3$ and 8.4 Hz), 2.85 (dq, 1H, $J = 4.3$ and 7.0 Hz), 1.37 (d, 3H, $J = 7.0$ Hz); IR (neat) 3430, 1645, 1595, 1495 cm^{-1} . The diastereomer ratio was determined on the basis of the ^1H NMR integration ratio of the CHOH regions. The relative configuration of syn- and anti-isomers was determined on the basis of their ^1H NMR chemical shifts of the CHOH protons in comparison with the values of analogous amides in the literature.⁶
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