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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 Ph₃P/Sc(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 Ph₃P/Sc(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 Ph3P and GeCl4, 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 Ph3P/GeCl4 combination would be attributed to the activation of the carbon-halogen bond in 1 upon coordination of GeCl4 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 Ph3P/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 Ph3P/Sc(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 Ph₃P/Lewis acid combinations (Table 1, entries 1-5). Of the Lewis acids examined, Sc(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 Ph₃P/Sc(OTf)₃ combination (entries 5-9).⁵ The reaction of 1a with *n*PrCHO (4b) in the presence of the Ph₃P/Sc(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 Ph₃P/Sc(OTf)₃ combination (entry 7). Although α -bromo ester 1c was not a good Reformatsky donor (entry 8), α -bromo imide 1d was readily reduced with the Ph₃P/Sc(OTf)₃ combination to give the corresponding β -hydroxy imide 5e in good yield with moderate *anti*-selectivity (entry 9).

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\downarrow Ph ₃ P, Lewis acid \downarrow								
		γ χ + num 4	0	CH ₂ Cl ₂ , r	t Rr	Ť	X	
1 5								
Entry	Lewis acid	1 (X =)	4 (R =)	Condition ^a	Reaction time	5	Yield ^b (%)	syn : anti ^c
1	BF ₃ •OEt	NPh ₂ (1a)	Ph (4a)	Α	48 h	5a	82	95 : 5
2	TiCl ₄	1a	4a	Α	15 min	5a	92	76 : 24
3	Yb(OTf) ₃	1a	4a	Α	15 h	5a	83	83:17
4	Sc(OTf)3	1a	4 a	Α	15 min	5a	93	98:2
5	Sc(OTf)3	1a	4a	В	15 h	5a	84	98 : 2
6	Sc(OTf)3		<i>n</i> Pr (4b)	В	24 h	5b	71	97 : 3 ^d
7	Sc(OTf)3	N(1b)	4 a	В	24 h	5c	0	
8	Sc(OTf)3	$O(CH_2)_3Ph(1c)$	4a	в	24 h	5d	9	35 : 65
9	Sc(OTf) ₃	N (1d)	4 a	В	24 h	5e	62	11 : 89

 Table 1. The Reformatsky Reaction of α-Bromo Carboxylic Acid Derivatives 1 with Aldehydes 4 in the Presence of the Ph₃P/Lewis Acid Combination

^aA; 4:1:Ph₃P:Lewis acid = 1:2:2:2. B; 4:1:Ph₃P: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 Ph₃P and $Sc(OTf)_3$ 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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- 4. The use of other Lewis acids, such as TMSOTF, GeCl4, SnCl4, Et3AlCl, GaCl3, ZnCl2•OEt2, resulted in the formation of the corresponding adduct **5a** only in low yields (0-22%) under the condition A.
- 5. General Procedure for the Reformatsky Reaction (Table 1, entry 5): To a suspension of Sc(OTf)3 (265 mg, 0.54 mmol), predried at 150 °C for 6 h under reduced pressure, in CH₂Cl₂ (2 mL) were successively added dropwise **1a** (164 mg, 0.54 mmol) in CH₂Cl₂ (1 mL), Ph₃P (141 mg, 0.54 mmol) in CH₂Cl₂ (2 mL), and **4a** (48 mg, 0.45 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (3 × 5 mL). The combined CH₂Cl₂ extracts were washed with brine (1 × 10 mL) and dried over MgSO₄. 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 Ph₃P=O. The filtrate was concentrated, and the crude product was purified by PTLC (SiO₂, hexane/AcOEt = 5/1) to give **5a** (126 mg, 84%, *syn:anti* = 98:2). *Syn*-isomer: ¹H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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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