

Triphenylphosphine/Germanium(IV) Chloride Combination: A New Agent for the Reduction of α -Bromo Carboxylic Acid Derivatives

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Abstract: The $\text{Ph}_3\text{P}/\text{GeCl}_4$ combination was found to be effective for the reduction of various α -bromo carboxylic acid derivatives. When α -bromo carboxylic acid derivatives were treated with $\text{Ph}_3\text{P}/\text{GeCl}_4$, the corresponding dehalogenated products were obtained in good to excellent yields. Moreover, selected carboxylic acid derivatives were dehalogenated even when a catalytic amount (0.2 equiv) of GeCl_4 was employed in the presence of water (1.0 equiv). The present reduction was also applied to the selective half-reduction of an α,α -dibromo- β -lactam.

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Numerous procedures have been reported for the reductive removal of a halogeno substituent adjacent to a carbonyl group; various reducing agents, such as metals, low-valent metal species, and so on, have been used for the reduction of α -halo carbonyl compounds.¹ Although successful results were obtained in certain reactions, there are still some limitations to the methodology: (1) Low chemoselectivity when strong reducing agents are employed, (2) strict anhydrous conditions, and (3) low reactivity toward α -halo carboxylic acid derivatives although a few reducing agents² were used for their reduction.

Of a number of reducing agents, we paid particular attention to Ph_3P in view of its easy of handling and high solubility in common organic solvents. Although it has been reported^{1b,3} that some phosphines can reduce α -halo carbonyl compounds, their reducing ability is, in general, not so high so that the reduction has to be carried out under drastic conditions for α -halo carboxylic acid derivatives.^{3b-d} These facts prompted us to develop a new reducing agent on the basis of the consideration that the activation of the carbon-halogen bond in α -halo carbonyl compounds upon coordination of a Lewis acid to their carbonyl oxygen would compensate the rather low reducing ability of Ph_3P . Herein, we wish to describe a successful transformation of various α -bromo carboxylic acid derivatives into the parent carbonyl compounds with $\text{Ph}_3\text{P}/\text{GeCl}_4$.

First, we chose the reduction of α -bromo amide **1a**, which is difficult to reduce with Ph_3P alone,⁴ as a model reaction and examined the effect of Lewis acids (Table 1). The reactions were carried out in the presence of water as a protic species, because it is known that debromination of α -bromo ketones with Ph_3P occurs more rapidly in the presence of a protic species than it does in the absence of it.^{3e}

As can be seen from Table 1, the reaction rate highly depended upon the Lewis acid used. When 2.0 equiv of a Lewis acid was used (entries 1–7), the reaction proceeded smoothly. Among the Lewis acids examined, TMSOTf and GeCl_4 gave satisfactory results (entries 1 and 2), while the other Lewis acids required longer reaction time in order to complete the reaction (entries 3–7). Interestingly, the amount of a Lewis acid could be reduced to 0.2 equiv (entries 8–12); GeCl_4 effectively catalyzed the present reduction (entry 9).

Table 1. Reduction of α -Bromo Amide **1a** with Ph₃P/Lewis Acid^a

CC(Br)C(=O)Nc1ccccc1
 $\xrightarrow[\text{THF, rt}]{\text{Ph}_3\text{P, Lewis Acid, H}_2\text{O}}$
CC(=O)Nc1ccccc1

1a **2a**

entry	Lewis acid (equiv)	reaction time (h)	yield ^b (%)
1	TMSOTf (2.0)	0.5	94 (0)
2	GeCl ₄ (2.0)	0.5	96 (0)
3	SnCl ₄ (2.0)	4	94 (0)
4	BF ₃ •OEt ₂ (2.0)	24	96 (3)
5	ZnCl ₂ (2.0)	24	94 (0)
6 ^c	TiCl ₄ (2.0)	5	92 (0)
7	Sc(OTf) ₃ (2.0)	8	96 (0)
8	TMSOTf (0.2)	2	88 (4)
9	GeCl ₄ (0.2)	2	95 (0)
10	SnCl ₄ (0.2)	6	90 (3)
11 ^c	TiCl ₄ (0.2)	6	92 (0)
12	Sc(OTf) ₃ (0.2)	6	60 (38)

^aMolar ratio; **1a**:Ph₃P:H₂O = 1:2:1. ^bIsolated yields. The values in parenthesis represent recovery of **1a**. ^cThe reaction was carried out in CH₂Cl₂.

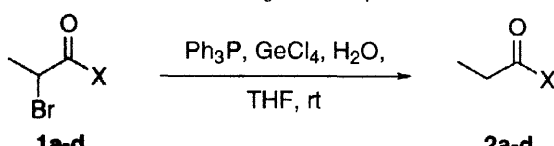
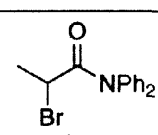
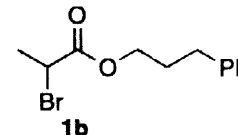
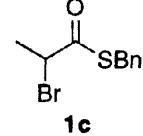
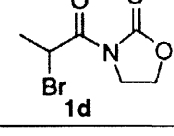
Under the optimized conditions (Table 1, entry 9), the reduction of various α -bromo carboxylic acid derivatives with the Ph₃P/GeCl₄ combination was carried out.⁵ The results are summarized in Table 2. In contrast to the case of α -bromo amide **1a**, the reduction of α -bromo ester **1b** did not complete at room temperature (**2b**: 52%; **1b**: 36%); in order to realize an acceptable yield, the reaction was carried out under reflux (entry 2). Although the reduction of α -bromo thioester **1c** required prolonged reaction time, **2c** was obtained in excellent yield (entry 3). α -Bromo imide **1d** was readily reduced with the Ph₃P/GeCl₄ combination to give the corresponding imide **2d** in high yield under the catalytic conditions (entry 4). In all cases, the dehalogenated product could be easily isolated from the mixture with unreacted Ph₃P and Ph₃P=O by chromatography.

We next applied the present Ph₃P/GeCl₄ combination to the selective half-reduction of α,α -dibromo- β -lactam **3**⁶ (Scheme 1). Of the reducing agents, *n*Bu₃SnH has been used for the reaction so far.⁷ Considering the toxicity of the organotin compound, the development of a new reducing agent in place of it is desirable.

Under the catalytic conditions (0.2 equiv of GeCl₄), α -bromo- β -lactam **4**⁸ was obtained in 45 % yield. The yield was highly improved, while maintaining high diastereoselectivity, when 2.0 equiv of GeCl₄ was employed. Thus, the selective half-reduction proceeded completely, and **4** was obtained in good yield with high diastereoselectivity (77% yield, *cis:trans* = 93:7).

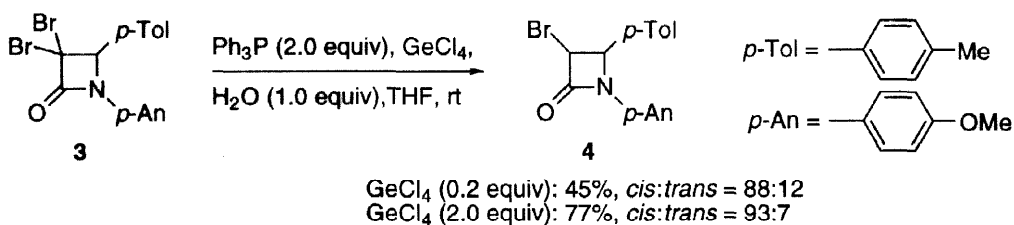
In summary, we developed a new reducing agent, the combination of Ph₃P and GeCl₄. This combination was applicable for the reduction of various α -bromo carboxylic acid derivatives under mild

Table 2. Reduction of α -Bromo Carboxylic Acid Derivatives **1a-d** with $\text{Ph}_3\text{P}/\text{GeCl}_4^a$

			
entry	1	reaction time (h)	yield ^b (%)
1	 1a	2	95
2	 1b	24 ^c	96
3	 1c	48	96
4	 1d	6	90

^aMolar ratio; $1:\text{PPh}_3:\text{GeCl}_4:\text{H}_2\text{O} = 1:2:0.2:1$. ^bIsolated yields. ^cThe reaction was carried out under reflux.

Scheme 1



conditions. In the present reaction, the formation of an intermediary germanium(IV) enolate is plausible. Development of a synthetically useful carbon-carbon formation reaction of the germanium(IV) enolate with carbonyl compounds (the Reformatsky reaction) based on the present $\text{Ph}_3\text{P}/\text{GeCl}_4$ system is in progress.

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 4. When the reaction was carried out in the absence of a Lewis acid (**1a**, Ph₃P, and H₂O in THF at room temperature), no **2a** was detected and **1a** was recovered in 96%.
 5. A typical procedure for the reduction of α -bromo carboxylic acid derivatives: To a solution of **1a** (76 mg, 0.25 mmol) and Ph₃P (131 mg, 0.50 mmol) in THF (1.5 mL) was added in succession H₂O (4.5 μ L, 0.25 mmol) and a solution of GeCl₄ (11 mg, 0.05 mmol) in THF (1 mL) at room temperature. After being stirred for 0.5 h at this temperature, a phosphate buffer (5 mL) was added to the solution, and volatiles were evaporated. The resultant mixture was extracted with CH₂Cl₂ (3 \times 10 mL). The combined CH₂Cl₂ extracts were washed with brine (2 \times 20 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by PTLC (hexane/AcOEt = 5/1) to give **2a** (53 mg, 95%).
 6. This compound was prepared from trimethylsilyl tribromoacetate and *N*-(4-methylbenzylidene)-4-methoxyaniline by a modification of the literature procedure⁷ for an analogous β -lactam: 24% yield; mp 128-130 °C (hexane/AcOEt); ¹H NMR (270 MHz, CDCl₃) δ 7.3-6.8 (m, 8H), 5.55 (s, 1H), 3.76 (s, 3H), 2.38 (s, 3H); IR (KBr) 1760, 1520, 1385, 1260, 810 cm⁻¹.
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 8. *cis*-**4**: mp 153-155 °C (hexane/AcOEt); ¹H NMR (270 MHz, CDCl₃) δ 7.3-6.8 (m, 8H), 5.35 (d, *J* = 5.3 Hz, 1H), 5.33 (d, *J* = 5.3 Hz, 1H), 3.76 (s, 3H), 2.38 (s, 3H); IR (KBr) 1760, 1520, 1390, 1255, 830 cm⁻¹. *trans*-**4**: mp 94-96 °C (MeOH); ¹H NMR (270 MHz, CDCl₃) δ 7.3-6.8 (m, 8H), 5.00 (d, *J* = 1.7 Hz, 1H), 4.58 (d, *J* = 1.7 Hz, 1H), 3.72 (s, 3H), 2.33 (s, 3H); IR (KBr) 1760, 1520, 1385, 1250, 830 cm⁻¹. The relative configurations of both *cis*- and *trans*-**4** were determined on the basis of their ¹H NMR coupling constants (*cis*-**4** (*J* = 5.3 Hz) and *trans*-**4** (*J* = 1.7 Hz), respectively) by comparison with the values of analogous β -lactams in the literature.^{7,9}
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