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

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Abstract: The $Ph_3P/GeCl_4$ 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 $Ph_3P/GeCl_4$, 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.

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 agents[2] 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 $Ph_3P/GeCl_4$.

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).

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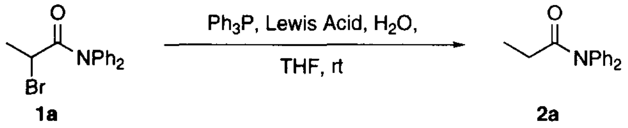
Table 1. Reduction of α-Bromo Amide **1a** with Ph_3P/Lewis Acid[a]



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)

[a]Molar ratio; **1a**:Ph_3P:H_2O = 1:2:1. [b]Isolated yields. The values in parenthesis represent recovery of **1a**. [c]The reaction was carried out in CH_2Cl_2.

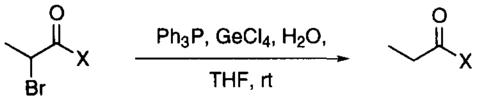
Under the optimized conditions (Table 1, entry 9), the reduction of various α-bromo carboxylic acid derivatives with the Ph_3P/$GeCl_4$ combination was carried out.[5] The results are summarized in Table 2. In contrast to the case of α-bromo amide **1a**, the reduction of α-bromo ester **1b** did not 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 Ph_3P/$GeCl_4$ 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 Ph_3P and Ph_3P=O by chromatography.

We next applied the present Ph_3P/$GeCl_4$ combination to the selective half-reduction of α,α-dibromo-β-lactam **3**[6] (Scheme 1). Of the reducing agents, *n*Bu_3SnH 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.

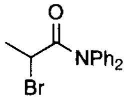
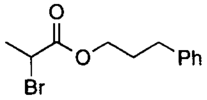
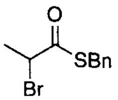
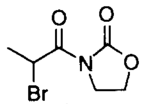
Under the catalytic conditions (0.2 equiv of $GeCl_4$), α-bromo-β-lactam **4**[8] was obtained in 45 % yield. The yield was highly improved, while maintaining high diastereoselectivity, when 2.0 equiv of $GeCl_4$ was employed. Thus, the selective half-reduction proceeded completely, and **4** was obtained in good yield with high diastereoselectivity (77% yield, *cis*:*trans* = 93:7).

In summary, we developed a new reducing agent, the combination of Ph_3P and $GeCl_4$. 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 $Ph_3P/GeCl_4$[a]

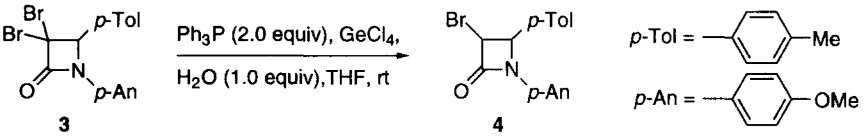


1a-d **2a-d**

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

[a] Molar ratio; $1{:}PPh_3{:}GeCl_4{:}H_2O$ = 1:2:0.2:1. [b] Isolated yields. [c] The reaction was carried out under reflux.

Scheme 1



$GeCl_4$ (0.2 equiv): 45%, *cis*:*trans* = 88:12
$GeCl_4$ (2.0 equiv): 77%, *cis*:*trans* = 93:7

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 $Ph_3P/GeCl_4$ system is in progress.

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4. When the reaction was carried out in the absence of a Lewis acid (**1a**, Ph_3P, and H_2O 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 Ph_3P (131 mg, 0.50 mmol) in THF (1.5 mL) was added in succession H_2O (4.5 μL, 0.25 mmol) and a solution of $GeCl_4$ (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 CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 extracts were washed with brine (2 × 20 mL), dried over $MgSO_4$, 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 procedure[7] for an analogous β-lactam: 24% yield; mp 128-130 °C (hexane/AcOEt); ^{1}H NMR (270 MHz, $CDCl_3$) 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); ^{1}H NMR (270 MHz, $CDCl_3$) 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); ^{1}H NMR (270 MHz, $CDCl_3$) 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 ^{1}H 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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