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Hydrosilane-Promoted Facile Deprotection of *tert*-Butyl Groups in Esters, Ethers, Carbonates, and Carbamates

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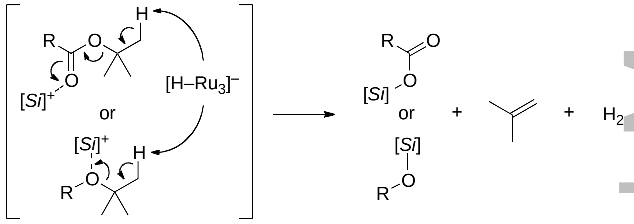
Abstract. Combination of $PdCl_2$ with 1,1,3,3-tetramethyldisiloxane in the presence of activated carbon was found to be an effective catalyst system for the cleavage reaction of C–O bond of O–*t*-Bu moieties. The present catalytic reaction offers a practical method for the deprotection of *tert*-butyl esters, *tert*-butyl ethers, *O*–Boc, and *N*–Boc derivatives under mild conditions. The addition of activated carbon in the reaction mixture was proved to be crucial for not only sustaining the catalytic activity but also trapping the palladium species after the reaction.

Keywords: activated carbon; deprotection; hydrosilane; palladium; *tert*-butyl group

The development of novel transformation method of organic molecules, especially by virtue of catalysis, is one of the most challenging and formidable endeavours in organic synthesis. In addition, facile removal of the metallic species from the product is quite important for the design of the metal-catalyzed reaction systems.[1]

The *tert*-butyl substituent (*t*-Bu), which possesses prominent stability under a variety of reaction conditions, is widely recognized as one of the most powerful protecting groups for alcohols and carboxylic acids.[2] However, the harsh conditions are commonly required to cleave the C–O bond of *tert*-butoxy moiety (deprotection) by using strong Brønsted- or Lewis acids.[2,3] In the past decades, Jaime-Figueroa *et al*. developed a new deprotection method of *tert*-butyl esters and carbonates using fluorinated alcohols as a solvent at 100 °C.[4] Bartoli and Sambri also developed a simple procedure for the deprotection of *tert*-butyl esters and ethers: the reaction proceeded smoothly in CH_3CN at 40–70 °C by using stoichimetric amounts of $CeCl_3$ and NaI.[5]

In 2010, Nagashima and co-workers firstly reported a catalytic method for C–O bond cleavage of *tert*-butoxy moiety (O–*t*-Bu) using $(\mu^3,\eta^2,\eta^3,\eta^5$-acenaphthylene$)Ru_3(CO)_7$ complex and Me_2PhSiH.[6] In this reaction, heterolytic cleavage of the Si–H bond of hydrosilane is induced by the triruthenium cluster to form an ionic intermediates, $[Si]^+$•••$[Ru_3–H]^–$, then the Lewis acidic $[Si]^+$ species interacts with carbonyl- or ether oxygen atom followed by deprotonation of the *t*-Bu group by the $[Ru_3–H]^–$ species resulting in the formation of silyl ester, isobutene, and hydrogen gas (Scheme 1).[7] This catalytic system is attractive because the procedure is simple and reaction proceeds under neutral conditions, but the preparation of triruthenium cluster complex is unavoidable.[8] In addition, this system is not compatible towards a compound having other ester groups in a molecule because they are reduced under reaction conditions to afford the corresponding silyl ethers.

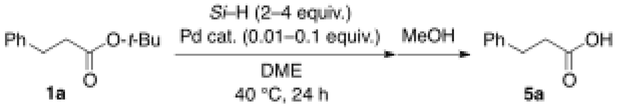


Scheme 1. Reaction mechanisms for the silane-induced deprotection of *tert*-butyl esters and ethers by using triruthenium cluster as a catalyst.

We have recently reported the catalytic silane-reduction of carbonyl compounds using commercially available palladium on carbon (Pd/C) as a catalyst.[9] During the course of these studies, we became aware of the gas evolution and formation of silyl esters and isobutene as a by-product in the Pd-catalyzed reaction of *tert*-butyl esters with hydrosilanes.[10] Similar to the triruthenium cluster system, the present Pd-hydrosilane system also initiates the ring-opening oligomerization of THF[7] (details see, Supporting Information). Our efforts to achieve the selective conversion of *tert*-butyl esters to the corresponding carboxylic acids resulting the discovery that the combination of 1,1,3,3-tetramethyldisiloxane (TMDS)[11] and $PdCl_2$ in the presence of activated carbon provides an efficient deprotection process of *tert*-butyl groups in not only esters but also ethers, carbonates, and carbamates under mild conditions.

Table 1 summarizes the results when *tert*-butyl 3-phenylpropionate (**1a**) was treated with several palladium compounds[12] and hydrosilanes in dimethoxyethane (DME) at 40 °C for 24 h followed by workup with methanol. Although the chemical yield of the reaction of **1a** and Me_2PhSiH using Pd/C as a catalyst was quite low, the reaction with palladium salts or complexes proceeded smoothly in the presence of activated carbon (AC) to give 3-phenylpropionic acid (**5a**) in good to high yields (Entries 1 vs. 2–5). The presence of AC in the reaction mixture was crucial for the present deprotection: when the reaction was carried out without addition of AC, only trace amount of **5a** was obtained along with the formation of palladium residues as black precipitates (Entry 6). As shown in Entries 7–10, TMDS and alkoxysilanes were also effective for the present reaction; Me_2PhSiH and TMDS gave the best results among them by the reaction using 1 mol% of $PdCl_2$ in the presence of AC (details, see Supporting Information). It is noteworthy that the present reaction was highly dependent on the solvent used: no reaction took place in toluene and hexane, however, the C–O bond cleavage reaction smoothly proceeded in DME and dichloromethane (see, Supporting Information).

Table 1. Catalytic deprotection of *t*-Bu group in **1a**.[a]

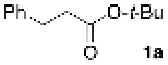
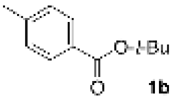
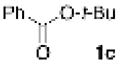
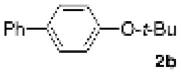
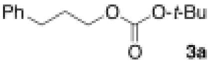
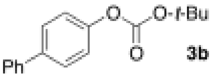
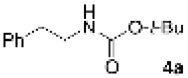
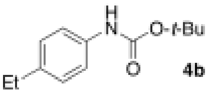
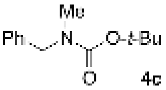
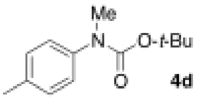


Entry	Catalyst	*Si*–H	Yield [%][b]
1	Pd/C	Me_2PhSiH	10
2	$Pd(OAc)_2$–AC	Me_2PhSiH	82
3	$Pd(dba)_2(H_2O)$–AC	Me_2PhSiH	>99
4	$Pd(acac)_2$–AC	Me_2PhSiH	>99
5	$PdCl_2$–AC	Me_2PhSiH	>99
6	$PdCl_2$	Me_2PhSiH	<1
7[c]	$PdCl_2$–AC	Me_2PhSiH	>99
8[c,d]	$PdCl_2$–AC	TMDS	>99
9[c]	$PdCl_2$–AC	$(EtO)Me_2SiH$	65
10[c]	$PdCl_2$–AC	$(EtO)_2MeSiH$	39

[a] All reactions were carried out by using **1a** (0.5 mmol), hydrosilane (2 mmol), catalyst (0.1 equivalent to **1a**), activated carbon (AC: 100 mg) in DME (0.5 mL) at 40 °C for 24 h. [b] Determined by ^1H NMR analysis of the crude material. [c] **1a** (1 mmol), $PdCl_2$ (0.01 mmol), AC (50 mg), and DME (2 mL) was used. [d] TMDS (1 mmol) was used.

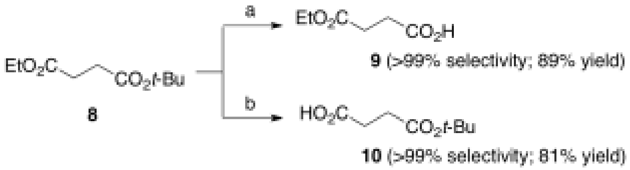
The combination of TMDS and a catalytic amount of $PdCl_2$ (1–2 mol%) in the presence of AC also induced deprotection of other *tert*-butyl esters **1** as well as *tert*-butyl ethers **2**, *O*-Boc and *N*-Boc derivatives **3** and **4** in DME at 40 °C (Table 2). Conversion of both aliphatic and aromatic *tert*-butyl esters **1** to the corresponding carboxylic acids **5** was accomplished within 6 h (Entries 1–3). Similarly, deprotection of *O*-Boc derivatives **3a** and **3b** proceeded smoothly under the same conditions (Entries 6 and 7). Comparing with the *tert*-butyl esters and *O*-Boc derivatives, the reaction of *tert*-butyl ethers **2a** and **2b** required prolonged reaction time (20–24 h) to afford the desired alcohols **6a** and **6b** in high yields (Entries 4 and 5). Although the reactivity of the *N*-Boc derivatives **4a**, **4c** and **4d** were relatively lower than that of the others, using 2 mol% of $PdCl_2$ led to satisfactory yields (Entries 8, 10, and 11). Finally, the present procedure is adaptable to a gram-scale reaction. For example, the reaction of 1.782 g (10 mmol) of **1c** with TMDS (10 mmol) in the presence of $PdCl_2$ (0.5 mol% to **1c**) at 40 °C for 24 h afforded 1.118 g (92%) of **5c**.

Table 2. Deprotection of *tert*-butyl esters, *tert*-butyl ethers, *O*-Boc, and *N*-Boc derivatives.[a]

Entry	Substrate	Time [h]	Product	Yield [%][b]
1	 **1a**	4	**5a**	>99 (97)
2	 **1b**	6	**5b**	>99 (95)
3	 **1c**	6	**5c**	>99 (97)
4	 **2a**	24	**6a**	>99 (86)
5	 **2b**	20	**6b**	>99 (98)
6	 **3a**	6	**6a**	>99 (84)
7	 **3b**	6	**6b**	>99 (99)
8[c]	 **4a**	24	**7a**	>99 (80)[d]
9	 **4b**	6	**7b**	>99 (90)
10[c]	 **4c**	24	**7c**	>99 (72)[d]
11[c]	 **4d**	24	**7d**	>99 (92)

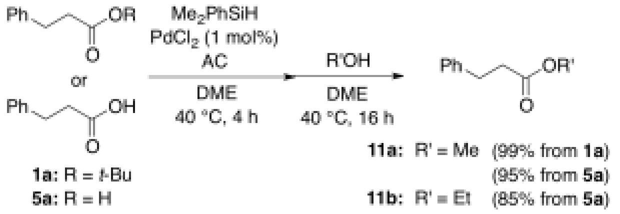
[a] All reactions were carried out by using substrate (1 mmol), TMDS (1 mmol), $PdCl_2$ (0.01 mmol), AC (50 mg) in DME (2 mL) at 40 °C followed by workup with methanol or n-Bu_4NF. [b] Determined by ^1H NMR analysis of the crude material. The yield in parentheses was the isolated yield. [c] 0.5 mmol of substrate was used. [d] The product was isolated as the corresponding acetamide.

Hydrolysis of esters is generally performed by treatment with strong bases, but *tert*-butyl esters are not hydrolyzed under these conditions.[2] One aspect of the present hydrosilane-promoted reaction system is the preparation of half esters from mixed esters by the selective deprotection of *t*-Bu group. For example, *tert*-butyl ethyl succinate (**8**) was selectively converted to mono-*tert*-butyl succinate (**10**) in 81% isolated yield by treatment with NaOH in methanol. In sharp contrast, the reaction of **8** with TMDS (1 equiv. to **8**) in the presence of $PdCl_2$ (1 mol%) and activated carbon in DME at 40 °C for 6 h afforded monoethyl succinate (**9**) in 89% isolated yield as a single product (Scheme 2).[13]



Scheme 2. Selective conversion of *tert*-butyl ethyl succinate (**8**) to monoethyl succinate (**9**). Conditions: a) $PdCl_2$/TMDS/DME/40 °C; b) NaOH/MeOH/25 °C

Another interesting application of the present system is the preparation of esters from *t*-butyl esters or carboxylic acids (Scheme 3). The reaction of *t*-butyl ester **1a** with Me_2PhSiH followed by the addition of MeOH gave methyl ester **11a** in quantitative yield.[14] Similarly, dehydrogenative silylation of carboxylic acid **5a** with Me_2PhSiH gave the corresponding silyl ester, which then was treated with alcohols to afford esters **11** in good yields. The source of alkyl groups of **11** was determined as alcohols by the formation of $PhCH_2CH_2CO_2\mathit{CD_3}$ from CD_3OD (see, Supporting Information).



Scheme 3. Esterification or transesterification of **5a** and **1a**.

When developing a practical synthetic process using metal catalyst, it is important for removal of metal residues from the reactions, especially in pharmaceutical synthesis.[15] Therefore, we checked the amounts of residual palladium species in the crude material obtained by the reaction of **1a** as described in Table 2, Entry 1 followed by workup process. Microwave plasma-atomic emission spectrometer (MP-AES) analysis revealed that only 0.121 μg of Pd exists in the crude materials: this corresponds to 0.01% of the Pd species used (calculated amounts of charged Pd was 1.08 mg). The remaining Pd species was trapped on the recovered activated carbon (*ca*. 1 mg, 92% of the Pd species used). *It is noteworthy that the palladium on activated carbon thus obtained (Pd/AC) showed catalytic activity towards silane-induced deprotection of tert-butyl groups.* After the reaction of **1a** as described in Table 2, Entry 1 (at 40 °C for 4 h), the carbon material was recovered by decantation and subjected to another catalytic run (Table 3). Although the catalytic activity of the recovered Pd/AC gradually decreased, the catalyst recovery/reuse cycle was successfully repeated three times in almost quantitative yields by extension of the reaction time to 24 h. We also checked the transmission electron microscopy (TEM) images of the recovered Pd/AC and found that there is only trace amount of Pd nanoparticles observed after the reaction as shown in Table 2, Entry 1 (Figure 1, left). In sharp contrast, many nano-sized particles were existed on the AC after four recycling experiment (Figure 1, right).

Table 3. Recycle experiments of recovered Pd/AC in the reaction of **1a**.[a)]

Run	Yield [%][b)]		
	4 h	10 h	24 h
1st	>99	–	–
2nd	99	–	–
3rd	49	89	>99
4th	20	–	60

[a)] All reactions were carried out by using **1a** (1 mmol), TMDS (1 mmol), recovered Pd/AC in DME (2 mL) at 40 °C followed by workup with methanol. [b)] Determined by ^1H NMR analysis of the crude material.

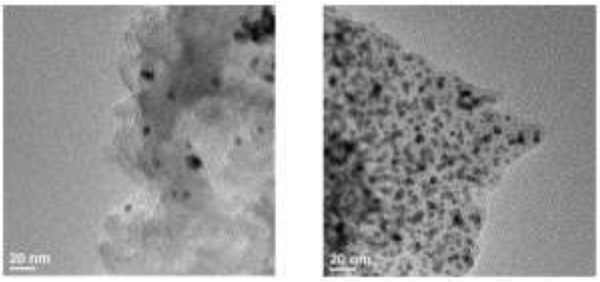
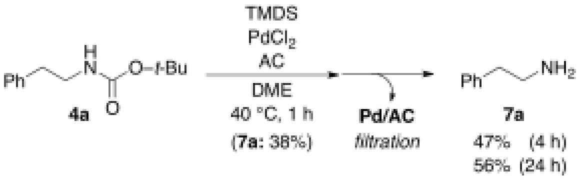


Figure 1. TEM images of the recovered Pd/AC: after the reaction as shown in Table 1, Entry 1 (left), and after four recycling experiment (right).

In the Pd/C-catalyzed Heck reaction, it is well known that the soluble Pd species, which is generated by the reaction of Pd/C with aryl halides, is the catalytically active species.[16] Therefore, we next examined the amounts of palladium species in the solution obtained by the reaction of *N*-Boc compound **4a** as shown in Table 2, Entry 8. After the reaction at 40 °C for 1 h, the solid AC was removed by filtration with membrane filters (Durapore HV, 0.45 μm) to afford the brown solution, in which contained silane residue, unreacted TMDS, 38% of the product, 62% of **4a** remained, and 41.9 μg of Pd species (3.9% of charged Pd). In addition, the filtrate thus obtained was continuously stirred at 40 °C resulting in the further formation of the product **7a**: 47% for 4 h, and

56% for 24 h (Scheme 4). These results and the TEM images suggested that the catalytically active species of the present reaction is the small-sized, soluble Pd clusters, which are initially formed by the reaction of $PdCl_2$ with TMDS. In the absence of carbon materials, these Pd clusters are in contact with each other to form black precipitates. While in the presence of activated carbon, such palladium species is immobilized on the AC and regenerates by the reaction with TMDS.[17] During such reversible immobilization-regeneration step, the Pd species on the AC was gradually aggregated resulting in the formation of large-size of palladium particles.



Scheme 4. Deprotection of **4a** after removal of the solid carbon materials.

In conclusion, we have developed a simple process for the Pd-catalyzed cleavage reaction of C–O bond of O–*t*-Bu groups leading to the facile deprotection of *tert*-butyl esters, *tert*-butyl ethers, *O*-Boc, and *N*-Boc derivatives under mild conditions. The addition of activated carbon was found to be crucial for the present silane-induced deprotection. It is of practical importance that inexpensive $PdCl_2$ and 1,1,3,3-tetramethyldisiloxane (TMDS) can be used, and the present procedure can be scaled up to a gram-quantity reaction. Further mechanistic studies on the catalytically active species and detailed reaction pathway are now under investigation.

Experimental Section

Deprotection of 1c (10 mmol Scale). To a suspension of AC (250 mg), **1c** (1.782 g, 10 mmol), and $PdCl_2$ (8.9 mg, 0.5 mol%) in DME (0.5 mL) was added a 0.83 mol•L^{-1} solution of TMDS in DME (12 mL, 10 mmol) at 25 °C. After it was stirred at 40 ºC for 24 h, the reaction was quenched by the addition of MeOH (3 mL). Following stirring at 25 °C for 30 min, the reaction mixture was filtered and the filtrate was concentrated. Purification by silica gel chromatography gave **5c** in 92% yield (1.118 g).

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References

[1] a) C. E. Garrett, K. Prasad. *Adv. Synth. Catal.* **2004**, *346*, 889-900; b) C. J. Welch, J. Albaneze-Walker, W. R. Leonard, M. Biba, J. DaSilva, D. Henderson, B. Laing, D. J. Mathre, S. Spencer, X. Bu, T. Wang, *Org. Process Res. Dev*. **2005**, *9*, 198-205; c) N. Galaffu, S. P. Man, R. D. Wilkes, J. R. H. Wilson, *Org. Process Res. Dev*. **2007**, *11*, 406-413.

[2] P. G. M. Wuts in *Greene's Protective Groups in Organic Synthesis, 5th ed*., John Wiley & Sons, New Jersey, **2014**, pp. 97-99, 750-758.

[3] L. Sambri, G. Bartoli, G. Bencivenni, R. Dalpozzo, *Curr. Org. Synth*. **2012**, *9*, 137-148.

[4] a) J. Choy, S. Jaime-Figueroa, L. Jiang, P. Wagner, *Synth. Commun*. **2008**, *38*, 3840-3853; b) J. Choy, S. Jaime-Figueroa, T. Lara-Jaime, *Tetrahedron Lett*. **2010**, *51*, 2244-2246.

[5] a) E. Marcantoni, M. Massaccesi, E. Torregiani, G. Bartoli, M. Bosco, L. Sambri, *J. Org. Chem.* **2001**, *66*, 4430-4432; b) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, E. Marcantoni, P. Melchiorre, L. Sambri, *Adv. Synth. Catal*. **2006**, *348*, 905-910.

[6] S. Hanada, A. Yuasa, H. Kuroiwa, Y. Motoyama, H. Nagashima, *Eur. J. Org. Chem*. **2010**, 1021-1025.

[7] Nagashima *et al*. reported that the formed ionic intermediates, $[Si]^{+}$•••$[Ru_3–H]^{–}$, initiates cationic ring-opening polymerization of cyclic ethers and addition polymerization of vinyl ethers, see a) H. Nagashima, A. Suzuki, T. Iura, K. Ryu, K. Matsubara, *Organometallics*, **2000**, *19*, 3579-3590; b) H. Nagashima, C. Itonaga, J. Yasuhara, Y. Motoyama, K. Matsubara, *Organometallics*, **2004**, *23*, 5779-5786.

[8] Y. Motoyama, C. Itonaga, T. Ishida, M. Takasaki, H. Nagashima, *Org. Synth*. **2005**, *82*, 188-195.

[9] a) S. Hosokawa, K. Teramoto, Y. Motoyama, *ChemistrySelect* **2016**, *1*, 2594-2602; b) S. Hosokawa, M. Toya, A. Noda, M. Morita, T. Ogawa, Y. Motoyama, *ChemistrySelect* **2018**, *3*, 2958-2961.

[10] ^{1}H NMR ($CDCl_3$) of isobutene in the reaction mixture: δ = 1.72 (bs, 6H, CH_3) and 4.65 (bs, 2H, *vinylic proton*).

[11] Review: J. Pesti, G. L. Larson, *Org. Process Res. Dev*. **2016**, *20*, 1164-1181.

[12] For preliminary screening, we found some Ru, Rh, Ir, and Pt compounds show catalytic activity towards the deprotection reaction of **1a**, see Supporting Information.

[13] We also examined the reactions of some compounds having other functional groups and found that reduction of formyl-, keto-, amido-, imino-, and nitro groups proceeded smoothly, but methyl ether and nitrile groups were tolerant under the present conditions. Details see Supporting Information.

[14] Interestingly, the present Pd-catalyzed esterification and transesterification did not proceed with TMDS.

[15] a) Guideline for Elemental Impurities: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Pr

oducts/Guidelines/Quality/Q3D/Q3D_Step2b.pdf; b) Implementing the Guideline on the Specification Limits for Metal Residues of Metal Catalysts or Metal Reagents:http://www.dgra.de/media/pdf/studium/masterthesis/master_reichert_u.pdf.

[16] Review: a) A. M. Trzeciak, J. J. Ziólkowski, *Coord. Chem. Rev*. **2007**, *251*, 1281-1293. Representarive papers: b) F. Zhao, M. Shirai, M. Arai, *J. Mol. Cat. A: Chem*. **2000**, *154*, 39-44; c) F. Zhao, K. Murakami, M. Shirai, M. Arai, *J. Catal*. **2000**, *194*, 479-483; d) R. G. Heidenreich, J. G. E. Krauter, J. Pietsch, K. Köhler, *J. Mol. Catal. A: Chem*. **2002**, *182-183*, 499-509; e) F. Zhao, M. Arai, *React. Kinet. Catal. Lett.* **2004**, *81*, 281-289; f) K. Köhler, W. Kleist, S. S. Pröckl, *Inorg. Chem*. **2007**, *46*, 1876-1883.

[17] We previously reported that the catalytically active species in the Pd/C-catalyzed silane-reduction of carboxamides is the soluble palladium species leached out from the carbon support, see: ref. 9a.

COMMUNICATION

Hydrosilane-Promoted Facile Deprotection of *tert*-Butyl Groups in Esters, Ethers, Carbonates, and Carbamates

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