Note

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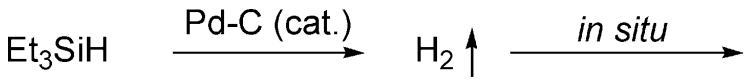

Reduction of multiple bonds, nitro groups, azides
benzyl /allyl deprotection, etc.

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JOC*Note*

Pd−C-Induced Catalytic Transfer Hydrogenation with Triethylsilane

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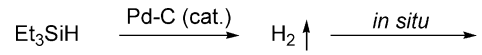

In situ generation of molecular hydrogen by addition of triethylsilane to palladium−charcoal catalyst results in rapid and efficient reduction of multiple bonds, azides, imines, and nitro groups, as well as benzyl group and allyl group deprotection under mild, neutral conditions.

The reduction of alkenes, alkynes, nitrates, etc. is often carried out by hydrogenation reactions using metal catalysts. Catalytic transfer of hydrogen (CTH) is a widely accepted alternative method that does not require the use of potentially dangerous hydrogen gas.[1] For this simple operation H_2 is replaced by a hydrogen donor such as 1,4-cyclohexadiene,[2] hydrazine,[3] formic acid,[4] ammonium formate,[5] phosphinic acid,[6] or sodium hypophosphite[7] with Pd−C as the catalyst. Though these methods are elegant, some transfer agents require high temperature, and some are not applicable to acid-sensitive or base-sensitive substrates. Following the lead of Fukuyama et al.,[8] we found that TES/Pd−C is a widely applicable, very convenient CTH reagent. The reactions are carried out at room temperature and are rapid, often complete in 10 min or less using excess TES and 10−20% Pd−C (by weight) in MeOH. The conditions are neutral, and thus acid- or base-sensitive substrates can be reduced without harm. In this communication, we present several examples of TES/Pd−C-mediated CTH of a wide variety of substrates.

Table 1 illustrates the utility of the reaction. Compounds **1**−**6** show that reduction of simple alkene, alkyne, and conjugate double and triple bonds occurs rapidly and in high yield. Mirza-Aghayan et al. demonstrated that treatment of 1-alkenes with 1 equiv of TES with Pd−C catalysis resulted in partial reduction and double bond migration.[9] However, with 2 equiv of the silane, only the alkane was observed. In keeping with this work, our results show that excess TES leads to complete reduction of unsaturated bonds.

The Fmoc group is stable to these conditions (compounds **5**, **9**, **15**, and **21**). This protecting group, highly used in peptide synthesis, is subject to hydrogenolysis using H_2 and Pd−C.[10]

Interestingly, substrates **7a** and **8a**, containing both benzylic alcohol functionality and multiple carbon−carbon bonds, were reduced completely to alkyl arenes. Benzyl esters and *N*-benzyloxycarbonyl (Z) groups are removed in 5−10 min (entries 9 and 10). Previous studies using TES and $PdCl_2$ or $Pd(OAc_2)$ required extended reaction times at elevated temperatures to cleave benzyl-based protecting groups in peptide applications.[11] Transprotection to a Boc-amino acid[12] was achieved by the TES/Pd−C-mediated hydrogenolysis of the Z group in **11a** in the presence of di-*tert*-butyl dicarbonate (**11b**). Cleavage of benzyl ethers requires longer reaction times than benzyl esters or the Z group (**12** and **13**). Aromatic benzyl ethers are removed more rapidly than aliphatic ones (compare **14** versus **12** and **13**). Azetidine-2-ones bearing 4-aryl substituents are susceptible to 1,4-ring cleavage reactions by hydrogenolysis.[13] As shown in **14**, the β-lactam ring is stable to TES/Pd−C, whereas the benzyl ether was cleaved.

Allylic protecting groups such as the allyl ester (All) for protection of carboxylic acids and the allyloxycarbonyl (Alloc) group for amine protection are widely used in synthetic organic chemistry and in peptide synthesis. These groups can be removed with catalytic palladium ($Pd(PPh_3)_4$ or $Pd(OAc)_2$) π-allyl methodology using hydride donors such as HCO_2H, Bu_3SnH, $NaBH_4$, $PhSiH_3$, and TES.[14] We were able to deprotect both All and Alloc groups using simple TES/Pd−C (**15** and **17**). For substrate **16a** simple reduction of the triple bond to the alkane was observed. We did not detect formation of allyl esters or cleavage of the presumed allyl ester intermediate. Alloc-to-Boc transprotection was also achieved by treating allyloxycarbamates with TES/Pd−C in the presence of di-*tert*-butyl dicarbonate (**18**).

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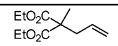
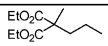
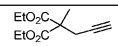
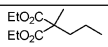
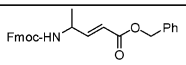
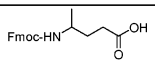
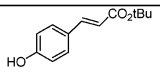
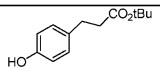
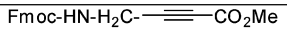
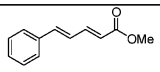
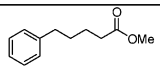
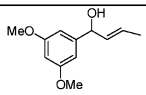
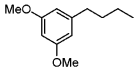
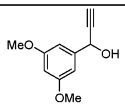
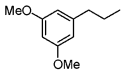
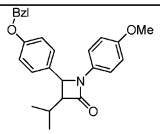
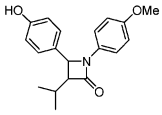
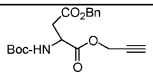
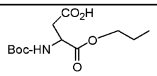
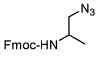
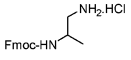
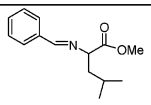
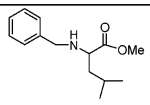
TABLE 1. Substrates and Products of TES/Pd−C-Mediated Catalytic Transfer Hydrogenation Reactions

Substrate		Product		%wt Pd-C	Time (min)	Yield[a] (%)
1a		**1b**		10	10	90
2a		**2b**		10	10	91
3a		**3b**		20	10	88
4a		**4b**		15	15	91
5a		**5b**	Fmoc-NH-$(CH_2)_3$-CO_2Me	15	5	94
6a		**6b**		15	10	93
7a		**7b**		10	5	90
8a		**8b**		10	5	91
9a	Fmoc-Leu-OBn	**9b**	Fmoc-Leu-OH	20	5	90
10a	Z-Tyr-OMe	**10b**	H-Tyr-OMe	20	10	quantative[b]
11a	Z-Val-OMe	**11b**	Boc-Val-OMe	20	50	88
12a	Boc-Ser(OBzl)-OMe	**12b**	Boc-Ser(OH)-OMe	20	60	91
13a	Boc-Thr(OBzl)-OMe	**13b**	Boc-Thr(OH)-OMe	20	72	90
14a		**14b**		20	20	92
15a	Fmoc-Asp(OMe)-OAllyl	**15b**	Fmoc-Asp(OMe)-OH	20	5	92
16a		**16b**		10	10	86
17a	Alloc-Leu-OMe	**17b**	H-Leu-OMe	20	5	quantative[b]
18a	Alloc-Leu-OMe	**18b**	Boc-Leu-OMe	20	30	88
19a	Methyl 3,4-dinitrobenzoate	**19b**	Methyl 3,4-diaminobenzoate	10	10	quantative[b]
20a	Methyl 4-nitrobutyrate	**20b**	NH_2-$(CH_2)_3$-CO_2Me	10	30	quantative[b]
21a		**21b**		20	5	quantative[b]
22a		**22b**		10	5	92

[a] Isolated yields after silica gel column chromatography. [b] Reactions were performed in 10:1 MeOH−$CHCl_3$. Products were isolated as HCl salts and titurated with hexane−ether.

Reduction of both aromatic and aliphatic nitro groups, imines, and azide moieties is also readily achieved using TES/Pd−C (**19**−**22**). Note that the benzylamine in **22a** was stable to the short reaction conditions.

Chemoselectivity can be achieved by altering the solvent. 4-Benzyloxybenzaldehyde, on treatment with TES/Pd−C in acetone, resulted in reduction of the carbonyl to a methyl group. In chloroform the reduction halted at the alcohol stage. In both cases the benzyloxy group remained untouched. However, using methanol as the solvent, all functional groups were reduced and *p*-hydroxy toluene was obtained.

The deprotection of benzyl carboxylates and carbamates, benzyl ethers, and reduction of multiple bond, nitro, azide, and imine groups suggests that Et_3SiH/Pd−C behaves as a hydrogenation reagent through in situ generation of H_2.[9] Indeed, effervescence was observed on adding TES to the Pd−C catalyst. On the other hand, it is likely that removal of allyl carboxylates and carbamates proceeds via palladium activation of the π-allyl system with triethylsilane as a hydride donor.

It should be noted that catalytic transfer hydrogenation using TES as a hydrogen donor has been used with other metal catalysts. For example, a combined metathesis and olefin hydrogenation using ruthenium Grubbs-type catalyst[15a] and dehalogenation of halides using $PdCl_2$ were recently reported.[15b,c] However, owing to the rapid reaction times and neutral conditions and simplicity of method, the combination of TES and Pd−C has great potential for use in all types of organic synthesis.

Experimental Section

General Procedure. To a stirred solution of substrate (1 mmol) and 10%Pd−C (10−20% by weight) in MeOH (2−3 mL) was added neat TES (10 mmol) dropwise from a pressure-equalizing dropping funnel under an argon-filled balloon. When the reaction was complete (TLC), the mixture was filtered through celite and the solvent was removed in vacuo. The product was chromatographically purified on a short silica gel column. Note: Although we ran all of our reactions in MeOH, this methodology is likely to be successful using ethanol, which has a better safety profile with Pd−C reactions.

Preparation of *N*-(9-Fluorenylmethoxycarbonyl)-4-methyl-4-aminobutyric Acid (3b). To a stirred suspension of 4(*S*)-[(9-fluorenylmethoxycarbonyl)amino]-2-pentenoic acid benzyl ester (**3a**) (0.5 g, 1.2 mmol) and 10% Pd−C (100 mg) in 5 mL of methanol was added triethylsilane (1.8 mL, 11.7 mmol) dropwise under argon. The reaction started with evolution of gas. After completion of the reaction (TLC), the mixture was filtered through celite, and the solvent was removed in vacuo. The crude product was purified by short silica gel column chromatography, eluting with 2% hexane−ethylacetate, followed by hexane−ethlyacetate−methanol (3:6:1) to obtain 0.348 g of **3b**, a white solid. ^{1}H NMR (DMSO-d_6) δ 1.24 (d, J = 6.6 Hz, 2H), 1.62 (m, 2H), 2.2 (m, 2H), 3.51 (m, 1H), 4.18−4.35 (m, 3H), 7.15 (d, J = 6.6 Hz, 1H), 7.3−7.43 (m, 4H), 7.69 (d, J = 7.2 Hz, 2H), 7.88 (d, J = 7.2 Hz, 2H). HRMS (M + H) calcd for $C_{20}H_{22}NO_4$ 340.1549, found 340.1556.

Transprotection of Alloc-Leu-OMe (17a) to Boc-Leu-OMe (18b). To a stirred suspension of Alloc-Leu-OMe (**17a**) (0.3 g, 1.3 mmol), 10% Pd−C (60 mg), and Boc-anhydride (0.340 g, 1.56 mmol) in 5 mL of methanol was added triethylsilane (2.1 mL, 13 mmol) dropwise under argon. After completion of reaction (TLC), the mixture was filtered through celite, and the filtrate was concentrated under vaccum. The residue was diluted with 30 mL of ether, and the organic layer was then washed with 10% $NaHCO_3$ solution followed by brine and dried over $MgSO_4$. The crude product was purified by short silica gel column chromatography, eluting with 10% hexane−ethylacetate, to get 0.280 g of **18b** as an oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (m, 6H), 1.38 (s, 9H), 1.44−1.66 (m, 3H), 3.67 (s, 3H), 4.25 (m, 1H), 4.9 (brs, 1H).

Acknowledgment. We are grateful to the National Cancer Institute (CA096652) and the M. D. Anderson Cancer University Cancer Fund for support of this work. We also acknowledge the NCI Cancer Center Support Grant CA016672 for the support of our NMR facility.

Supporting Information Available: Procedures for the synthesis of substrates **1a**−**22a**, characterizarion of products **1b**−**22b**, and ^{1}H and ^{13}C NMR spectra for compounds **3a**, **3b**, **5a**, **8a**, **14a**, **14b**, **15a**, **16a**, and **16b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0706123

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