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Rhodium-Catalyzed, Efficient Deutero- and Tritiosilylation of Carbonyl Compounds from Hydrosilanes and Deuterium or Tritium

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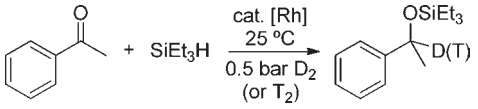
ABSTRACT



A cationic rhodium compound which is an active catalyst for both the hydrogen isotope exchange in hydrosilanes and the hydrosilylation of carbonyl compounds permits, in a one-flask, two-step procedure, efficient deutero- and tritiosilylations using $SiEt_3H$ under D_2 (0.5 bar) or T_2, at low catalyst loadings (0.1−0.5 mol %).

There is great demand for molecules labeled with the hydrogen isotopes deuterium (D) and tritium (T) for a variety of research and technical purposes, but most importantly in pharmaceutical investigations that lead to drug discovery and in many clinical studies.[1] Tritium is the most versatile radionucleide in chemical and biochemical research, in which development of tritiated radioligands is a crucial issue.[2]

As already noted,[3,4] of the basic methods for introducing tritium (or deuterium) into organic molecules, synthetic procedures such as, for example, reductions with a hydride source (e.g., labeled borohydrides, organotinhydrides, etc.) are convenient as they provide high T- or D-incorporation, although they find important limitations by the chemistry required. This has restricted so far the use of labeled hydrosilanes.[3,4] Hydrosilanes constitute one of the most powerful tools in synthetic organic chemistry.[5] For example, the catalytic hydrosilylation of carbonyl functionalities is an extremely useful industrial and laboratory method for the synthesis of a wide range of organosilicon compounds.[6−13] The process combines in one step selective regiocontrol by formation of a C−H bond with protection

(1) (a) Elmore, C. S.; John, E. M. *Annu. Rep. Med. Chem.*; Academic Press: 2009; Vol. 44, pp 515−534. (b) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7744–7765.

(2) (a) Skaddan, M. B.; Yung, C. M.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 11–13. (b) Skaddan, M. B.; Bergman, R. G. *J. Label. Compd. Radiopharm.* **2006**, *49*, 623–634.

(3) (a) Heys, J. R. *J. Label. Compd. Radiopharm.* **2007**, *50*, 770–778. (b) Lockley, W. J. S. *J. Label. Compd. Radiopharm.* **2007**, *50*, 256–259.

(4) (a) Elander, N.; Jones, J. R.; Lu, S.-Y.; Stone-Elander, S. *Chem. Soc. Rev.* **2000**, *29*, 239–249. (b) Saljoughian, M. *Synthesis* **2002**, 1781–1801.

(5) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009–4092.

(6) (a) Marciniec, B. *Hydrosilylation: a comprenhensive review on recent advances*; Springer: 2009. (b) Roy, A. K. *Adv. Organomet. Chem.* **2007**, *55*, 1–59. (c) Malacea, E.; Poli, R.; Manoury, E. *Coord. Chem. Rev.* **2010**, *254*, 729–752. (d) Morris, R. H. *Chem. Soc. Rev.* **2009**, *38*, 2282–2291.

(7) (a) Park, S.; Brookhart, M. *Organometallics* **2010**, *29*, 6057–6064. (b) Yang, J.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **2008**, *130*, 17509–17518.

(8) Tondreau, A. M.; Lobkovsky, E.; Chirik, P. J. *Org. Lett.* **2008**, *10*, 2789–2792.

(9) Yang, J.; Tilley, T. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 10186–10188.

(10) Blackwell, J. M.; Morrison, D. J.; Piers, W. E. *Tetrahedron* **2002**, *58*, 8247–8254.

(11) Buchan, Z. A.; Bader, S. J.; Montgomery, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4840–4844.

(12) Tran, B. L.; Pink, M.; Mindiola, D. J. *Organometallics* **2009**, *28*, 2234–2243.

(13) (a) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612–3676. (b) Díez-González, S.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 349–358.

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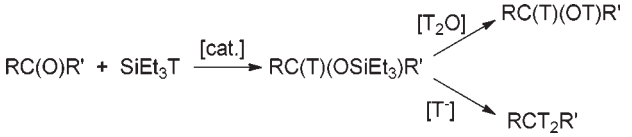
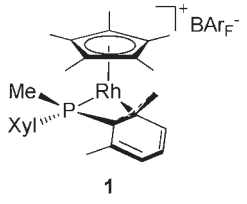
of the alcohol as an alkoxysilane. Accordingly, Si-D or Si-T addition to C=O units would place the label exclusively at the carbonyl carbon, while at the same time allowing facile, subsequent introduction of a second label by appropiate derivatization of the resulting alkoxysilane (for instance by deutero- or tritiodesilylation, by reduction with a labeled hydride source, etc., as shown in Scheme 1).

Scheme 1. General, Two-Step Labeling of a Carbonyl Compound by Catalytic Tritiosilylation[a]



[a] For simplicity, only tritiodesilylation and reduction of the alkoxysilane product have been considered.

We have recently disclosed a very efficient catalytic synthesis of deuterated and tritiated silanes, using D_2 or T_2 as the hydrogen isotope source, that is applicable to a wide range of hydrosilanes.[14] The catalyst is the cationic rhodium compound **1** shown in Figure 1 that contains a cyclometalated $PMeXyl_2$ ligand (Xyl = 2,6-$Me_2C_6H_3$) coordinated in a κ^4-*P*,*C*,*C*′,*C*″ fashion. Since this compound is also very active for the catalytic hydrosilylation of C=O bonds, we have developed a wide-scope, one-flask, two-step atom-economic process for the deutero- and tritiosilylation of aldehydes and ketones. As discussed below, this catalytic synthesis is routinely performed at room temperature (or at 50 °C), with low catalyst loading (usually 0.1 mol % for Si−H and 0.5 mol % for Si-D and Si-T), and requires only stirring of reagents and the catalyst under subatmospheric pressure of D_2 (0.5 bar) or T_2.



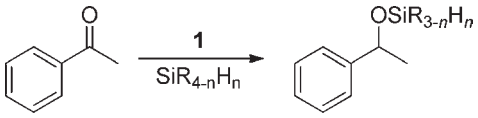
1

Figure 1. Structure of catalyst **1**.[14]

As a first step in this development, several hydrosilanes were tested utilizing acetophenone as the reference substrate, with catalyst loadings of 0.1 mol %. Dry silanes are needed, for compound **1** catalyzes also H_2 production from the hydrosilane and water. The results collected in Table 1 reveal that in most cases (entries 1−4) full conversion to the corresponding silyl alkyl ether was obtained after 1 h at

(14) (a) Campos, J.; Esqueda, A. C.; López-Serrano, J.; Sánchez, L.; Cossio, F. P.; de Cozar, A.; Álvarez, E.; Maya, C.; Carmona, E. *J. Am. Chem. Soc.* **2010**, *132*, 16765–16767. (b) Campos, J.; Esqueda, A. C.; Carmona, E. *España* **2010**, No. P201000507.

Table 1. Screening of Silanes[a]



Entry	Silane	temp (°C)	*t* (h)	conv (%)
1	$SiEt_3H$	25	1	99
2	$SiEt_2MeH$	25	1	99
3	$SiMe_2PhH$	25	1	99
4	$Si(^nPr)_3H$	25	1	99
5	$Si(^iPr)_3H$	50	12	0
6	$Si(SiMe_3)_3H$	50	12	0
7	$Si(Si(OMe)_3)_3H$	50	12	0

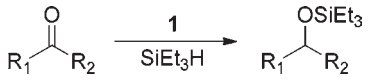
[a] Conditions: acetophenone (0.5 mmol), 0.1 mol % of **1**, 2.2 equiv of silane, CD_2Cl_2 (0.5 mL).

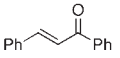
room temperature. However, the bulky tertiary silanes SiR_3H (R = ^{i}Pr, $SiMe_3$, $Si(OMe)_3$) resulted in no reaction even at 50 °C overnight (entries 5−7).

With these results in hand, a broad range of ketones (Table 2) and aldehydes (Table 3) were hydrosilylated with $SiEt_3H$. Excellent activities to the expected silyl ethers were attained at 25 °C, with a reaction time of 1 h and a catalyst concentration of 0.1 mol %. A competition experiment ran with equimolar amounts of RC(O)Me (R = Me, ^{i}Pr, ^{t}Bu) against 1 equiv of $SiEt_3H$ resulted in the formation of the expected silyl ethers (Scheme 2) in a ratio of 9(Me):2(^{i}Pr):1(^{t}Bu). These results, along with those pertaining to the addition of Si−H to di(*iso*-propyl)ketone (entry 4) and to 1- and 2-acetonaphtone (entries 8−10), show that an increase in the steric properties of the ketone substituents has a detrimental effect in the hydrosilylation reaction. On the other hand, comparison of the reactivity of the *para*-X acetophenones (X = H, CH_3, F) disclosed a moderate increase in the rate with the basicity of the substrate (Scheme 2), as products formed in the ratio 3(CH_3):1(H) and 2(H):1(F). Other ketones such as benzophenone and cyclohexanone were efficiently hydrosilylated by catalyst **1**.

Similarly, cyclic 2-cyclohexen-1-one and *trans*-chalcone reacted readily with $SiEt_3H$ in the presence of **1** (entries 13−14) to give exclusively (13) or mostly (14) the 1,4-addition products. To complete this study several aldehydes were also tested (Table 3). Once again, reactions were fast and gave the expected silyl alkyl ethers. Additional reduction of the latter to produce the alkane and $(Et_3Si)_2O$ was not observed.[7] The very high efficiency of catalyst **1** was demonstrated by the room temperature hydrosilylation of heptaldehyde with a S/C ratio of 10 000 (entry 1). Other aliphatic aldehydes hydrosilylated were propionaldehyde, hydrocinnamaldehyde, and 2-phenylpropionaldehyde (entries 2−4). Reduction of aromatic aldehydes (entries 5−8) was carried out with a catalyst concentration of 1 mol %, since lower catalyst loadings gave incomplete conversions. It seems that under the hydrosilylation conditions catalyst **1** reacts slowly with these aldehydes becoming partially deactivated.

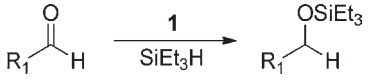
Table 2. Screening of Ketones[a]



Entry	R_1	R_2	S/C	temp (°C)	t (h)	conv (%)
1	Me	Me	1000	25	1	99
2	^{i}Pr	Me	1000	25	1	99
3	^{t}Bu	Me	1000	25	1	99
4	^{i}Pr	^{i}Pr	1000	50	24	75
5	Ph	Me	1000	25	1	99
6	4-Me-Ph	Me	1000	25	1	99
7	4-F-Ph	Me	1000	25	1	98
8	2-Naph	Me	1000	25	1	99
9	1-Naph	Me	1000	50	24	15
10	1-Naph	Me	100	50	16	75
11	Ph	Ph	100	25	1	99
12	c-$C_6H_{10}O$		100	25	1	99
13			100	25	1	99[b]
14			100	25	1	99[c]

[a] Conditions: 0.1−0.5 mmol of substrate, 2.2 equiv of $SiEt_3H$; CD_2Cl_2 (0.5 mL). [b] Exclusively 1,4-addition product. [c] A mixture of 94% of 1,4-addition products (2:1 ratio of Z/E isomers) and 6% of 1,2-addition product.

Table 3. Screening of Aldehydes[a]

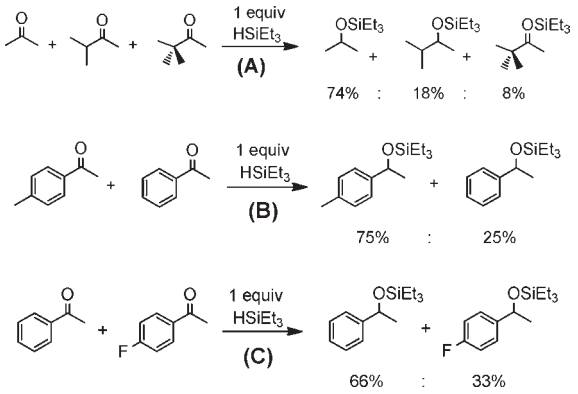


Entry	Substrate	S/C	temp (°C)	t (h)	conv (%)
1	$CH_3(CH_2)_5C(O)H$	10000	25	1	99[b]
2	$CH_3CH_2C(O)H$	1000	25	1	99[b]
3		1000	25	1	99[b]
4		1000	25	1	99[b]
5	PhC(O)H	100	25	1	99
6	2-F-PhC(O)H	100	50	8	99
7	4-Cl-PhC(O)H	100	50	12	98
8	4-NO_2-PhC(O)H	100	50	72	99

[a] Conditions: 0.1−0.5 mmol of substrate, 2.2 equiv of $SiEt_3H$, CD_2Cl_2 (0.5 mL). [b] Minor amounts of dialkyl ethers (< 10%).

As already reported, complex **1** is also a very effective catalyst for the hydrogen isotope exchange of

Scheme 2. Competition Studies



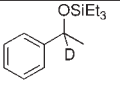
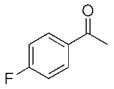
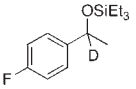
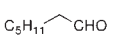
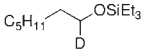
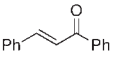
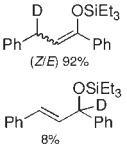
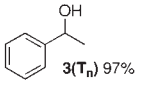
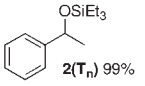
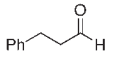
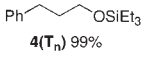
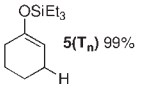
hydrosilanes.[14] Accordingly, deutero- and tritiosilanes, e.g. $SiEt_3D$ and $SiEt_3T$, can be generated *in situ* and used as reagents for deutero- and tritiosilylations, under conditions similar to those in Tables 2 and 3 for the analogous Si−H additions. Moreover, as both the latter catalytic process and the hydrosilylation reaction are fast at room temperature, a convenient two-step but one-flask method, whereby the labeled silane is generated first from $SiEt_3H$ and D_2 or T_2 in the presence of **1** and then reacted with the organic substrate, can be applied for the efficient, atom-economic deutero- and tritiosilylation of carbonyl compounds. For deuterium labeling, if ≥99% D-incorporation into the product is needed, full deuteration of the silane can be achieved by subjecting the $SiEt_3H$-plus-catalyst mixture to three D_2 loadings, each involving cooling at 0 °C/vacuum (0.1 bar)/0.5 bar D_2 (see Supporting Information).

Clearly, these D- and T-labeling procedures represent an important simplification of those presently utilized, that require previous synthesis and isolation of $SiEt_3D$ or $SiEt_3T$, usually from $SiEt_3Cl$ and an isotopically labeled hydride reagent.[15,16] For example, the reported synthesis of $SiEt_3T$ uses LiT, which must be prepared *in situ* from $LiBu^n$ and T_2 in the presence of $Me_2NCH_2CH_2NMe_2$ (tmed) and then reacted with $SiEt_3Cl$ in boiling triglyme.[15] This is followed by controlled distillation of $SiEt_3T$, which is always contaminated by undesirable amounts of tmed that are difficult to eliminate. In contrast, our catalytic synthesis of $SiEt_3T$ (or $SiEt_3D$) is clean, rapid, and simple, and it is performed in one step[1,3,4] and permits subsequent use of the silane reagent in the same flask for the silylation reaction. Entries 1−7 in Table 4 summarize deuterosilylation reactions in which the substrate is added after $SiEt_3D$ has been formed from $SiEt_3H$, D_2, and **1**. Both ketones and aldehydes converted quantitatively into deuterated silyl ethers. For acetophenone a kinetic isotope effect k_H/k_D

(15) Neu, H.; Andres, H. *J. Label. Compd. Radiopharm.* **1999**, *42*, 992–993.

(16) (a) Than, C.; Morimoto, H.; Andres, H.; Williams, P. G. *J. Org. Chem.* **1996**, *61*, 8771–8774. (b) Zippi, E. M.; Andres, H.; Morimoto, H.; Williams, P. G. *Synth. Commun.* **1995**, *25*, 2685–2693. (c) Jaiswal, D. K.; Andres, H.; Morimoto, H.; Williams, P. G. *J. Chem. Soc., Chem. Commun.* **1993**, 907–909. (d) Andres, H.; Morimoto, H.; Williams, P. G. *J. Chem. Soc., Chem. Commun.* **1990**, 627–628.

Table 4. Deuterosilylations and Tritiosilylations[a]

Entry	Substrate	*t* (h)	conv (%)	Products
1		5	99	
2		5	99	
3		5	99	
4		5	99	
5		5	99[b]	
6		5	99	
7		5	99	
8[c]		192	99	
9[d]		24	99	
10[d]		24	99[b]	
11[d]		24	99	

[a] Conditions: 0.5 bar of D_2 (3 D_2/vacuum cycles, 30 min), 0.25 mmol of substrate, 0.5 mol % **1**, 2.2 equiv of $SiEt_3H$, CD_2Cl_2 (0.5 mL), 25 °C. [b] Minor amounts of dialkyl ethers $R_1C(O)R_1$ (< 10%). [c] 2.2 mmol of substrate, 0.1 mol % **1(T$_n$)**, 0.9 equiv of $SiEt_3H$, CD_2Cl_2 (0.5 mL), 50 °C. [d] 0.44 mmol of substrate, 0.5 mol % **1**, 0.9 equiv of $SiEt_3H(T_n)$, CD_2Cl_2 (0.5 mL), 50 °C

of *ca.* 1.9 was measured. It is worth mentioning that α,β-unsaturated ketones like 2-cyclohexen-1-one and *trans*-chalcone (entries 6,7), that provided with high selectivity products labeled at position 4, could add a second label at position 3 after deuterolysis.

The same concept of labeling may be used for tritiosilylations. However, considering the very small amounts of the radioisotope needed for the labeling and taking additionally into account reasons of security and convenience of handling, the tritiated complex **1(T$_n$)** was employed as a very efficient tritium transferring reagent in the experiment in entry 8 of Table 4. Thus, a mixture of **1(T$_n$)** (4 mCi/mg), $SiEt_3H$, and acetophenone yielded the corresponding silyl ether **2(T$_n$)** with a nonoptimized reaction time of 8 days to ensure complete T transfer. The resulting **2(T$_n$)** was subsequently hydrolyzed and isolated by column chromatography as 1-phenylethanol **3(T$_n$)** with a specific activity of 5.88 mCi/mmol (*ca.* 97% T-incorporation).

From a practical point of view, the same tritiation was performed with previously labeled $SiEt_3H(T_n)$ (0.19 mCi/mmol) and provided 99% tritium incorporation into **2(T$_n$)** (entry 9). With the latter procedure, the scope of tritiosilylation was also extended successfully to aldehydes and α,β-unsaturated ketones, like hydrocinnamaldehyde (entry 10) and 2-cyclohexen-1-one (entry 11), with T-incorporation of 99% into both **4(T$_n$)** and **5(T$_n$)**.

In summary, we have exploited the capacity of the rhodium compound **1** to catalyze both the hydrosilylation of carbonyl compounds and the hydrogen isotope exchange in hydrosilanes to develop efficient, one-pot, two-step procedures for the selective labeling of aldehydes and ketones at the carbonyl atom.

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Supporting Information Available. Experimental procedures, characterization data of new compounds, and determination of kinetic isotope effect. This material is available free of charge via the Internet at http://pubs.acs.org.