disorder in native and reconstituted hemoproteins.

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Chemoselective Desilylation of Silyl Enol Ethers with Tributyltin Fluoride Catalyzed by Palladium

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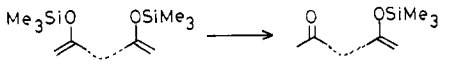
Differentiation of more than two types of ketone functions is often required in organic synthesis. For years, selective protections (e.g., ketalization or reduction) have been conventionally used as exemplified in various natural product syntheses. Considering that silyl enol ethers have found widespread use in synthetic organic chemistry,[1] selective silylation of a certain ketone group of diketo compounds may provide another useful tool for this purpose. Although many methods have been developed for ketone silylation, only a few examples are reported for selective monosilylation of diketones that rely on differences in kinetic acidities.[2] We wish to describe here an alternative approach based on selective desilylation of bis(silyl enol ethers) that could be prepared readily by a variety of methods.

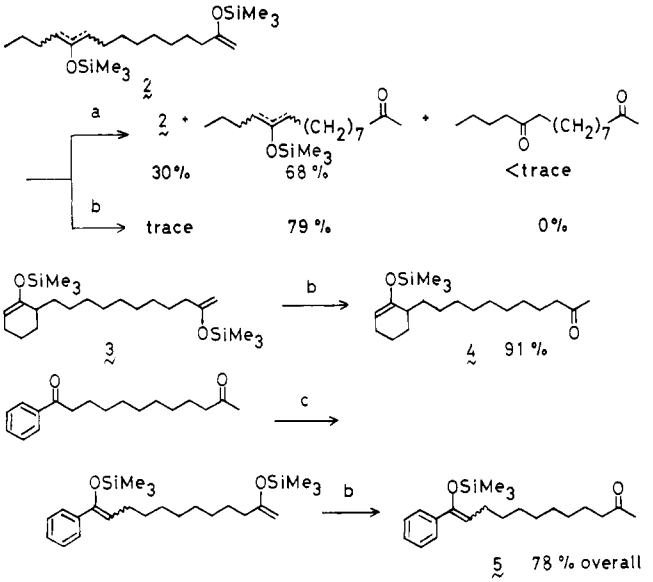


(1)

We have found that tributyltin fluoride[3] removes the silyl group from silyl enol ethers quite selectively under the influence of a palladium catalyst. As the catalyst, $PdCl_2(P(o\text{-}MeC_6H_4)_3)_2$ has proved to be the most effective.[4] Although the reaction proceeds in the absence of the catalyst, the catalyst accelerates the desilylation dramatically to complete the process within a reasonable period. The efficacy of the catalyst has been demonstrated by the following experiments. 5-Methyl-2-(trimethylsiloxy)-1-hexene (**1**) was treated with Bu_3SnF (1.05 equiv) and a palladium catalyst (3 mol %) in refluxing benzene for 30 min. After quenching the reaction mixture with wet acetone, isopentyl methyl ketone (and **1**) was recovered in 19 (80)% (without a catalyst); 21 (78)% ($Pd(PPh_3)_4$); 28 (67)% ($PdCl_2(CH_3CN)_2$); 31 (52)% ($PdCl_2(PPh_3)_2$); 96 (2)% ($PdCl_2(P(o\text{-}MeC_6H_4)_3)_2$).

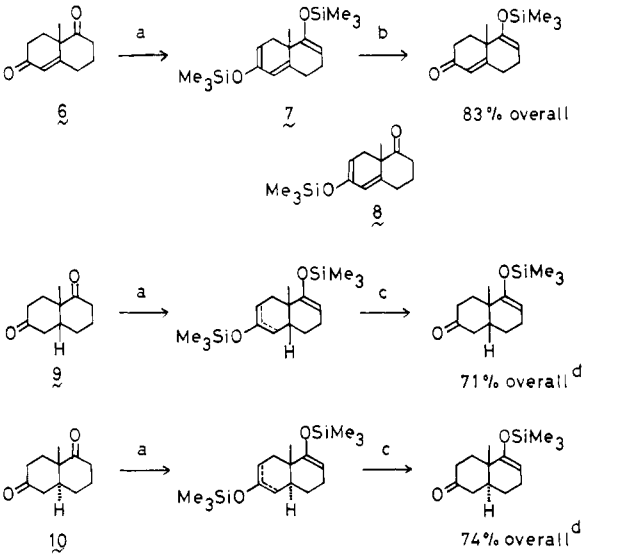
Of particular interest, the reaction rate was highly dependent on a steric congestion around the double bond of the silyl enol ether: less hindered cases undergo desilylation much more rapidly than more hindered ones. Thus, silyl enol ethers of methyl ketones could be desilylated under standard conditions as above where other hindered silyl enol ethers remained unattacked. However, the observed selectivity may not be due to the Pd catalyst, but intrinsically due to Bu_3SnF as evidenced by running the reaction without the catalyst (cf. the first equation of Scheme I). Several results are shown in Scheme I.

Scheme I



[a] Bu_3SnF (1.05 equiv), C_6H_6, reflux, 7 h. [b] Bu_3SnF (1.05 equiv), $PdCl_2(P(o\text{-}MeC_6H_4)_3)_2$ (3 mol %), C_6H_6, reflux, 0.5 h. [c] LDA, THF, −78 °C; Me_3SiCl, −78 °C → room temperature; no purification.

Scheme II



[a] LDA, THF, −78 °C; Me_3SiCl, −78 °C → room temperature. [b] Bu_3SnF (2.5 equiv), $PdCl_2(P(o\text{-}MeC_6H_4)_3)_2$ (8 mol %), C_6H_6, reflux, 4 h. [c] Bu_3SnF (5 equiv), $PdCl_2(P(o\text{-}MeC_6H_4)_3)_2$ (15 mol %), C_6H_6, reflux, 11 h. [d] The relatively low yield is partly due to incompletion of the reaction.

In each case, after column chromatography on silica gel, the product can be isolated without any contamination of the regioisomer arising from reversed selectivity. Moreover, no formation of the parent diketone was confirmed by TLC analysis of the crude reaction mixture.[5] These facts clearly indicate the high selectivity of the present method.

Further, selective removal can also be achieved with other types of enol ethers by employing forcing conditons (e.g., use of an excess amount of Bu_3SnF and a prolonged reaction period).[6] The results

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(2) Selective silylation of a saturated ketone in the presence of an unsaturated one or vice versa: (a) Grieco, P. A.; Ferrino, S.; Oguri, T. *J. Org. Chem.* **1979**, *44*, 2593. (b) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699. (c) Danishefsky, S.; Prinsbylla, M.; Lipisko, B. *Tetrahedron Lett.* **1980**, *21*, 805.

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(4) Similarly, higher efficacy of this catalyst has also been observed in the arylation of silyl enol ethers. See ref 3.

(5) Desilylation of **2** with tetrabutylammonium fluoride (1 equiv in THF at 0 °C or even at −78 °C) gave a considerable amount of the diketone.

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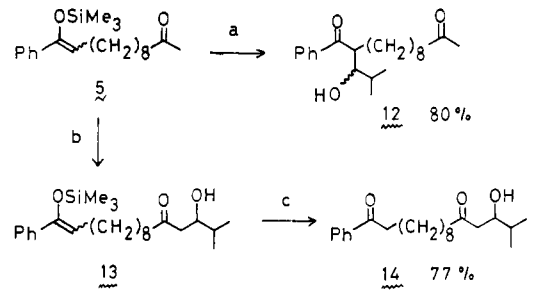
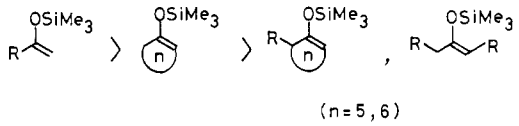
Scheme III



[a] Isobutyraldehyde (1.1 equiv), $TiCl_4$ (1.1 equiv), CH_2Cl_2, −78 °C. [b] LDA (1.1 equiv), THF, −78 °C; isobutyraldehyde (1.2 equiv). [c] Aqueous HCl-THF.

of competition reactions using an equimolar mixture of two types of silyl enol ethers have revealed the following guidelines on the selelctivity; (i) an acyclic enol ether except a methyl ketone derivative is not affected by the present method and (ii) an α'- as well as α-substitutent greatly retard the desilylation. Namely, the rate of the reaction drops in the following order.



(n = 5, 6)

Such difference of reactivity should account for the selective transformation of cyclic ketones as shown in Scheme II. The desilylation of **7** proceeds cleanly with formation of neither **6** nor **8**. The mono(silyl ethers) of the Wieland–Mischer ketone **6**[2a,7,8] and its hydrogenated ketones **9**[9] and **10**[9] seem to be quite important for terpene and steroid synthesis.

Another synthetic advantage is that this method allows for removal of regioisomeric impurities from thermodynamically favorable silyl enol ethers of methyl ketones. For example, pure 5-methyl-2-(trimethylsiloxy)-2-hexene (**11**) was obtained in 91% yield by treating a mixture of **1** and **11** (14:86) with Bu_3SnF (0.17 equiv) and the Pd catalyst (0.005 equiv) under standard conditions.

A representative procedure for the desilylation is as follows. A mixture of the bis(silyl enol ether) **3** (81 mg, 0.2 mmol), Bu_3SnF (64 mg, 0.205 mmol), and $PdCl_2(P(o\text{-}MeC_6H_4)_3)_2$ (6 mg, 0.006 mmol) in benzene (1 mL) was heated to reflux for 30 min under nitrogen. The reaction mixture was diluted with ether,[10] treated briefly with 1 N NaOH under vigorous stirring, and extracted with ether. Drying and removal of the solvent from the combined extracts followed by silica gel column chromatography[11] afforded the mono(silyl enol ether) **4** (60.2 mg, 91%).

Application of this methodology to further selective transformation has been demonstrated as follows. The reaction of **5** with isobutyraldehyde in the presence of $TiCl_4$ afforded the aldol **12**, whereas treatment of **5** with LDA followed by addition of the same aldehyde gave the isomeric aldol **14** (Scheme III). It is noteworthy that the silyl enol ether is employed for activation of the ketone in the former reaction, while in the latter sequence it acts as a protecting group of the ketone functionality.

(6) We found that *tert*-butyldimethylsilyl enol ether was not affected even under forcing conditions: cf. the trimethylsilyl enol ether of cyclohexanone suffered desilylation in >85% with 2 equiv of Bu_3SnF and the Pd catalyst for 8 h, while the *tert*-butyldimethylsilyl enol ether was recovered in >85% under the same conditions.

(7) Other selective transformation of W.-M. Ketone: McMurry, J. E. *J. Am. Chem. Soc.* **1968**, *90*, 6821. Piers, E.; de Waal, W.; Britton, R. W. *Ibid.* **1971**, *93*, 5113. Selective deketalization of a bis(thioketal) of W.-M. ketone: Muxfeldt, H.; Unterweger, W.-D.; Helmchen, G. *Synthesis* **1976**, 694. Smith, R. A. J.; Hannah, D. J. *Synth. Commun.* **1979**, *9*, 301.

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(10) On using an excess amount of Bu_3SnF (as in Scheme II), the remaining fluoride was readily removed by filtration at this stage.

(11) Flash chromatography (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923) was performed at 4 °C to prevent the possible hydrolysis of silyl enol ethers during the operation.

Further synthetic application as well as mechanistic studies on the present reaction, especially on the exact role of the palladium catalyst, is now in progress.

Registry No. 1, 73503-97-6; **2**, 86497-50-9; **3**, 86497-36-1; **4**, 86497-37-2; **5**, 86497-38-3; **6**, 20007-72-1; **7**, 86497-39-4; **9**, 4707-05-5; **10**, 4707-04-4; **11**, 86497-40-7; **12**, 86497-41-8; **13**, 86497-42-9; **14**, 86497-43-0; Bu_3SnF, 1983-10-4; $Pd(PPh_3)_4$, 14221-01-3; $PdCl_2(CH_3CN)_2$, 14592-56-4; $PdCl_2(PPh_3)_2$, 13965-03-2; $PdCl_2(P(o\text{-}MeC_6H_4)_3)_2$, 40691-33-6; $TiCl_4$, 7550-45-0; isopentyl methyl ketone, 110-12-3; isobutyraldehyde, 78-84-2; 11-[(bimethylsilyl)oxy]pentadecen-2-one, 86507-85-9; 2,11-pentadecanedione, 86497-44-1; 1-phenyl-1,11-dodecanedione, 15288-89-8; 2,2,16,16-tetramethyl-14-methylene-4-phenyl-3,15-dioxa-2,16-disilaheptadecane, 86497-45-2; 4,4a,7,8-tetrahydro-4a-methyl-5-[(trimethylsilyl)oxy]-2(3*H*)-naphthalenone, 86497-46-3; *cis*-[3,4,4a,5,8,8a(or 3,4,4a,7,8,8a)-hexahydro-8a-methyl-1,6-naphthalenediylbis(oxy)]bis[trimethylsilane], 86497-52-1; *cis*-3,4,4a,7,8,8a-hexahydro-4a-methyl-5-[(trimethylsilyl)oxy]-2(1*H*)-naphthalenone, 86497-47-4; *trans*-[3,4,4a,5,8,8a(or 3,4,4a,7,8,8a)-hexahydro-8a-methyl-1,6-naphthalenediylbis(oxy)]bis[trimethylsilane], 86497-54-3; *trans*-3,4,4a,7,8,8a-hexahydro-4a-methyl-5[(trimethylsilyl)oxy]-2(1*H*)-naphthalenone, 86497-48-5.

Reaction-Coordinate Tunneling in Hydride-Transfer Reactions[1]

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Quantum-mechanical tunneling[3] in the transition state for hydride-transfer reactions, including the action of NAD^+/NADH-dependent dehydrogenases, is shown by model vibrational-analysis calculations[4] to explain observed anomalies in the α-deuterium secondary kinetic isotope effects,[5,6] which exceed the corresponding equilibrium effects in these systems.

α-Deuterium secondary kinetic isotope effects[7-11] lie between unity and the equilibrium isotope effect for reactions in which the proximal atom of the group departing from or arriving at the isotope-bearing center is oxygen or a heavier atom (as in S_N1 reactions[8] and nucleophilic reactions at carbonyl[9-12]). Their magnitudes are taken to reflect progress from reactants toward products at the transition state.[7-12]

(1) This research was supported by the National Institutes of Health through research grant No. GM-20198 from the National Institute of General Medical Sciences.

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