Palladium-catalyzed conjugate reduction of enones into α,β-dideuterioketones with hexamethyldisilane and deuterium oxide†

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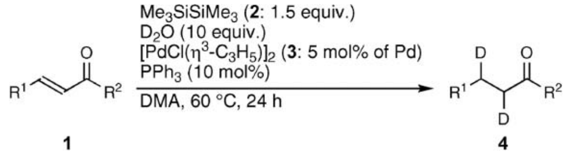
Conjugated enones are reduced by readily available $Me_3SiSiMe_3$ and D_2O in the presence of a catalytic amount of $[PdCl(\eta^3\text{-}C_3H_5)]_2$–$PPh_3$ to give α,β-dideuterioketones.

Deuterated organic compounds are important for biological research[1] and the elucidation of reaction mechanisms.[2] Among the deuterium sources used for chemical transformations to deuterated compounds, deuterium oxide is undoubtedly the most inexpensive and easy to handle. In this context, we recently reported the palladium-catalyzed reduction of alkynes to 1,2-dideuterioalkenes using hexamethyldisilane and deuterium oxide as a reductant and a deuterium source, respectively.[3] Here, we report that the combination of a palladium catalyst, hexamethyldisilane and deuterium oxide is applicable to the conjugate reduction of enones into α,β-dideuterioketones. There are some precedents for the α,β-dideuteration of conjugated enones using deuterium oxide as a deuterium source.[4,5] A plausible reaction mechanism based on the experimental results, including that from a stoichiometric reaction using an intermediate equivalent, is also described.

We first examined the conjugate reduction of 1-phenyl-2-nonen-1-one (**1a**) under essentially the same conditions as we used for the reduction of alkynes, but at a lower temperature.[3] Thus, treatment of **1a** with hexamethyldisilane (**2**: 1.5 equiv.), D_2O (10 equiv.), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (**3**: 5 mol% of Pd) and PPh_3 (10 mol%) in DMA at 60 °C for 24 h gave 2,3-dideuterio-1-phenyl-1-nonanone (**4a**) (eqn. (1) and Table 1, entry 1). More than one deuterium atom was incorporated at both α- (125%) and β- (120%) positions. The overdeuteration of the α-position is probably due to acid-catalyzed H–D exchange *via* an enol form of product **4a**,[6] whereas that of the β-position is caused by H–D exchange of enone **1a** before reduction. The actual deuterium ratios of recovered **1a** at 63% conversion were 2% (α) and 29% (β).[6] How the H–D exchange at the β-position takes place will be discussed later. The deuteration was found to be applicable to various conjugated enones having aliphatic and/or aromatic substituents on the alkene and carbonyl carbons (Table 1).‡ Substitution on the benzene rings of the chalcon with an electron-donating or -withdrawing group did not inhibit the reaction, except for a CF_3 group on the 1-phenyl group of the chalcon, which resulted in moderate yields (Table 1 entries 4–9).



(1)

Table 1 Palladium-catalyzed conjugate reduction of enones to α,β-dideuterioketones[a]

Entry	R^1	R^2	Yield (%)[b]	Deuterium ratio[c] α (-*d*)	β (-*d*)
1	Hex	Ph	82	1.25/2	1.20/2
2	*i*-Pr	Ph	93	1.44/2	1.13/2
3	$Cl(CH_2)_3$	Ph	85	1.56/2	1.17/2
4	Ph	Ph	81	1.21/2	1.02/2
5	4-MeOC_6H_4	Ph	86	1.31/2	1.09/2
6	$4\text{-CF}_3C_6H_4$	Ph	85	1.35/2	0.97/2
7	Ph	4-MeOC_6H_4	92	1.45/2	1.05/2
8[d]	Ph	$4\text{-Me}_2NC_6H_4$	95	1.58/2	0.96/2
9	Ph	$4\text{-CF}_3C_6H_4$	69	1.31/2	1.05/2
10	Ph	Me	92	1.56/2	0.98/2
11	Pent	Me	80	1.05/2	1.06/2
12	Ph	(*E*)-Styryl	81	3.22/4[e]	2.00/4[e]

[a] The reaction was carried out in DMA (0.50 mL) at 60 °C for 24 h under a nitrogen atmosphere using enone (0.40 mmol), $Me_3SiSiMe_3$ (0.60 mmol) and D_2O (4.0 mmol) in the presence of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (10 μmol) and PPh_3 (40 μmol). [b] Isolated yield based on the enone. [c] D/(D + H) determined by ^1H NMR. [d] Reaction time = 48 h. [e] Both of the double bonds are deuterated.

In our report on the palladium-catalyzed silylation of alcohols with **2**,[7] it was shown that **3** is transformed into $PdH(Cl)(PPh_3)_2$ (**5**)[8] as a catalytically active complex by treatment with **2** and an alcohol in the presence of PPh_3, and that the Si–Si bond of disilane **2** is cleaved with ROH in the presence of hydridopalladium catalyst **5** to give Me_3SiH (**6a**) and Me_3SiOR. In the present dideuteration system, where D_2O is used in place of ROH, deuteridopalladium $PdD(Cl)(PPh_3)_2$ (**5-*d***), Me_3SiD (**6a-*d***) and Me_3SiOD should be generated in place of hydridopalladium **5**, hydrosilane **6a** and Me_3SiOR, respectively. Thus, we are tempted to consider that **5-*d*** catalyzes the dideuteration of enones **1**, with **6a-*d*** as a reductant, with the aid of D_2O, as shown in eqn. (2).[9] Actually, the combination of **5** (5 mol%) and $PhMe_2SiD$ (**6b-*d***: 3.0 equiv.), instead of **5-*d*** and **6a-*d***, in the presence of D_2O (10 equiv.), worked effectively in the conjugate reduction of **1a** at 60 °C for 24 h to give **4a** in 76% yield (α: 1.47/2-*d*, β: 1.05/2-*d*).

We investigated the reaction mechanism based on eqn. (2). Deuteriopalladation of enone **1** with D–Pd–Cl **5-*d***, giving β-deuterio-α-palladioketone **7**, is probably the first step (Scheme 1). The corresponding hydropalladation of alkenes is a

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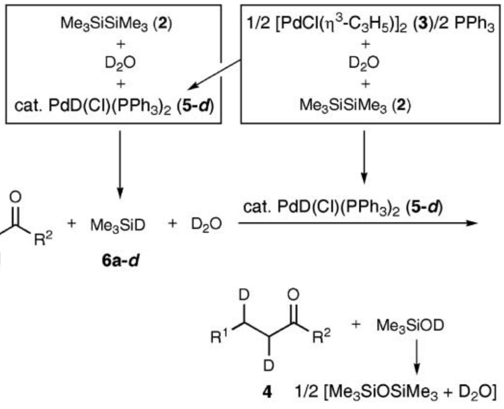
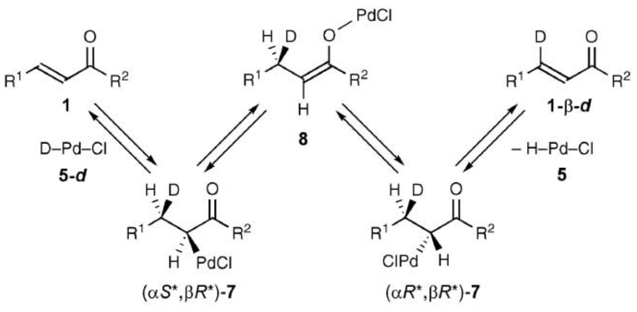


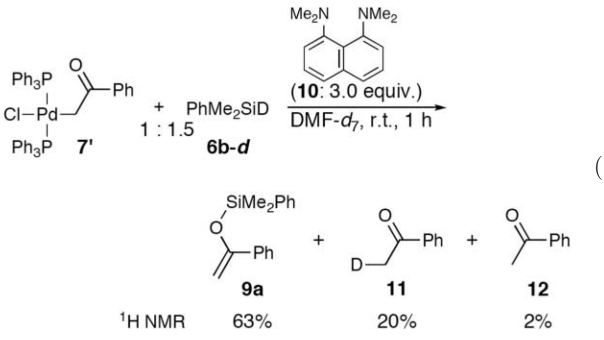
(2)



Scheme 1

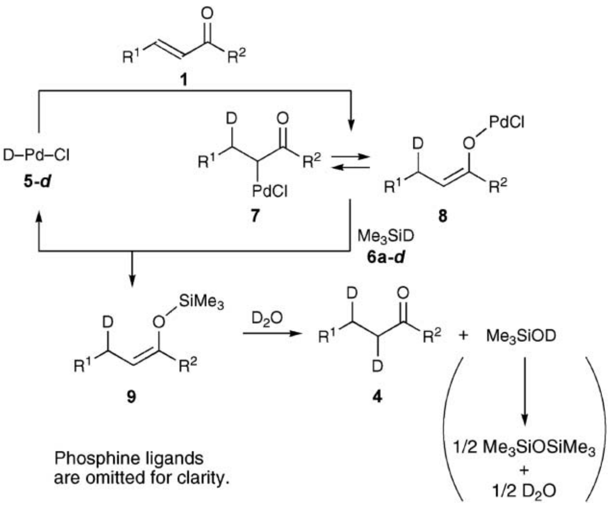
well known process,[10] but it is difficult to observe α-palladioketone **7** because of the facile reverse reaction, β-hydride elimination.[11] The H–D exchange at the β-position of enone **1** prior to the reduction (*vide supra*) is possibly ascribed to a series of reactions initiated by deuteriopalladation (Scheme 1). Thus, (α*S**,β*R**)-**7**, generated by the deuteriopalladation, undergoes a 1,3-Pd shift, giving palladium enolate **8**. The reverse 1,3-Pd shift to the opposite side, followed by β-hydride elimination, gives β-deuterioenone **1-β-*d*** *via* (α*R**,β*R**)-**7**.[12]

Next, we examined which of the remaining substrates, **6a-*d*** and D_2O, reacts with α-palladioketone **7**. We used a less volatile deuteriosilane, $PhMe_2SiD$ (**6b-*d***), and a more stable α-palladioketone, $Pd(CH_2COPh)Cl(PPh_3)_2$ (**7′**), [13] which is free from β-hydride elimination. α-Palladioketone **7′** was intact upon treatment with D_2O (rt, 1 h), whereas **6b-*d*** readily reacted with **7′** in the presence of 1,8-bis(dimethylamino)naphthalene (**10**: 3.0 equiv.)[14] to give silyl enolate **9a** in 63% yield (eqn. (3)).



(3)

α-Deuterioacetophenone (**11**), a major by-product, was probably produced by the reaction of **9a** with **5-*d***, generated during the formation of **9a**. The reaction of **7′** with **6b-*d*** in the presence of D_2O and the absence of **10** gave **11** (58%, along with 10% of **12**) but not **9a**. A plausible overall catalytic cycle is shown in Scheme 2. Deuteriopalladation of **1** gives α-palladioketone **7**, which is in equilibrium with palladium enolate **8**. Palladium complex **7** and/or **8** reacts with **6a-*d*** to regenerate **5-*d*** and give silyl enolate **9**,[15] which undergoes deuteriolysis under slightly acidic conditions to give α,β-dideuterioketone **4**.



Scheme 2

In conclusion, we have disclosed a new dideuteration method for conjugated enones using readily available deuterium oxide as the deuterium source, a palladium complex as the catalyst and hexamethyldisilane as the reductant.

Notes and references

‡ General procedure for the dideuteration of enones: To a solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (**3**: 3.7 mg, 0.010 mmol) and PPh_3 (10.5 mg, 0.0400 mmol) in DMA (0.50 mL) were added, successively, the enone (**1**: 0.40 mmol), hexamethyldisilane (**2**: 87.9 mg, 0.600 mmol) and D_2O (72 μL, 4.0 mmol). After stirring at 60 °C for 24 h, the resulting mixture was diluted with diethyl ether (20 mL), washed with water (10 mL × 5) and brine (10 mL), and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent followed by PTLC on SiO_2 (hexane–ethyl acetate), column chromatography on SiO_2 (hexane–ethyl acetate) or bulb-to-bulb distillation gave the corresponding α,β-dideuterioketone **4**. Deuterium ratios were determined by ^1H NMR. The results are summarized in Table 1.

1 For examples, see: (*a*) K. Liu, J. Williams, H. Lee, M. M. Fitzgerald, G. M. Jensen, D. B. Goodin and A. E. McDermott, *J. Am. Chem. Soc.*, 1998, **120**, 10199–10202; (*b*) I. Sack, Y. S. Balazs, S. Rahimipour and S. Vega, *J. Am. Chem. Soc.*, 2000, **122**, 12263–12269.
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6 We examined the deuteration of **1a** for short (3.5 h) and prolonged (72 h) reaction times to obtain a time profile for the deuteration ratios of the α- and β-positions of **4a**. The resulting profile for α/β was 1.01/1.16 (3.5 h), 1.25/1.20 (24 h: Table 1, entry 1) and 1.82/1.25 (72 h), where the conversions **1a**/yields **4a** were 63%/45% (3.5 h), >99%/82% (24 h) and >99%/88% (72 h). The time profile clearly shows that H–D exchange at the α-position takes place at least mainly after the reduction.

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9 $PdD(Cl)(PPh_3)_2$ (**5-*d***) is also considered to be a catalyst in the dideuteration of alkynes. See ref. 3.

10 For reviews, see: (*a*) V. V. Grushin, *Chem. Rev.*, 1996, **96**, 2011–2033; (*b*) E.-i. Negishi, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E.-i. Negishi, Wiley, New York, 2002, pp. 135–139; (*c*) The hydropalladation of acrylonitrile, a similar alkene to enones, is reported to proceed to give $Pd[CH(CN)CH_3](S_2CNMe_2)(PEt_3)$: D. L. Reger and D. G. Garza, *Organometallics*, 1993, **12**, 554–558.

11 α-Palladio carbonyl compounds are known to be typical but rarely observable intermediates leading to β-substituted enones in the Mizoroki–Heck reaction. For a review of the Mizoroki–Heck reaction, see: I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009–3066.

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