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Palladium-Catalyzed Regio- and Stereoselective Reduction of Allylic Compounds with $LiHBEt_3$. Application to the Synthesis of Co-enzyme Q_{10}

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Regio- and stereoselective desulfonylation of allylic sulfones with $LiHBEt_3$ in the presence of a catalytic amount of $[PdCl_2(dppp)]$ was successfully applied to the synthesis of co-enzyme Q_{10}. It was found that this reduction system was applicable to a wide variety of allylic functional groups.

In the previous papers,[1,2] we reported the regio- and stereoselective synthesis of homoallylic alcohols and terpenoids such as squallene by the reductive desulfonylation of allylic sulfone derivatives with the combination of (1) $NaBH_4$/a catalytic amount of $[Pd(PPh_3)_4]$[1] and (2) $LiHBEt_3$/a catalytic amount of $[PdCl_2(dppp)]$,[2] respectively. We herein discuss the probable course of the reductive desulfonylation using the latter combination to account for the high regioselectivity and also describe an application of the reduction system to the synthesis of co-enzyme Q_{10} and to other various kinds of allylic compounds.

The combination of $LiHBEt_3$ and a catalytic amount of $[PdCl_2(dppp)]$ was first employed to 3-tosyl-1-cyclohexene derivatives (1) as shown in Table 1. It was found that the double bond migrated completely when R^2 is a substituent and R^1 is hydrogen (Entries 1 and 3), except Entry 5 in which the double bond is partially preserved on the original position, while the olefin migration was not observed at all in the case of the opposite substitution (Entries 2, 4, and 6). These results seemed to be due to the preferential attack of a hydride of the bulky reducing agent ($^-HBEt_3$) on a less hindered carbon atom of the intermediary π-allyl complex 3.

In order to confirm whether this speculation is also correct for acyclic system, the detosylation of 4 was examined as a preliminary experiment for the synthesis of co-enzyme Q_{10}. Desulfonylated products (6 and 7) were isolated totally in 85% yield and their ratio was 6/7 = 80/20. It may be rationalized by the consideration of the intermediary π-allyl complex 5 in which (a) and (b) are both secondary carbon atoms, therefore $^-HBEt_3$ will be able to attack both of them in a similar probability. A preferential formation of 6, however, indicates that the reduction tends to proceed in a S_N2-like fashion toward

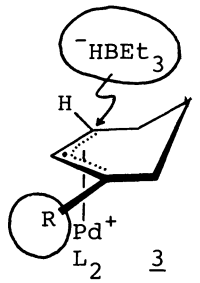

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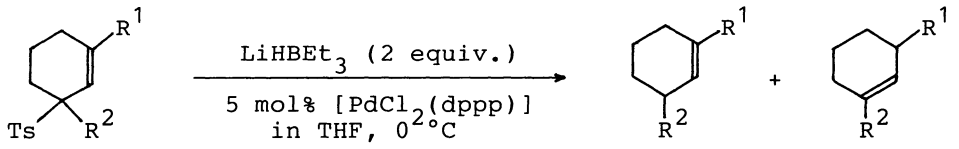
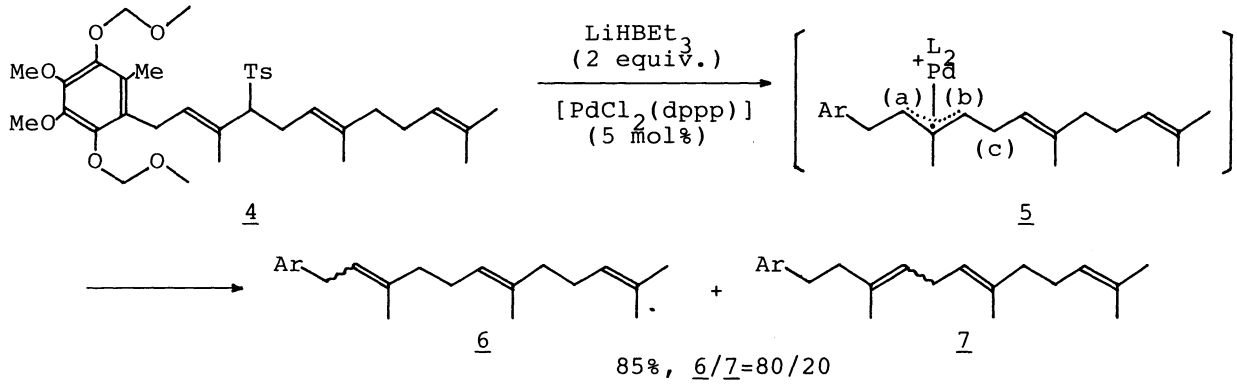
Table 1. Palladium-Catalyzed Reduction of 3-Tosyl-1-cyclohexene Derivatives



1 2a 2b

Entry	Substrate R^1	Substrate R^2	Reaction time/min	Isolated yield/%	Ratio[a] 2a : 2b
1	H	$C_6H_5CH_2$	30	89	- : >99
2	$C_6H_5CH_2$	H	30	84	>99 : -
3	H	$C_6H_5(CH_2)_2$	30	99	- : >99
4	$C_6H_5(CH_2)_2$	H	30	89	>99 : -
5	H	$CH_3(CH_2)_{10}$	60	91	31 : 69
6	$CH_3(CH_2)_{10}$	H	40	97	>99 : -

a) Determined by 400 MHz ^{1}H-NMR spectra.



4 5

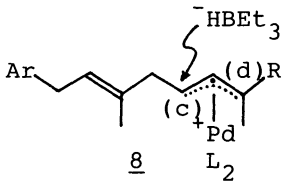
6 7

85%, 6/7=80/20

σ-complex of palladium on carbon (b) originally attached to a tosyl group in 4.

From the argument described above, we should choose the synthon bearing a tosyl group on carbon (c), which could be led to the π-allyl complex (8) having a similar environment as that of 3, namely (c) is a secondary and (d) is a tertiary carbon atom, in a synthetic design of co-enzyme Q_{10}.

The synthesis of co-enzyme Q_{10} (14) was achieved according to Scheme 1. The E-allyl alcohol (10, 712 mg, 2 mmol), prepared from 9 by the method developed by Sato and his co-workers,[3] was mesylated with Et_3N (242 mg, 2.4 ml) and mesyl chloride (275 mg, 2.4 mmol) in ether (5 ml) at room temperature for 3 h. After quenching with phosphate buffer (pH 7), the ether extract was dried over $MgSO_4$ and evaporated to give the crude mesylated product (11). On the other hand, solanesyl p-tolyl sulfone (770 mg, 1 mmol) was lithiated with butyl lithium (1.05 mmol) in THF (20 ml) at - 78 °C for 30 min followed by the addition of a THF solution (2 ml) of 11 prepared above. The reaction



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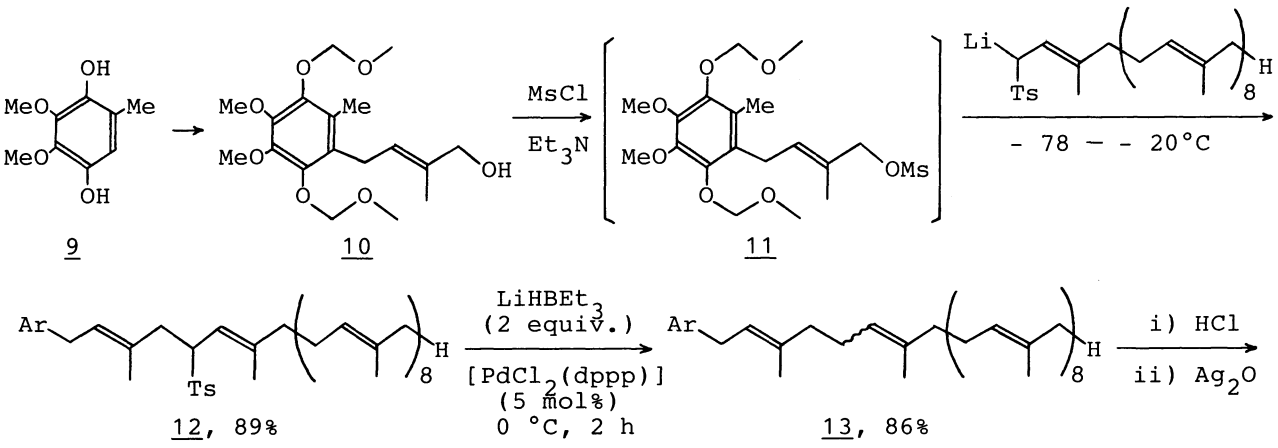
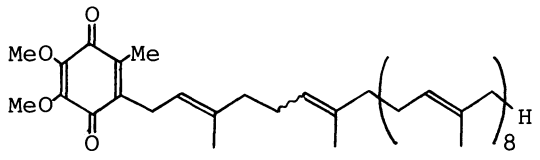




14, 94%, E/Z=95/5

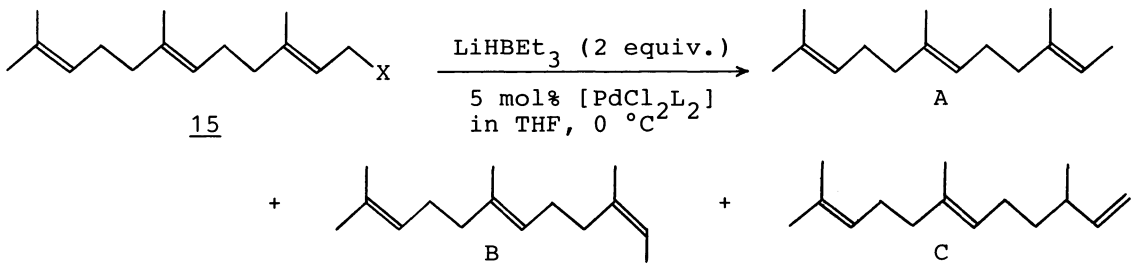
Scheme 1. Synthesis of Co-enzyme Q_{10}.

mixture was gradually warmed to - 20 °C and quenched with phosphate buffer at - 20 °C. The product 12 was separated from the AcOEt extract by a preparative TLC (SiO_2, hexane/AcOEt = 7/1) in 89% yield (986 mg) as an oil. The subsequent desulfonylation was accomplished in a similar manner reported previously[2] with 2 equiv. of $LiHBEt_3$ in the presence of 5 mol% of [$PdCl_2$(dppp)] in THF at 0 °C for 2 h to give 13 (oil) in 86% yield. 400 MHz ^{1}H-NMR spectrum of 13 thus prepared indicated that the migration of the double bond did not occur at all during the reduction. After a simple acid-catalyzed deprotection of 13 (72 mg, 0.075 mmol) in MeOH/$CHCl_3$ (2 ml/1 ml) containing one drop of conc. HCl with stirring overnight under nitrogen and a usual work-up followed by the oxidation with Ag_2O (52 mg, 0.225 mmol) in hexane at room temperature for 30 min with vigorous stirring, co-enzyme Q_{10} (14) was isolated by a preparative TLC (SiO_2, hexane/AcOEt = 10/1) in 94% yield (62 mg) as an yellow oil which gradually solidified. HPLC [Waters, μ-PORASIL Column No. 27477; hexane/AcOEt = 40/1, 3.0 ml/min; Retention time 8.2 (Z-isomer), 9.5 (E-isomer) min] analysis showed the contamination of a small amount of Z-isomer (E/Z = 95/5).

The present palladium-catalyzed reduction system proved to be applicable to other wide variety of allylic compounds (15) as listed in Table 2.[4] It was found that [$PdCl_2$(dppb)] was also an effective catalyst, especially toward the p-tolyl sulfone (Entry 1'), chloride (2'), phenyl ether (3'), and ammonium salt (12') with respect to stereoselectivity. The methyl sulfide (Entry 8) and amine (11) were hardly reduced.

Further work is in progress to elucidate the scope and limitation of the present reduction system in our laboratory.

Table 2. Palladium-Catalyzed Reduction of Allylic Compounds



Entry	X	Ligand[a] L	Reaction time	Isolated yield/%	Recovery of 15	Ratio[b] A : B : C
1	Ts	dppp	30 min	87	-	97 : 2 : 1
1'	Ts	dppb	30 min	86	-	>99 : - : -
2	Cl	dppp	15 min	95	-	92 : 3 : 5
2'	Cl	dppb	<5 min	86	-	98 : 1 : 1
3	OPh	dppp	10 min	87	-	99 : 1 : 0
3'	OPh	dppb	<5 min	81	-	>99 : - : -
4	OCH_2Ph	dppp	25 min	78	-	>99 : - : -
5	OMe	dppp	20 min	92	-	>99 : - : -
5'	OMe	dppb	4 h	78	-	>99 : - : -
6	$OSiMe_2Bu^t$	dppp	5 h	80	-	>99 : - : -
6'	$OSiMe_2Bu^t$	dppb	12 h	13	74	96 : 1 : 3
7	SPh	dppp	3.5 h	85	-	96 : 4 : 0
8	SMe	dppp	3.5 h	10	81	98 : 1 : 1
9	SOMe	dppp	15 min[c]	83	-	94 : 6 : 0
9'	SOMe	dppb	10 h[c]	77	-	92 : 7 : 1
10	SO_2Me	dppp	1 h	84	-	98 : 2 : 0
10'	SO_2Me	dppb	7 h	92	-	96 : 3 : 1
11	$N(CH_2)_5$	dppp	overnight	-	89	
12	$^+N(CH_2)_5Me$	dppp	1 h	91	-	93 : 3 : 4
12'	$^+N(CH_2)_5Me$	dppb	1 h	90	-	97 : 2 : 1

a) dppp and dppb mean 1,3-bis(diphenylphosphino)propane and 1,4-bis(diphenylphosphino)butane, respectively. b) Determined by GLPC [2% OV-17/Chromosorb W (AW-DMCS), 60-80 mesh, 3m; N_2, 60 ml/min; 110 °C; Retention time: 19.2 (C), 26.4 (B), 29.2 (A) min]. c) 3 equiv. of $LiHBEt_3$ was used.

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3) K. Sato, O. Miyamoto, S. Inoue, T. Yamamoto, and Y. Hirasawa, J. Chem. Soc., Chem. Commun., 1982, 153.
4) The Pd-catalyzed reduction of allylic compounds has recently been demonstrated in the following papers: H. Hey and H. J. Arpe, Angew. Chem., Int. Ed. Engl., 12, 928 (1973); J. Tsuji and T. Yamakawa, Tetrahedron Lett., 1979, 613; R. O. Hutchins, K. Learn, and R. P. Fulton, Tetrahedron Lett., 21, 27 (1980); R. O. Hutchins and K. Learn, J. Org. Chem., 47, 4380 (1982); E. Keinan and N. Greenspoon, Tetrahedron Lett., 23, 241 (1982); E. Keinan and N. Greenspoon, J. Org. Chem., 48, 3545 (1983); J. Tsuji, I. Shimizu, and I. Minami, Chem. Lett., 1984, 1017.

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