Palladium-catalyzed isomerization of (homo-)allylic alcohols in molten tetrabutylammonium bromide, a recyclable system

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Abstract

Saturated ketones have been produced by heating secondary allylic alcohols and catalytic amounts of PdCl$_2$ or Pd(OAc)$_2$ in molten n-Bu$_4$NBr. After extraction of the organic material with diethyl ether, the ionic layer and the catalyst can be reused directly. Linear secondary homoallylic alcohols led also to the corresponding saturated ketones as main products. The procedure was less selective for primary allylic alcohols.
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1. Introduction

Generally speaking, isomerization is expressed as "Atom Economical Reaction" which means no increase or decrease of atoms before and after the reaction [1]. As pointed out in a recent review, "isomerization of allylic alcohols forms an elegant shortcut to carbonyl compounds, which otherwise would have to be made in a two-step sequence", i.e. oxidation of the alcohol and subsequent reduction of the C=C double bond [2]. This one-pot reaction of allylic alcohols can be carried out using metal-catalysts, this field being dominated by ruthenium, rhodium, iridium and iron complexes [2–5]. Although palladium complexes mediate an impressive array of chemical reactions [6], such an isomerization has been scarcely documented by Pd-catalysts [2,3,7–11] and was rather observed as an undesirable side reaction [12–16].

Recently, we have revealed the palladium-catalyzed dehydrogenation of benzylic alcohols in molten tetra-n-butyl ammonium bromide [17]. Since the system, catalyst + ammonium salt, is recyclable and does not require any additive, this procedure is of interest in the emerging context of ionic liquids and molten salts as solvents for "green" chemical reactions.[1] We report herein that under similar

conditions, secondary allylic alcohols may lead to saturated ketones with modest to high yields (Eq. (1)). In addition, the process was extended to homoallylic alcohols.

2. Results and discussion

A mixture of 1-octen-3-ol (**1**) (1 mmol), PdCl$_2$ (**2**) (0.03 mmol) and n-Bu$_4$NBr (1.5 g) was heated at 120 °C under argon atmosphere for 3.5 h. After extraction of the mixture with diethyl ether, GC/MS analysis showed the partial consumption of **1** and the formation of 3-octanone (**3**), 1-octen-3-one (**4**) and 3-octanol (**5**), the saturated ketone being obtained with 90% selectivity (Eq. (1), Table 1, entry 1). Increasing the reaction time to 5.5 h led to the full consumption of the substrate without any change in the product ratio (Entry 2). Interestingly, five successive recyclings of both catalyst and n-Bu$_4$NBr were performed with negligible loss of activity and selectivity (entries 3–7).

$$\text{R: } n\text{-C}_5\text{H}_{11}, \text{"Pd": PdCl}_2 \text{ (2), Pd black (6), Pd(OAc)}_2 \text{ (7)}$$
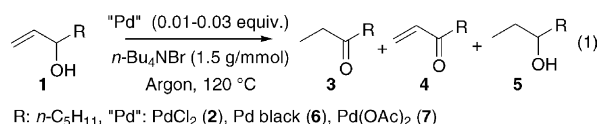
The conversion of **1** was slightly reduced with Pd black (**6**) as catalyst (Entry 8). To facilitate the work up, we tested the use of toluene as a co-solvent [29,30]. High conversion and selectivity were obtained for the first run with **2** as

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[1] For reviews, see refs. [18–28].

Table 1
Reaction of 1-octen-3-ol (1 mmol) catalyzed by palladium (0.03 equiv.) at 120 °C under argon atmosphere

Entry	"Pd"	Solvent	Conversion %[a]	3, %[a]	4, %[a]	5, %[a]
1[b]	2	n-Bu$_4$NBr[c]	80	72	3	3
2[d]	2	n-Bu$_4$NBr[c]	100	89	5	4
3[d]	Reuse	Reuse	98	90	2	2
4[d]	Reuse	Reuse	98	91	5	2
5[d]	Reuse	Reuse	98	87	2	2
6[d]	Reuse	Reuse	96	87	2	2
7[d]	Reuse	Reuse	97	86	2	2
8[d]	6	n-Bu$_4$NBr[c]	91	80	4	4
9[d]	2	n-Bu$_4$NBr[c] + PhMe[e]	99	86	7	6
10[d]	Reuse	n-Bu$_4$NBr (reuse) + PhMe[e]	25	10	6	4
11[d]	2	n-Bu$_4$NBr[c] + PhMe[e,f]	96	83	7	5
12[d]	Reuse	n-Bu$_4$NBr (reuse) + PhMe[e]	65	54	3	3
13[d]	6	n-Bu$_4$NBr[c] + PhMe[e]	2	1	0	0
14[d]	2	PhMe[e]	93	63	16	11
15[d]	2	DMF[e]	10	7	3	0
16[d]	6	DMF[e]	99	78	3	3
17[d]	7	DMF[e]	100	92	4	3
18[d,g]	7	DMF[e]	86	50	32	0
19[d]	7	n-Bu$_4$NBr[c]	100 (96)	92 (89)	5 (5)	1 (3)
20[d]	Reuse	Reuse	100 (99)	93 (90)	4 (4)	3 (3)
21[d]	Reuse	Reuse	100 (97)	92 (88)	2 (3)	2 (3)
22[d]	Reuse	Reuse	100 (95)	92 (87)	2 (2)	2 (2)
23[d]	Reuse	Reuse	100 (96)	92 (86)	<2 (2)	<2 (2)
24[d]	Reuse	Reuse	100	92	<2	<2

[a] Calculated by GC with 1-octanol as standard; values in brackets are results obtained using 0.01 equiv. of catalyst.
[b] Reaction time: 3.5 h.
[c] 1.5 g.
[d] Reaction time: 5.5 h.
[e] 1.5 ml.
[f] PhMe introduced 1 h after the start of the reaction.
[g] Reaction carried out at room temperature.

catalyst but the conversion dropped in the recycling experiment (entries 9 and 10). When toluene was introduced in the mixture 1 h after the start of the reaction, the recycling was improved (entries 11 and 12). This indicates lower leaching of palladium, i.e. lower transfer of palladium species from the molten salt to the organic phase. These experimental conditions were however not enough effective for recyclings. Almost no reaction was observed with 6 in using the n-Bu$_4$NBr/PhMe association (Entry 13); this may be due to the dissolution of 1 in toluene rather than in n-Bu$_4$NBr while the catalyst would remain exclusively in the molten salt. This leads us to suspect that with the 2/n-Bu$_4$NBr/PhMe system, the reaction took place in both phases. Performing the reaction with 2 without n-Bu$_4$NBr in either PhMe (Entry 14) or DMF (Entry 15) afforded low selectivity or low conversion respectively. In contrast to 2, 6 in DMF was an effective catalyst (Entry 16). Actually, the best activity and selectivity in this solvent was reached with Pd(OAc)$_2$ (7) as catalyst (Entry 17). The catalysis by 7 in DMF at room temperature instead of 120 °C decreased considerably the yield of 3 to the benefit of 4 (Entry 18). Since in DMF with 6 and also with 7, agglutination of palladium on the walls of the flask precluded recovery of the catalyst, the reaction was examined, once more, in n-Bu$_4$NBr but with 7 as catalyst. Thus, conversion, selectivity and recycling, all superior to

2, were obtained and no deactivation of the catalytic system was observed even for six successive runs (entries 19–24). Furthermore, the catalyst loading may be lowered to 1% with solely a slight decrease of the efficiency (entries 19–24).

These results urged us to examine the reactivity of other allylic alcohols in n-Bu$_4$NBr using 2 and 7 as catalysts. The results assembled in Table 2 indicate the limits of the procedure and in general, the superiority of 7 as catalyst. The efficiency of the isomerization of linear secondary allylic alcohols decreased with the substitution of the double bond. As expected from the results of Table 1, high conversion and selectivity were obtained from alcohols having a monosubstituted terminal double bond (Table 2, entries 1 and 2). The conversion remained high but the selectivity decreased with a phenyl group in β-position (entries 3 and 4), the α,β-unsaturated ketone becoming even the main product from 1,3-diphenylpropan-1-ol. With an alkyl group in β-position instead of a phenyl, the conversion was lower but the isomerization product resulted in a better selectivity (entry 5). A substituent in α-position led to a drop of the conversion but to a fair selectivity (entries 6 and 7). A similar trend was observed from Z-2-benzyliden-1-cyclohexanol (entry 8). Cholest-4-en-3β-ol (entry 9) showed a different reactivity since the main product was cholesta-3,5-diene whose structure was unambiguously established from comparison

Table 2
Reaction of various secondary allylic alcohols (1 mmol) in n-Bu$_4$NBr (1.5 g) catalyzed by PdCl$_2$ (**2**) or Pd(OAc)$_2$ (**7**) (0.03 equiv.) at 120 °C under argon atmosphere

Entry	Substrate	Time, h using		Conversion % using		Products	Yields % using	
		2	**7**	**2**	**7**		**2**	**7**
1	CH$_2$=CH-CH(OH)-(CH$_2$)$_{16}$Me	20	20	100	100	EtCO-(CH$_2$)$_{16}$Me	88[a]	90
						EtCH(OH)-(CH$_2$)$_{16}$Me	7[a]	6
2	CH$_2$=CH-CH(OH)-Ph	36	16	>95	>95	EtCO-Ph	71	85[b]
3	Ph-CH=CH-CH(OH)-Me	72[c]	36	76	>95	Ph-CH$_2$CH$_2$-CO-Me	41	57
						Ph-CH=CH-CO-Me	19	25
						Ph-CH$_2$CH$_2$-CH(OH)-Me	12	14
4	Ph-CH=CH-CH(OH)-Ph	24	24	66	89	Ph-CH$_2$CH$_2$-CO-Ph	13	16
						Ph-CH=CH-CO-Ph	41	59
5	n-Pr-CH=CH-CH(OH)-Ph	24	24	48	60	n-Pr-CH$_2$CH$_2$-CO-Ph	31	38
						n-Pr-CH=CH-CO-Ph	10	13
6	CH$_2$=C(Me)-CH(OH)-Ph	22	24	39	51	(Me)$_2$CH-CO-Ph	26	36
						CH$_2$=C(Me)-CO-Ph	8	12
7	CH$_2$=C(Ph)-CH(OH)-Me	48	48	27	25	Ph-CH(Me)-CO-Me	21	17
8	2-(phenylmethylene)cyclohexan-1-ol	72	72	32	38	2-(phenylmethyl)cyclohexanone	25	22
9	Cholest-4-en-3β-ol	48	48	100	100	5α-Cholestan-3-one	12	4
						Cholest-4-en-3-one	8	3
						Cholesta-3,5-diene	76	88

[a] First recycling, 3 days time: 78 and 10%.
[b] Recyclings, 16 h time; 1st: 83%, 2nd: 81%, 3rd: 84%.
[c] This reaction carried out at 120 °C for 72 h in DMF led to 72% conversion with formation of PhCH$_2$CH$_2$COMe (9%), PhCH = CHCOMe (40%) and PhCH$_2$CH$_2$C(OH)Me (16%).

of its NMR spectra[2] with literature data. Only traces of the isomerization product were also obtained from primary allylic alcohols, such as cinnamyl alcohol and geraniol, the procedure leading to a complex mixture.

The procedure was finally applied to a few homoallylic alcohols (Eq. (2)). Both **2** and **7** induced high conversion of 1-dodecen-4-ol (**8a**) to afford mainly the saturated ketone **9a** (Table 3, entries 1 and 2); α,β-unsaturated ketone **10a**, allylic alcohol **11a** and saturated alcohol **12a** were also isolated and the ratio between the products depended on the nature of the catalyst used. Lower reactivity was observed when the terminal double bond was substituted by a methyl group,

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[2] The NMR data of cholesta-3,5-diene [31–33] differ strongly from those of cholesta-2,4-diene [34] and cholesta-4,6-diene [35].

Table 3
Reaction of homoallylic alcohols (1 mmol) in *n*-Bu$_4$NBr (1.5 g) catalyzed by PdCl$_2$ (**2**) or Pd(OAc)$_2$ (**7**) (0.03 equiv.) at 120 °C under argon atmosphere

Entry	Alcohol	"Pd"	Time (h)	Conversion %	Products (%)
1	**8a**	**2**	48	96	**9a** (43%) + **10a** (10%) + **11a** (5%) + **12a** (17%)
2	**8a**	**7**	48	98	**9a** (54%) + **10a** (22%) + **11a** (8%) + **12a** (10%)
3	**8b**	**2**	96	68	**9b** (50%)
4	**8b**	**7**	96	73	**9b** (56%)
5	**8c**	**2**	48	[a]	**9c** (26%) + **10c** (6%)[a]
6	**8c**	**7**	48	[b]	**9c** (55%) + **10c** (22%)[b]

[a] A mixture of alcohols including **8c** was recovered ($\approx$60%).
[b] A mixture of alcohols including **8c** was recovered ($\approx$16%).

the saturated ketone **9b** being however selectively formed (entries 3 and 4). The benzylic alcohol **8c** led mainly to ketones **9c** and **10c** (entries 5 and 6). In contrast to the above homoallylic alcohols, 3β-cholesterol was reluctant to react under these conditions.

a: R^1 = *n*-C$_8$H$_{17}$, R^2 = H; b: R^1 = *n*-C$_8$H$_{17}$, R^2 = Me; c: R^1 = Ph, R^2 = H.
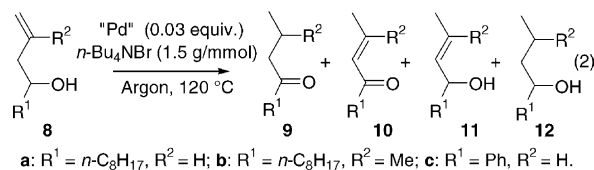
3. Conclusion

Molten tetra-*n*-butyl ammonium bromide may act as a good medium for isomerization of secondary unsaturated alcohols to corresponding saturated ketones by catalytic amounts of palladium, the system, catalyst + ammonium salt, being recyclable. Nevertheless, the efficiency and the selectivity of the method are highly sensitive to the substitution at the double bond. As we have previously suspected [13,16,17], the ammonium salt apparently stabilizes the palladium species which are active for catalysis. These results broaden the scope of molten ammonium salts as solvents for recyclable Pd-catalytic processes.

4. Experimental

^{1}H and ^{13}C NMR (250 and 63 MHz) spectra were obtained on a Bruker AC 250 spectrometer using TMS as internal standard and CDCl$_3$ as solvent. GC analyses were carried out using a HP 5890 series II apparatus equipped with an Innowax capillary column (isotherm at 110 °C, octan-1-ol as internal standard). GC/MS analyses were carried out using a Thermoquest Trace 2000 series apparatus equipped with a HP1 capillary column.

4.1. Typical procedure

Palladium salt (0.03 mmol) and tetra-*n*-butylammonium bromide (1.5 g) were mixed under vacuum (5 × 10^{-2} to 10^{-1} mbar) at 120 °C for 2 h in a round-bottomed

flask equipped with a magnetic stir bar and a reflux condenser. Then, the mixture was placed under argon and the (homo-)allylic alcohol (1 mmol) was added. After heating at 120 °C for the time indicated in tables, the mixture was cooled and extracted with diethyl ether (3 × 10 ml). The solid phase is thus ready for use in a new run. The organic phase was evaporated under reduced pressure and the residue was purified by flash-chromatography. The products were identified by mass and NMR spectroscopies, and comparison with authentic samples or literature data [31–33,36,37].

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