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# Enantioselective Hydrogenation of $\alpha,\beta$ -Unsaturated Ketones over Palladium on Charcoal in the Presence of (-)-Ephedrine

Claire Thorey, Françoise Hénin, Jacques Muzart\*

Unité de Recherche "Réarrangements Thermiques et Photochimiques" Associée au CNRS,  
Université de Reims Champagne-Ardenne, B.P. 1039, 51687 Reims Cédex 2, France

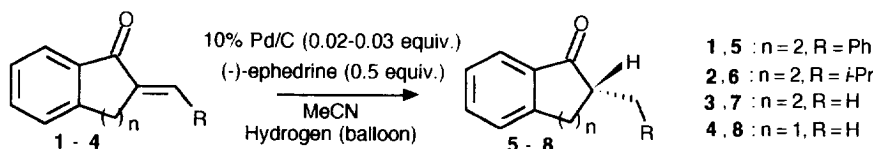
**Abstract:** The title reaction carried out under an atmosphere of hydrogen led to the corresponding saturated ketones with enantiomeric excesses of up to 36 %.

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Palladium-catalyzed heterogeneous hydrogenation of the double bond of  $\alpha,\beta$ -unsaturated ketones is a traditional method whose mechanism has been extensively studied.<sup>1</sup> Depending on the experimental conditions, the reaction could involve either direct 1,2-addition to the double bond or 1,4-addition of hydrogen. The occurrence of the latter process can be inferred from the isolation of the enol on hydrogenation of certain  $\alpha,\beta$ -unsaturated ketones.<sup>2</sup>

Our interest in the aminoalcohol-catalyzed enantioselective ketonisation of enol species<sup>3</sup> led us to envisage whether the hydrogenation of a prochiral  $\alpha,\beta$ -unsaturated ketone over palladium could lead readily to the corresponding optically active saturated ketone when carried out in the presence of enantiopure aminoalcohols.

While the enantioselective heterogeneous hydrogenation of the C=C bond of  $\alpha,\beta$ -unsaturated acids and esters, particularly those bearing a nitrogen atom in  $\alpha$ -position, has been relatively well studied,<sup>4</sup> such a reaction has barely been documented for  $\alpha,\beta$ -unsaturated ketones.<sup>5</sup> Thus, the subject was challenging. Two recent papers describing the enantioselective hydrogenation of isophorone over modified palladium catalysts<sup>6</sup> urged us to disclose our main preliminary results which have been obtained with 1-4 as substrates (Eq., Table).



In using (-)-ephedrine to induce the chirality and 10% palladium on charcoal from the Janssen Company as catalyst, the hydrogenation of (*E*)-1 in acetonitrile at room temperature and under an atmospheric pressure led effectively to 5 with a moderate enantiomeric excess (run 1). Similar results were obtained on changing the solvent to DMF, Et<sub>2</sub>O or EtOAc or in using samples of supported palladium from Engelhard or Johnson Matthey Companies. The modification of the reaction temperature between +40 and -10°C did not greatly influence the *ee* (runs 2 to 4).

It was interesting to compare the behavior of (*E*)- and (*Z*)- $\alpha,\beta$ -unsaturated ketones towards hydrogenation since the geometry of the C=C bond could reverse the asymmetric induction.<sup>7</sup> The hydrogenation of a mixture of (*E*)- and (*Z*)-2-benzylidenetetral-1-ones containing mainly the (*Z*)-isomer afforded (*S*)-5 (28 % *ee*, run 5). Therefore, it appears that i) the same enantiomer was mainly obtained whatever the geometry of the double bond of the precursor (compare runs 1 and 5), ii) the *ee* was slightly lower for (*Z*)-1. Such observations have been confirmed in analyzing the reactivity of (*E*)- and (*Z*)-2 which have been readily obtained in pure geometrical form.<sup>8</sup> The hydrogenation of (*E*)-2 (run 6) was much more rapid than that of (*Z*)-2 (run 7). Nevertheless, both reactions led to (+)-6 as the major enantiomer, the best *ee* being again obtained from the (*E*)-isomer. It is also worthy of mention that these results do not seem to be due to a geometrical isomerization of the substrate during

the process since the recovered unreacted  $\alpha,\beta$ -unsaturated ketone was exclusively (*E*)-2 in run 6 and (*Z*)-2 in run 7.

The hydrogenation of  $\alpha$ -methylene ketones 3 and 4 was more enantioselective for the tetralone derivative (run 8) than for the indanone (run 9).

**Table.** Enantioselective hydrogenation of 1-4 to 5-8.

*Typical procedure:* A round-bottomed flask containing 10% Pd on C (from Janssen Company, 0.02-0.03 equiv.), (-)-ephedrine (0.5 equiv.), substrate (0.2 mmol) and MeCN (5 ml) was purged with a flow of hydrogen for a few min. Then, the flask was connected to a rubber balloon filled with hydrogen. The mixture was stirred for the time indicated in the Table. After filtration and evaporation of the solvents, the purification was carried out by preparative thin-layer chromatography.

Run	S.M.	t°C	Time h	Conver- sion %	5-8 Yield %	ee % (Conf.)
1	( <i>E</i> )-1	RT	1	100	5: 85	32 <sup>a</sup> ( <i>S</i> ) <sup>b</sup>
2	( <i>E</i> )-1	40	0.5	100	5: 85	29 <sup>a</sup> ( <i>S</i> ) <sup>b</sup>
3	( <i>E</i> )-1	0	1	100	5: 82	36 <sup>a</sup> ( <i>S</i> ) <sup>b</sup>
4	( <i>E</i> )-1	-10	6	100	5: 83	33 <sup>a</sup> ( <i>S</i> ) <sup>b</sup>
5	( <i>E</i> )/( <i>Z</i> )-1 <sup>c</sup>	RT	0.5	100	5: 93	28 <sup>a</sup> ( <i>S</i> ) <sup>b</sup>
6	( <i>E</i> )-2	RT	1	70 <sup>d</sup>	6: 67	30 <sup>e</sup> ( $\delta$ )
7	<i>Z</i> -2	RT	17.5	58 <sup>g</sup>	6: 32	20 <sup>e</sup> ( $\delta$ )
8	3	RT	3	72	7: 68	28 <sup>e</sup> ( <i>R</i> ) <sup>b</sup>
9	4	RT	0.75	100	8: 50	19 <sup>a</sup> ( <i>R</i> ) <sup>b</sup>

<sup>a</sup>ee determined from HPLC using a chiral column (Daicel, Chiralcel OB-H; eluant: n-hexane/*i*-PrOH, 90/10). <sup>b</sup>Configuration attributed from comparison of specific rotation with literature data.<sup>9</sup> <sup>c</sup>A 15/85 mixture of (*E*)-1 and (*Z*)-1 was used. <sup>d</sup>Pure (*E*)-isomer was recovered. <sup>e</sup>ee determined from HPLC using a chiral column (Daicel, Chiralcel OD; eluant: n-hexane/*i*-PrOH, 98/2). <sup>f</sup>(+) enantiomer was mainly obtained, its presumed absolute configuration is *S*. <sup>g</sup>Pure (*Z*)-isomer was recovered.

It is premature to make broad comments about the chiral interactions which afford optically active ketones under these hydrogenation conditions. Nevertheless, the independence of the configuration of the created stereogenic center *vis-à-vis* the olefin geometry and the comparison of the results with our studies on the aminoalcohol-induced tautomerization of photoenols<sup>10</sup> suggest that enol species are, at least in part, involved in the course of the process here reported.

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