Palladium on Charcoal plus Enantiopure Amino Alcohols as Catalytic Systems for the Enantioselective 1,4-Reduction of α-Substituted α,β-Unsaturated Ketones

Claire Thorey,[a] Sandrine Bouquillon,[a] Abdellatif Helimi,[a] Françoise Hénin,*[a] and Jacques Muzart*[a]

Keywords: Amino alcohols / Enantioselective hydrogenation / Ene-imines / Enones / Palladium

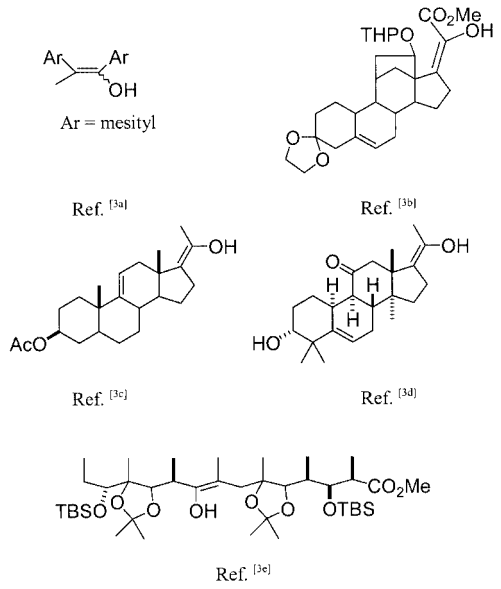
The chemoselective reduction of α,β-unsaturated cyclic ketones **1**–**7** to the corresponding saturated ketones **8**–**12** was shown to proceed mainly by 1,4-addition of hydrogen to the activated double bond, resulting in enolic species. These entities could be selectively protonated in the presence of enantiopure amino alcohols to afford the corresponding saturated ketones with *ee* values of up to 47%.

Introduction

The heterogeneous metal-catalysed hydrogenation of the double bond of α,β-unsaturated ketones is a traditional method widely used in organic chemistry,[1] the mechanism of which has been extensively studied.[1,2] Depending on the solvent and the acidic/basic character of the medium, it has been proposed[1,2] that the reaction could involve either direct 1,2-addition of hydrogen to the double bond or 1,4-addition to the conjugated system. The existence of the latter mechanism has been clearly demonstrated in a couple of cases, since stable enols have been isolated and characterized from the hydrogenation of the corresponding α-enones on supported palladium or platinum (Scheme 1).[3]

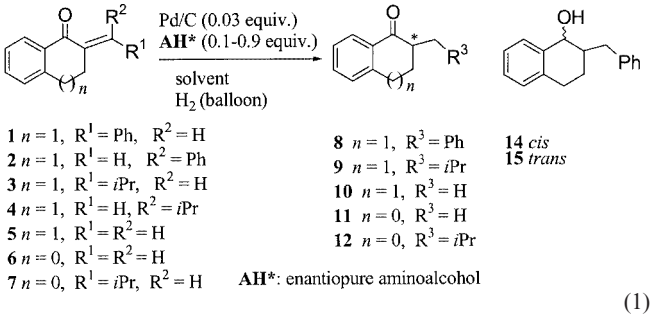
Our interest in the enantioselective ketonisation of enol species[4,5] led us to speculate that the transformation of an α-substituted α,β-unsaturated ketone into an optically active saturated ketone might be readily accomplished by heterogeneous palladium-catalysed hydrogenation in the presence of substoichiometric amounts of an enantiopure amino alcohol (**AH***), which would mediate the tautomerization of the enol intermediate.[6]

Such a subject was challenging.[7] Indeed, enantioselective heterogeneous hydrogenation of C=C bonds of α,β-unsaturated ketones has barely been documented; to the best of our knowledge, the enantiomeric excesses reported in the literature essentially concern the hydrogenation of cyclic enones in which a stereogenic centre was created in the β-position (*ee* values of up to 85%).[8−11] When the stereogenic centres have been in the α-position, in contrast, the reduction of cyclic or acyclic enones has resulted in practically no *ee*.[8,12] Here we report results obtained with **1**−**7** as substrates [Equation (1)] under various experimental hydrogenation conditions, these substrates having been chosen for purposes of comparison with our previous methodologies.[4,5]



Scheme 1 . Examples of enols generated by the heterogeneous hydrogenation of α-enones

[a] Unité Mixte de Recherche "Réactions Sélectives et Applications" C.N.R.S., Université de Reims Champagne-Ardenne,
B. P. 1039, 51687 Reims Cedex 2, France
Fax: (internat.) + 33-3/26913310
E-mail: francoise.henin@univ-reims.fr
jacques.muzart@univ-reims.fr



1 $n = 1$, $R^1 = Ph$, $R^2 = H$
2 $n = 1$, $R^1 = H$, $R^2 = Ph$
3 $n = 1$, $R^1 = iPr$, $R^2 = H$
4 $n = 1$, $R^1 = H$, $R^2 = iPr$
5 $n = 1$, $R^1 = R^2 = H$
6 $n = 0$, $R^1 = R^2 = H$
7 $n = 0$, $R^1 = iPr$, $R^2 = H$

8 $n = 1$, $R^3 = Ph$
9 $n = 1$, $R^3 = iPr$
10 $n = 1$, $R^3 = H$
11 $n = 0$, $R^3 = H$
12 $n = 0$, $R^3 = iPr$

AH*: enantiopure aminoalcohol

14 *cis*
15 *trans*

(1)

Results

Enantioselective hydrogenation conditions have been studied in particular detail with (*E*)-2-benzylidene-1-tetralone (**1**) as substrate and (−)-ephedrine (**13**) as **AH***. In the course of previous studies on the formation of optically active ketones produced from a cascade reaction involving deprotection, decarboxylation and enantioselective protonation steps in the presence of Pd catalysts,[5] we established that:

i. the enantiomeric excesses could be strongly dependent on the nature of the heterogeneous catalyst[5b,5c] and the temperature,[5d,5e]

ii. 0.3 equiv. of the amino alcohol was the optimum amount for the protonation of enolic species,[5b,5c]

iii. acetonitrile was a suitable solvent.[5c]

We therefore firstly examined the influence of these factors on the hydrogenation of **1** (Figure 1, Tables 1 and 2).

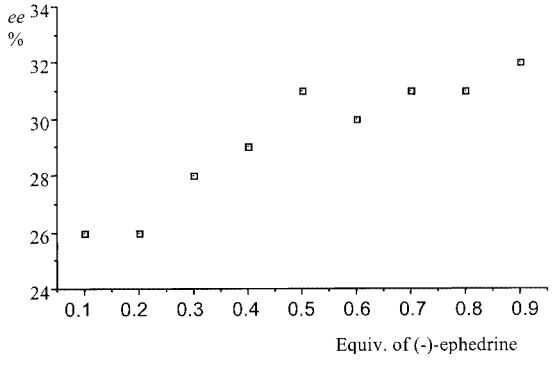


Figure 1. Influence of the quantity of (−)-ephedrine on the *ee* of 2-benzyl-1-tetralone; experimental conditions: 0.03 equiv. of 10% palladium on charcoal (Janssen, ref. no. 19.503.06) was added to a solution containing **1** and different quantities of **13** in anhydrous acetonitrile (30 mL per mmol of **1**); the suspension was saturated with dihydrogen and stirred for 40 min at room temperature under hydrogen (rubber balloon); compound (*S*)-**8** was isolated in 84−98% chemical yields; the (*S*) configuration was attributed to the main enantiomer by comparison of its optical rotation with literature data;[13] the *ee* was determined by HPLC analysis

From Figure 1,[13] in which the obtained *ee* values of **8** are plotted against the amounts of **13** added, it appeared that the enantioselectivity increased from 26 to 31% when the quantity of the amino alcohol was varied from 0.1 to 0.5 equiv., and then remained unchanged.

In contrast to previous observations,[5b,5c,14] the results summarized in Table 1 show that the nature of the supported palladium catalyst[15] had no effect on the *ee* of **8** for reactions carried out at room temperature (Entries 2, 6, 8, 10 and 11). We observed that the *ee* was slightly decreased when the reaction temperature was 40 °C and slightly improved when the reaction was carried out at 0 °C (Entries 1−4). Reduction of the reaction temperature below 0 °C, however, did not increase the enantioselectivity (Entry 5) but eventually inhibited the process (Entry 7). No racemization of the resulting ketone occurred under the experimental conditions, as its optical activity was not modified with the reaction time (Entries 2 and 3). An increase in the reaction time (Entry 3) or the temperature (Entry 1), however, induced overreduction, resulting in *cis*- and *trans*-2-benzyltetrahydro-1-naphthols (**14** and **15**, respectively). We should note that the presence of the amino alcohol reduces this overreduction; indeed, hydrogenation of **1** in the absence of **AH*** under the conditions of Entry 2 reduced the yield of **8** to 78%, and 18% of **14** + **15** were isolated. Thus, to avoid excessive carbonyl reduction, it was necessary to add an amino alcohol to the medium and not to prolong the reaction time. Actually, **14** and **15** were detected by TLC in the other experiments, but only in minute amounts. The order of introduction of the reagents was also important, the *ee* of **8** being reduced from 32 to 22% when the supported palladium was introduced as the first reagent instead of the last one (Entries 8 and 9); this is discussed below. Note also that the use of rhodium on alumina powder in ethyl acetate in place of a Pd catalyst in acetonitrile also afforded **8**, but with no enantioselectivity, and the reaction was slower (Entry 12). We also examined the use of soluble catalysts such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and Pd(ephedrinate)$_2$ (**16**)[16] (Pd^{II} catalysts have already been efficiently used in hydrogenation reactions[17]). Neither of the first two catalysts promoted hydrogenation of **1**, whereas on use of **16** the saturated ketone was produced in a good chemical yield, but was almost racemic (Entry 13).

After these results, further experiments concerning solvent effects were carried out at room temperature with 0.03 equiv. of Pd/C and 0.5 equiv. of (−)-ephedrine (Table 2). In reduction reactions, the use of polar solvents may favour stereoselectivity[18] or the 1,4-addition process.[2b] From the results in Table 2,[19] no correlation could be found between the polarity of the solvent and the *ee* of **8**. Use of acetonitrile as solvent provided the best *ee* values even in the presence of water (Entries 2 and 14). In contrast, addition of water to DMF decreased the *ee*, and the substrate was not completely consumed after 1 h (Entries 15 and 16); furthermore, the hydrogenation process under these aqueous conditions was accompanied by (*E*)/(*Z*) isomerization of **1**. In protic solvents, the *ee* in methanol was lower than that in ethanol (Entries 20, 21).

The hydrogenation of **1** was also carried out in the presence of the enantiopure additives **17** to **26** (Scheme 2) to examine the influence of their structures on the selectivity of the reaction (Table 3). As was to be expected, a change from (−)-ephedrine (Entry 2) to (+)-ephedrine (Entry 22)

Table 1. Effects of the support and catalyst on the enantioselective reduction of **1**

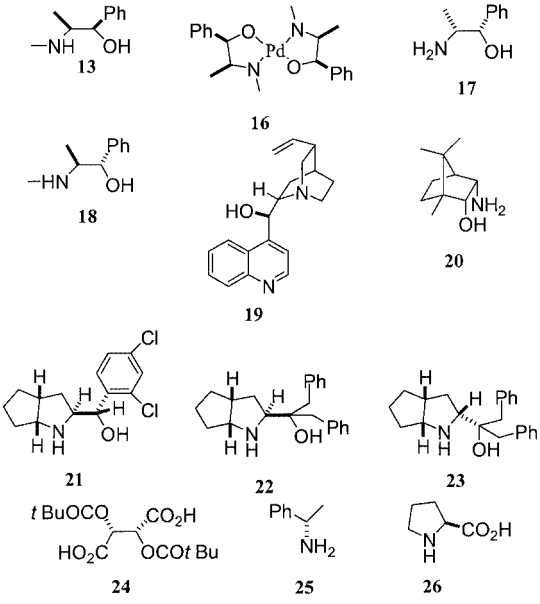
Entry[a]	Catalyst	Temp.	Time	**8**	
				Yield (%)	*ee* (%)[b]
1	10% Pd/C (Janssen)	40 °C	40 min	87	26
2	10% Pd/C (Janssen)	room temp.	30 min	86	31
3	10% Pd/C (Janssen)	room temp.	2 h	78[c]	30
4	10% Pd/C (Janssen)	0 °C	1 h	82	36
5	10% Pd/C (Janssen)	−10 °C	6 h	90	33
6	5% Pd/C (Engelhard 5105)	room temp.	40 min	90	32
7	5% Pd/C (Engelhard 5105)	−20 °C	19 h	0[d]	−
8	5% Pd/C (Engelhard 5011)	room temp.	45 min	89	32
9	5% Pd/C (Engelhard 5011)[e]	room temp.	40 min	89	22
10	10% Pd/C (Johnson Matthey 490)	room temp.	40 min	90	30
11	5% $Pd/BaSO_4$ (Aldrich)	room temp.	1.7 h	86	31
12[f]	5% Rh/Al_2O_3	room temp.	22 h	66	0[g]
13[h]	**16**	room temp.	3.5 h	78	2[i]

[a] Experimental: 0.03 equiv. of the metal catalyst was added to a solution of **1** and 0.5 equiv. of (−)-ephedrine in anhydrous acetonitrile (30 mL per mmol of **1**); the suspension was saturated with hydrogen and stirred under hydrogen (rubber balloon). [b] Determined by HPLC analysis, the main enantiomer having the (*S*) configuration.[13] [c] Also isolated: **14** (9%) and **15** (4%). [d] No reaction. [e] The supported catalyst was introduced into the flask before the other reagents. [f] Carried out with 0.02 equiv. of catalyst in ethyl acetate. [g] Determined by polarimetry. [h] In the absence of (−)-ephedrine, 0.1 equiv. of **16** was used. [i] Compound **8** had the (*R*) configuration.

Table 2. Influence of the nature of the solvent on the enantioselective reduction of **1**

Entry[a]	Solvent	ε[b]	Time	Yield (%)	*ee* (%)[c]
2	MeCN	37.5	30 min	86	31
14	$MeCN/H_2O$ (98:2)	38.4[d]	30 min	80	30
15	DMF	37	50 min	90	24
16	DMF/H_2O (4:1)	45.7[d]	1 h	67[e]	12
17	EtOAc	6.02	50 min	98	28
18	Et_2O	4.34	50 min	85	17
19	PhMe	2.38	1 h	83	11[f]
20	EtOH	24.5	30 min	86	15
21	MeOH	32.7	20 min	85	3

[a] General conditions: see Table 1; the Pd/C catalyst was obtained from Janssen (ref. no. 19.503.06) or Engelhard (type 5011). [b] Dielectric constant of the pure solvent at 25 °C.[19] [c] Determined by HPLC analysis. [d] Deduced from a linear effect of the volume composition. [e] Compound **2** also isolated (16%). [f] Determined by polarimetry.



Scheme 2. Chiral inducing entities

resulted in the same degree of enantioselectivity, but in the opposite sense. Lower *ee* values were obtained with (+)-pseudoephedrine (Entry 23) and (−)-norephedrine (Entry 24). Derivatives of (−)-cinchonidine have often been used as chiral modifiers in heterogeneous enantioselective hydrogenations,[7] but in our case the *ee* values dropped dramatically when cinchonidine was used (Entries 25 and 26). Higher *ee* values were observed with bornyl and azabicyclo compounds **20**, **21** and **23** (Entries 27, 28 and 30). The enantioselectivity observed with the azabicyclo compounds **22** and **23**, which present the same bicyclic geometry and no hydroxylic stereogenic centre, was greatly dependent on the configuration of the carbon atom bearing the nitrogen atom (Entries 29 and 30). Either no or very low enantioselectivity was obtained from the use of chiral inductors such as a diacid (Entry 31), an amine (Entry 32) or an amino acid (Entry 33).

The study was extended to the hydrogenation of α,β-unsaturated ketones **2**−**7** in the presence of (−)-ephedrine (Table 4).[20] The hydrogenation of a mixture of (*E*)- and (*Z*)-2-benzylidene-1-tetralones containing mainly the (*Z*) isomer afforded (*S*)-**8** (28% *ee*, Entry 34), the (*Z*)-enones **2** and **4** reacting more sluggishly than their corresponding (*E*) isomers **1** and **3** (Entries 2 and 34−38). It is fruitful to comment that both geometrical isomers afforded the same major enantiomer of the corresponding saturated ketone, without isomerization of the double bond of the starting unsaturated ketone under the reaction conditions (Entries 35 and 37). Hydrogenation of α-alkylideneindanones **6** and **7** (Entries 40−42) was less enantioselective than that of the tetralone derivatives. Aminoborneol **20**, which had been efficient

Table 3. Influence of the structure of the enantiopure additives on the enantioselectivity of the reduction of **1**

Entry[a]	Additive (C*O,C*N)[b]	Time	**8**		
			Yield (%)	*ee* (%)[c]	Config.[c]
2	**13** (*R*,*S*)	40 min	86	31	(*S*)
22	*ent*-**13** (*S*,*R*)	30 min	90	32	(*R*)
23	**17** (*S*,*S*)	30 min	91	22	(*S*)
24	**18** (*R*,*S*)	20 min	86	22	(*S*)
25[d]	**19** (*R*,*S*)	30 min	91	6	(*R*)
26[e]	**19** (*R*,*S*)	40 min	62	4[f]	(*R*)
27	**20** (*R*,*S*)	45 min	87	47	(*S*)
28	**21** (*S*,*S*)	35 min	89	38	(*S*)
29	**22** (−,*S*)	35 min	89	4	(*S*)
30	**23** (−,*R*)	30 min	85	41	(*R*)
31	**24**	1.5 h	69	0[f]	–
32	**25** (−,*S*)	40 min	69	2	(*S*)
33	**26** (−,*S*)	40 min	65	3	(*S*)

[a] Experimental conditions: see Table 1. [b] Absolute configuration of the C−O and C−N stereogenic centres of amino alcohols. [c] Configuration and *ee* determined as for Figure 1. [d] Reaction carried out at 50 °C to increase the solubility of cinchonidine. [e] Reaction carried out in a 99:1 acetonitrile/H_2O mixture as solvent. [f] Determined by polarimetry.

as an inductor of good enantioselectivities from **1**, gave disappointing results when other substrates were used (Entries 38 and 42).

Discussion

In this study, the first comments concern the chemoselectivity of the double-bond reduction of these α,β-unsaturated ketones under heterogeneous conditions. In the literature, the obtention of this chemoselectivity from this type of substrate either was easily attained[7d] or needed a particular solvent and the presence of an amine as additive.[21] The ability of an amine to poison the catalyst is well documented,[21,22] and our own results were quite well in agreement with that. Actually, **AH*** partially inhibited the carbonyl reduction, as hydrogenation of **1** usually resulted in minute amounts of alcohols **14** and **15**, detected by TLC analysis of the crude hydrogenation mixtures. The yields of **14** and **15** were increased in the absence of any amino alcohol (18% instead of traces) or the compounds started to appear mainly only after complete saturation of the C=C double bond (Entry 3). These remarks suggest a similarity with the chemoselective heterogeneous reduction of iodoarenes bearing other reducible functions,[23] with reduction of the other functions beginning only after complete hydrogenolysis of the iodide; this was explained as a consequence of the high affinity of the iodide for the catalyst. In our case, the amino alcohol additive did not react with hydrogen and so did not compete with the substrate; because of its adsorption, however, it probably reduced the affinity of the catalyst for the π-electrons of the conjugated enone.[24,25] The adsorption of the chiral amino alcohol onto the support has been verified by circular dichroism experiments,[25] and it seemed to prevent the carbonyl reduction of α,β-unsaturated ketones.

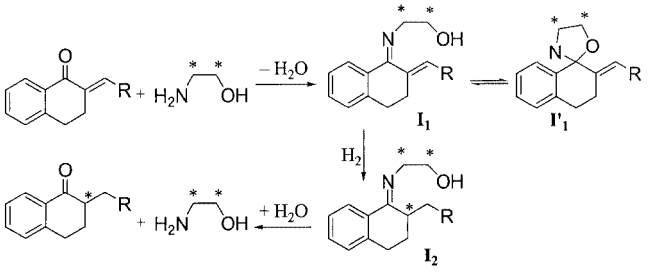
As far as stereoselectivity is concerned, various possibilities have to be explored to try to identify the mechanism that allows the formation of optically active ketones under our hydrogenation conditions. This aim is very ambitious if we consider, for example, the great deal of work that has been devoted to the enantioselective heterogeneous hydrogenation of ethyl pyruvate, which is still a subject of intensive debate.[26] Firstly, we evaluated the possible participation of a *diastereoselective process* in the discriminating step (Scheme 3).

Evidence for such a scheme has been found in the reduction of isophorone, and was termed "*substrate-modifier interactions*".[8,10] It has also been proposed in some cases to explain the heterogeneous reduction of ethyl pyruvate in the presence of amine derivatives.[27] Here, the process would involve the condensation of the amino group of **AH***, which would be the modifier, with the substrate to produce enimine $\mathbf{I_1}$ (or an iminium ion when **AH*** is a secondary amine) in equilibrium with its oxazolidine tautomer. The diastereo-

Table 4. Enantioselective reduction of α,β-unsaturated ketones **1**−**7** in the presence of (−)-ephedrine

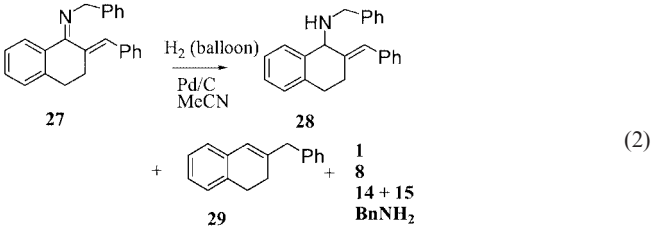
Entry[a]	Unsaturated ketone	Time	Conversion	Saturated ketone		
				Yield (%)	*ee* (%)	Config.
2	**1**	1 h	100%	**8**	86	31[b] (*S*)[c]
34	**1** + **2**[d]	0.5 h	100%	**8**	93	28[b] (*S*)[c]
35	**3**	1 h	70%[e]	**9**	67	30[b] (*S*)[f]
36	**3**	3 h	100%	**9**	73	30[b] (*S*)[f]
37	**3**[g]	0.70 h	76%	**9**	60	12[b] (*S*)[f]
38	**4**	14.5 h	88%[h]	**9**	48	20[b] (*S*)[f]
39	**5**	3 h	72%	**10**	68	28[b] (*R*)[c]
40	**6**	0.75 h	100%	**11**	50	19[b] (*R*)[c]
41	**7**	0.75 h	100%	**12**	77	3 (*R*)[i]
42[g]	**7**	0.75 h	100%	**12**	65	3 (*R*)[i]

[a] Experimental conditions: see Table 1. [b] Determined by HPLC analysis. [c] Configuration attributed by comparison of specific rotations with literature data.[13,20] [d] A 15:85 mixture of **3** and **4** was used. [e] Pure (*E*) isomer was recovered. [f] The (+)-enantiomer was mainly obtained, its (*S*) configuration being attributed by circular dichroism studies.[5d] [g] Aminoborneol **20** was used instead of ephedrine. [h] Pure (*Z*) isomer was recovered. [i] Configuration established by HPLC comparison.[5d]



Scheme 3. Diastereoselective hydrogenation process

selective hydrogenation of $\mathbf{I_1}$ to $\mathbf{I_2}$ would be followed by the regeneration of the carbonyl group, resulting in the nonracemic saturated ketone. This possibility prompted us to study the chemoselectivity of the hydrogenation of enimine **27** [Equation (2)]. We chose to study the reactivity of an enimine such as **27** [Equation (2)] rather than $\mathbf{I_1}$ (Scheme 3) since $\mathbf{I_1}$ would be in equilibrium with the oxazolidine tautomer $\mathbf{I'_1}$, and even if the C=C double bond of both $\mathbf{I_1}$ or $\mathbf{I'_1}$ could be saturated, an oxazolidine has been observed to undergo reductive cleavage of the OC−N bond under palladium-catalysed hydrogenation conditions;[28] such a reaction could not generate a ketone such as **8**.



(2)

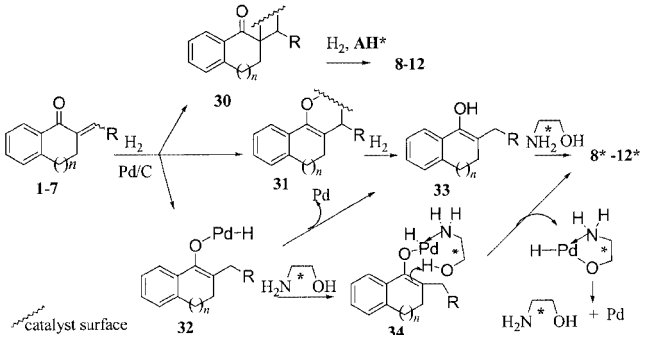
Hydrogenation of the labile compound **27**[29] for 5 min, 20 min or 24 h furnished approximately similar results as indicated by GC/MS analysis: 10−15% of **1** (this was probably due to the instability of **27** under not strictly anhydrous conditions), 16−20% of saturated ketone **8**,[30] 10−15% of the corresponding alcohols **14** and **15** and about 20% of the hydrocarbon **29**. Benzylamine was also formed in each experiment, whereas the amine **28** was identified only in the short-time experiment (5 min). These results clearly showed that *the saturation of the C=N double bond was much faster than that of a C=C bond* under our conditions, while the hydrogenolysis of the benzylic C−N single bond[29] was also efficient, explaining the concomitant formation of **29** and benzylamine. In contrast, during hydrogenation of **1** in the presence of amino alcohols, we never observed the formation of the saturated amine that would result from the hydrogenation of an intermediate such as $\mathbf{I_2}$; furthermore, it was possible in these experiments to recover the starting amino alcohol in nearly quantitative yield. These reasons ruled out a diastereoselective process for the formation of enantioenriched saturated ketone under our experimental conditions.[31] This was in agreement with the observation of enantioselection when water was present in the medium (Entries 14 and 16), while such selectivity would disappear if chiral iminium intermediates were produced.[8−10] On the other hand, if diastereoselective interactions were responsible for the selectivity obtained during the creation of a stereogenic centre in the hydrogenation of conjugated carbonyl compounds, the double bond geometry would have a great influence: most examples have reported that (*Z*) and (*E*) isomers give rise to opposite configurations at the new asymmetric carbon atom;[32] if (*Z*) and (*E*) compounds both afford the same enantiomer, this is at least in part a consequence of in situ (*Z*)/(*E*) isomerisation.[33] In our case, the (*Z*)- and (*E*)-unsaturated ketones did not isomerize in the medium, and afforded the same enantiomer with similar *ee* values, but at different rates[33,34] (Entries 2 and 34−37). This could be interpreted as resulting from a common enol intermediate obtained at different rates from each of the (*Z*) and (*E*) isomers.

It is also interesting to note that saturation of the C=C double bond of 2-benzyl-3,4-dihydronaphthalene (**29**), not conjugated with a carbonyl group, did not occur even after prolonged reaction times [Equation (2)], while the activated olefinic bond of **1** was saturated easily (Tables 1 and 2). Consequently, the presence of a chelating oxygen functionality seems to be a relevant factor in regard to the saturation of the conjugated double bond; the same observation has been made for the hydrogenation of enones catalysed by Ru/Binap complexes.[33]

In heterogeneous enantioselective reductions, the nature of the support and its alteration by the modifier have been often invoked as crucial parameters influencing the observed stereodifferentiation.[1,2,7,25] From Table 1, we have seen that the nature of the support had no effect on the *ee* of **8**. However, we noticed a decrease in the *ee* when Pd/C was introduced as the first reactant in the medium rather than as the last one (Entry 9). The good affinity of the polar amino alcohol for the catalyst surface[26] could explain this decrease: indeed, the amino alcohol added at first was anchored to the support, and the resulting decrease in its concentration in solution resulted in a lower *ee*. This observation indicates that the enantioselective step took place in solution. In agreement with this proposal, the enantioselectivity was nearly zero when (−)-ephedrine was engaged in a complex such as **16** (Entry 13).

Our proposed mechanism for the selective reduction of enones (Scheme 4) includes a classical heterogeneous Horiuti−Polanyi[1b] process giving intermediates **30** and **31**. The competitive formation of a (hydrido)palladium intermediate such as **32** also has to be considered, since it has been shown that palladium hydrides are involved in heterogeneous hydrogenation with palladium on activated carbon.[35−37] Intermediate **30** is a precursor that should allow the generation of the saturated ketone, probably racemic or nearly racemic, due to the poor influence of **AH***, even though it could play some role as a chiral ligand of palladium. Intermediates **31** and **32** could afford the enol species **33** through hydrogenation/desorption processes or reductive elimination of Pd, respectively. As proposed in our other previous studies,[4,5] this enol species could be asymmetrically protonated in the presence of **AH***. An in-

termediate such as **32** could also be stabilized by coordination of the nitrogen atom of **AH*** to the metal centre to afford **34**, the intramolecular protonation of the double bond of which by the hydroxy group of the coordinated amino alcohol would generate the corresponding ketone and an (alkoxy)(hydrido)palladium(II) complex, the subsequent reductive elimination of palladium regenerating **AH***.



Scheme 4. Proposed mechanism for the enantioselective hydrogenation process

For reasons of steric constraints, the formation of intermediates **30**−**32** from the (*E*) geometrical isomer of the enone would be easier than from its (*Z*) counterpart; this would explain the slower reaction of **2** and **4** relative to **1** and **3** (Entries 2 and 34−38). Since the combination of 1,2- and 1,4-processes is probably unavoidable under the hydrogenation conditions, even by changing the nature of the solvent, high *ee* values could not be attained. In fact the *ee* values were lower than those previously observed by use of procedures that would afford enol species selectively.[4,5] Furthermore, comparison of our results with those in the literature concerning the reduction of analogous compounds shows *ee* values in our work lower than those reported in homogeneous medium with a (chiral ligand)Ru complex,[33] but higher than those obtained under heterogeneous conditions.[12,31]

Correlation between the Absolute Configurations of the Inductor and of the Product

From our results, it appears that:

i. an amino alcohol is required to obtain some degree of discrimination between the *Si* and *Re* faces of the enolic species,

ii. the chiral inducing entity must be free in solution (Entries 9 and 13),

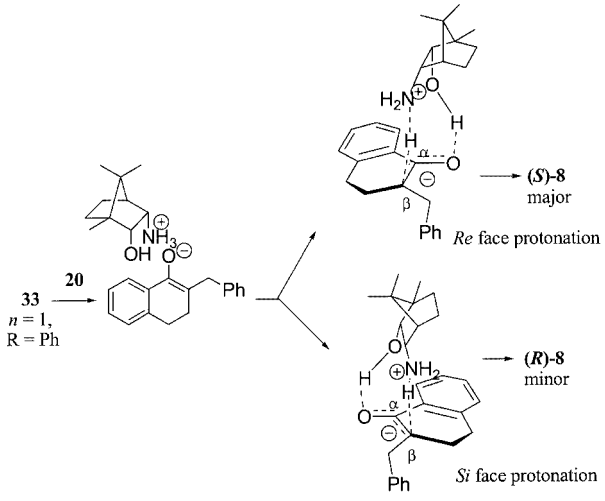
iii. the hydroxy group of the amino alcohol does not necessarily have to be bound to an asymmetric carbon atom to obtain fair *ee* values (Entry 30), and

iv. a strong correlation between the configuration of the new stereogenic centre of the ketone and the absolute configuration of the carbon atom bearing the nitrogen atom (C*N) of the amino alcohols is observed: when the amino group is primary or secondary, an (*S*) configuration of C* N mainly gives rise to (*S*)-**8** from **1** and **2**.

Similar observations have previously been established for the tautomerization of the enols produced by other procedures.[4,5] (−)-Cinchonidine, which bears two tertiary amino groups, does not fit into these correlations, as previously noted in the other procedures;[4,38] and so the mechanism involved for discrimination between the enantiofaces of prochiral enol species is probably particular to this alkaloid.

Nature of the Interactions of Amino Alcohol/Enolic Species

For the tautomerization of photoenols, we have proposed a nine-membered ring intermediate formed by polar interactions between the enol and the two functionalities of the amino alcohol.[4b] Such a scheme would be operative if the amino alcohol were coordinated to the palladium centre and the metal atom were to replace the enol proton in the nine-membered ring.[4b] Recent studies on the protonation of ammonium photoenolates[39] have encouraged us to propose that the current reaction might involve the formation of an ammonium enolate as a possible intermediate, with the amino group of **AH*** acting as a base (Scheme 5). In this hypothesis, the stereochemical control could be due to the β-substituents[39,40] of the enol, as shown in Scheme 5 with **20** as **AH***, the auxiliary remaining external to the enolic species substituents during *Re* face approach, whereas the other *Si* face approach is highly hindered.



Scheme 5. Major *Re* face protonation of the enol

Conclusion

This heterogeneous hydrogenation of prostereogenic α,β-unsaturated ketones uses two catalysts − palladium and an enantiopure amino alcohol − which are involved in the process separately rather than forming an enantioselective catalyst in situ. The resulting enantioselectivity therefore does not correlate solely with the ability of the amino alcohol to induce chirality, but also with the 1,2/1,4 adsorption ratio, this depending on the substrate and the reaction medium. This procedure constitutes a new addition to the formation

of optically active ketones with a stereogenic centre in the α-position.[41]

Experimental Section

General: Solvents were distilled under argon before use: toluene, THF and diethyl ether from Na/benzophenone, DMF and hexane from CaH_2, EtOH from sodium and acetonitrile successively from P_2O_5 and CaH_2. HPLC analyses were carried out with a Waters or Shimadzu (C-10AS) chromatograph with UV (SPD-10A) detection (254 nm) and chiral columns − Chiralcel OD or OB-H − from Daicel. NMR spectra were recorded in $CDCl_3$ with an AC 250 Bruker spectrometer, the coupling constants (*J*) are in Hz. IR spectra were recorded with an SP3-300 Philips spectrometer. Optical rotations were measured with a Perkin−Elmer 241 polarimeter. Mass spectra were recorded with a D 300-JEOL apparatus at the U.F.R of Pharmacy of this University. Literature procedures were used to prepare enones **1**−**4** and **7**,[42] and methylene ketones **5** and **6**.[43] The preparation of the enimine **27** has been described previously,[29] as have those of the noncommercially available chiral catalysts **20**,[44] **21**−**23**[45] and **24**.[46]

Enantioselective Hydrogenations. Typical Procedure: Acetonitrile (30 mL/mmol of substrate) and then the Pd catalyst (32 mg for the 10% Pd catalyst, 0.03 mmol) were added to a mixture of substrate (1 mmol) and amino alcohol (0.5 mmol) in a two-necked, round-bottomed flask. The flask was purged by a gentle flow of hydrogen without stirring for about 1 min. The flask was then connected to a rubber balloon filled with hydrogen, and stirring was started. At the end of the reaction time, the catalyst was immediately removed by filtration through a small pad of silica. After evaporation of the solvents under reduced pressure, the residue was purified by preparative TLC, eluting with EtOAc/petroleum ether (5:95 or 10:90). The spectroscopic data of the saturated ketones are in agreement with the literature: **8**,[47] **9**,[4b] **10** and **11**.[20] HPLC analyses of **10** and **11** were carried out with chiral columns as previously reported.[5d] For other ketones: **8**: Chiralcel OB-H; 2-propanol/hexane (10:90); flow rate: 1 mL/min; retention times: (*R*) enantiomer: 7.09 min, (*S*) enantiomer: 10.96 min; [α] = +1.92. **9**: Chiralcel OD; 2-propanol/hexane (1:99); flow rate: 0.6 mL/min; retention times: (*R*) enantiomer: 10.72 min, (*S*) enantiomer: 11.34 min; [α] = +1.16. **12**: Chiralcel OB-H; 2-propanol/hexane (1:99); flow rate: 0.5 mL/min; retention times: (*S*) enantiomer: 11.13 min, (*R*) enantiomer: 12.31 min; [α] = +1.25.

2-Isobutyl-1-tetralone (9): Liquid. $[\alpha]_D$= +1.6 (*c* = 1.62, CH_2Cl_2) for an (*S*)-configured sample of 30% *ee*, the CD spectrum of this compound being analogous to that of 2-(*S*)-benzyl-1-tetralone (**8**).

2-Isobutyl-1-indanone (12): 155 mg, 77%. ^{1}H NMR: δ = 0.90 (d, *J* = 5.0 Hz, 6 H, CH_3 of *i*Bu), 1.50 (m, 2 H, CH_2 of *i*Bu), 1.55 (m, 1 H, CH of *i*Bu), 2.06 (d, *J* = 9.0 Hz, 2 H, 3-H_2), 3.45 (m, 1 H, 2-H), 7.10−7.50 (m, 4 H, aromatic) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.3 (CH_3 of *i*Bu), 24.9 (CH of *i*Bu), 27.1 (C-3), 35.2 (CH_2 of *i*Bu), 48.2 (C-2), 124.4−138.5 (aromatic), 199.7 (C-1) ppm. $C_{13}H_{16}O$ (188.3): calcd. C 82.9, H 8.6; found C 82.4, H 8.4

***cis*-2-Benzyl-1-tetrahydronaphthol (14):** This compound is partially described in ref.[48] From a reaction carried out in methanol as solvent without any amino alcohol: 28 mg, 12%; liquid. ^{1}H NMR: δ = 1.5 (s large, 1 H, OH), 1.64−2.13 (3 H, 3-H_2 and 2-H), 2.76 (m, 3 H and dd, *J* = 7.4, 13.5 Hz, 4-H_2 and 11-H), 2.90 (dd, *J* = 13.5, 7.8 Hz, 1 H, 11-H), 4.5 (d, *J* = 2.8 Hz, 1 H, 1-H), 7.05−7.36 (9 H, Ph) ppm. ^{13}C NMR: δ = 22.6 (C-4), 29.2 (C-3), 38.2 (C-11), 41.7 (C-2), 69.4 (C-1), 125.9−130 (aromatic CH), 136.9−140.7 (quaternary C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1454, 1495, 1603, 2930, 3013, 3607 cm^{-1}. MS (70 eV): *m*/*z* (%) = 239 (42) [M^+ + 1], 238 (35), 147 (100), 91 (98).

***trans*-2-Benzyl-1-tetrahydronaphthalenol (15):** This compound is partially described in ref.[48] 38 mg, 16%; white solid, m.p. 110 °C. ^{1}H NMR: δ = 1.51 (m, 2 H, 3-H), 1.69 (1 H, wide s, OH), 2.02 (m, 2 H, 2-H and 3-H), 2.51 (dd, *J* = 13.4, 8.8 Hz, 1 H, 11-H), 2.75 (m, 2 H, 4-H_2), 3.0 (dd, *J* = 13.4, 5.2 Hz, 1 H, 11-H), 4.47 (d, *J* = 6.9 Hz, 1 H, 1-H), 7.02−7.6 (9 H, Ph) ppm. ^{13}C NMR: δ = 22.6 (C-4), 29.2 (C-3), 38.2 (C-11), 41.7 (C-2), 69.4 (C-1), 125.9−130 (aromatic CH), 136.9−140.7 (quaternary C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1455, 1493, 1603, 2926, 3013, 3592 cm^{-1}. MS (70 eV): *m*/*z* (%) = 239 (5) [M^+ + 1], 238 (12), 146 (100), 91 (78).

Hydrogenation of 27: The imine **27** (1 mmol), the palladium on charcoal (0.03 equiv.) and 30 mL of acetonitrile were placed in a two-necked, round-bottomed flask. The flask was purged by a gentle flow of hydrogen without stirring for about 1 min and connected to a rubber balloon filled with hydrogen. Stirring for the specified reaction time was then started. At the end of the reaction, the palladium was immediately removed by filtration through Celite. After evaporation of the solvent, the residue was analysed by GC/MS. Flash chromatography (petroleum ether/EtOAc, 90:10) followed by preparative TLC (petroleum ether/EtOAc/MeOH, 90:5:5) allowed the separation of **1**, **8**, **14**, **15** and **29**, identified by comparison with the described compounds.[49] GC-MS (EI) analyses were carried out with a Thermoquest Trace GC 2000 Series apparatus under the following conditions: Column Chrompack CP-Sil 5 CB-DB 1-125-1032 (0.53 mm i.d., 30 m length, film); temperature range: 100−250 °C, 15 °C/min. Under these conditions, the alcohols **14** and **15** were dehydrated and the corresponding signal was common with that of **29** (verified by injection of these alcohols separately).

5-min Experiments

Compound 8: 38 mg, 16%; T_r = 12.43 min. MS (70 eV): *m*/*z* (%) = 236 (47) [M^+], 145 (85) [$M^+ - C_6H_5CH_2$], 91 (100) [$C_6H_5CH_2$].

Compound 27: Not isolated, T_r = 22.11 min. MS (70 eV): *m*/*z* (%) = 323 (100) [M^+], 246 (87) [$M^+ - C_6H_5$], 128 (63) [$M^+ - C_6H_5CH_2 - C_6H_5CH_2N$], 91 (82) [$C_6H_5CH_2$].

Compound 28: Not isolated, T_r = 21.33 min. MS (70 eV): *m*/*z* (%) = 325 (8) [M^+], 234 (53) [$M^+ - C_6H_5CH_2$], 91 (100) [$C_6H_5CH_2$].

Compound 29: 29 mg, 13%; T_r = 12.34 min. MS (70 eV): *m*/*z* (%) = 220 (36) [M^+], 129 (100) [$M^+ - C_6H_5CH_2$], 91 (36) [$C_6H_5CH_2$].

$BnNH_2$: T_r = 7.93 min. MS (70 eV): *m*/*z* (%) = 105 (42) [M^+ − 2 H], 77 (100) [C_6H_5].

Acknowledgments

This study was carried out partly within the PROCOPE program. We are grateful to the "Région Champagne-Ardenne" for a PhD studentship to C. T., to Engelhard and Johnson Matthey for generous gifts of Pd catalysts, to Prof. J. Martens (University of Oldenburg) and Dr. L. Duhamel (University of Rouen) for samples of **21**−**24**, and to Dr. G. Bird (Zeneca Pharma, Reims) for help with the text of the manuscript.

[1] [1a] E. Keinan, N. Greenspoon, in *Comprehensive Organic Synthesis* (Ed.: B. M.Trost), Pergamon Press, New York, **1991**, vol. 8, p. 523−578. [1b] R. L. Augustine, *Heterogeneous Catalysis for the Synthetic Chemist*, M. Dekker, New York, **1996**, p. 345−386.

[2] [2a] G. V. Smith, J. F. Deany, *J. Catal.* **1966**, *6*, 14−19. [2b] R. L. Augustine, D. C. Migliorini, R. E. Foscante, C. S. Sodano, M. J. Sisbarro, *J. Org. Chem.* **1969**, *34*, 1075−1085. [2c] S. Nishimura, Y. Momma, H. Kawamura, M. Shiota, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 780−783. [2d] M. Bartok, *Stereochemistry of Heterogeneous Metal Catalysis*, Wiley, New York, **1985**, p. 115−177.

[3] [3a] R. C. Fuson, J. Corse, C. H. McKeever, *J. Am. Chem. Soc.* **1940**, *62*, 3250−3251. [3b] K. Heusler, P. Wieland, A. Wettstein, *Helv. Chim. Acta* **1954**, *42*, 1586−1603. [3c] J. Attenburrow, J. E. Connett, W. Graham, J. F. Oughton, A. C. Ritchie, P. A. Wilkinson, *J. Chem. Soc.* **1961**, 4547−4559. [3d] P. R. Enslin, *Tetrahedron* **1971**, *27*, 1909−1915. [3e] T. Nakata, M. Fukui, T. Oishi, *Tetrahedron Lett.* **1988**, *29*, 2223−2226.

[4] [4a] F. Hénin, J. Muzart, J. P. Pète, A. M′Boungou-M′Passi, H. Rau, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 416−418. [4b] F. Hénin, A. M'Boungou-M'Passi, J. Muzart, J. P. Pète, *Tetrahedron* **1994**, *50*, 2849−2864.

[5] [5a] F. Hénin, J. Muzart, *Tetrahedron: Asymmetry* **1992**, *3*, 1161−1164. [5b] S. Jamal Aboulhoda, F. Hénin, J. Muzart, C. Thorey, W. Behnen, J. Martens, T. Mehler, *Tetrahedron: Asymmetry* **1994**, *5*, 1321−1326. [5c] S. Jamal Aboulhoda, S. Létinois, J. Wilken, I. Reiners, F. Hénin, J. Martens, J. Muzart, *Tetrahedron: Asymmetry* **1995**, *6*, 1865−1868. [5d] J. Muzart, F. Hénin, S. Jamal Aboulhoda, *Tetrahedron: Asymmetry* **1997**, *8*, 381−389. [5e] S. Jamal Aboulhoda, I. Reiners, J. Wilken, F. Hénin, J. Martens, J. Muzart, *Tetrahedron: Asymmetry* **1998**, *9*, 1847−1850.

[6] For a preliminary communication, see: C. Thorey, F. Hénin, J. Muzart, *Tetrahedron: Asymmetry* **1996**, *7*, 975−976.

[7] For reviews, see: [7a] H.-U. Blaser, *Tetrahedron: Asymmetry* **1991**, *2*, 843−866. [7b] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**, p. 352−364. [7c] T. Mallat, Z. Bodnar, B. Minder, K. Borszeky, A. Baiker, *J. Catal.* **1997**, *68*, 183−193. [7d] R. L. Augustine, *Catal. Today* **1997**, *37*, 419−440. [7e] H.-U. Blaser, H.-P. Jalett, M. Müller, M. Studer, *Catal. Today* **1997**, *37*, 441−463.[7f] M. Besson, C. Pinel, *Top. Catal.* **1998**, *5*, 25−38.

[8] A. Tungler, M. Kajtar, T. Mathé, G. Tóth, E. Fogassy, J. Petro, *Catal. Today* **1989**, *5*, 159−171.

[9] [9a] A. Tungler, T. Mathé, T. Tarnai, K. Fodor, G. Tóth, J. Kajtar, I. Kolossvary, B. Herényi, R. A. Sheldon, *Tetrahedron: Asymmetry* **1995**, *6*, 2395−2402. [9b] A. Tungler, Y. Nitta, K. Fodor, G. Farkas, T. Mathé, *J. Mol. Catal. A: Chem.* **1999**, *149*, 135−140.

[10] A. Tungler, T. Tarnai, T. Mathé, J. Petro, R. A. Sheldon, in *Chiral Reactions in Heterogeneous Catalysis* (Eds.: G. Jannes, V. Dubois), Plenum Press, New York, **1995**, p. 121−133, 151−153.

[11] W. R. Huck, T. Mallat, A. Baiker, *J. Catal.* **2000**, *193*, 1−4.

[12] K. Borszeky, T. Mallat, A. Baiker, *Tetrahedron: Asymmetry* **1997**, *8*, 3745−3753.

[13] M. Murakata, M. Nakajima, K. Koga, *J. Chem. Soc., Chem. Commun.* **1990**, 1657−1658.

[14] [14a] G. Farkas, L. Hegedus, A. Tungler, T. Mathé, J. L. Figueiredo, M. Freitas, *J. Mol. Catal. A: Chem.* **2000**, *153*, 215−219. [14b] Y. Nitta, T. Kubota, Y. Okamoto, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2635−2641.

[15] The surface areas of 5% Pd/C, ref. no. 5011 and 5105 from Engelhard, were 1100 m^2/g and 900 m^2/g, respectively, each catalyst containing 50% of water. The carbon type was activated wood for the former and activated peat for the latter. The moisture of 5% Pd/C ref. no. 490 from Johnson Matthey, was 55.2% (technical information from Engelhard and Johnson Matthey).

[16] S. Bouquillon, F. Hénin, J. Muzart, unpublished results.

[17] Y. Aoyagi, R. M. Williams, *Synlett* **1998**, 1099−1101.

[18] Y. Nitta, K. Kobiro, *Chem. Lett.* **1995**, 165−165.

[19] P. Vogel, *Chimie Organique, Méthodes et modèles*, De Boeck, Paris, **1997**, p.623−624.

[20] G. Jaouen, A. Meyer, *J. Am. Chem. Soc.* **1975**, *97*, 4667−4672.

[21] G. Fogassy, L. Hegedus, A. Tungler, A. Lévai, T. Mathé, *J. Mol. Catal. A: Chem.* **2000**, *154*, 237−241.

[22] For a recent example see: K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron* **2000**, *56*, 8433−8441.

[23] Y. Ambroise, C. Mioskowski, G. Djéga-Mariadassou, B. Rousseau, *J. Org. Chem.* **2000**, *65*, 7183−7186.

[24] H. Sajiki, K. Hattori, K. Hirotta, *J. Chem. Soc., Perkin Trans. 1.* **1998**, 4043−4044.

[25] The adsorption of (−)-ephedrine was demonstrated by qualitative circular dichroism experiments: the addition of Pd/C to an acetonitrile solution of **13** brought about a decrease in its initial positive absorption (λ_{max} = 253, 260 and 267 nm). Whatever the amount of the catalyst introduced, we always observed weaker signals in solution, meaning an equilibrium between free and adsorbed species. This phenomenon was also observed when charcoal powder was used instead of Pd/C.

[26] For recent articles and leading references see: [26a] C. LeBlond, J. Wang, J. Liu, A. T. Andrews, Y.-K. Sun, *J. Am. Chem. Soc.* **1999**, *121*, 4920−4921. [26b] H. U. Blaser, H. P. Jalett, W. Lottenbach, M. Studer, *J. Am. Chem. Soc.* **2000**, *122*, 12675−12686. [26c] D. Ferri, T. Bürgi, A. Baiker, *Chem. Commun.* **2001**, 1172−1173.

[27] T. Heinz, G. Wang, A. Pfalz, B. Minder, M. Schürch, T. Mallat, A. Baiker, *J. Chem. Soc., Chem. Commun.* **1995**, 1421−1422.

[28] S. Létinois, F. Hénin, J. Muzart, *Tetrahedron: Asymmetry* **2000**, *11*, 2037−2044.

[29] S. Bouquillon, F. Hénin, J. Muzart, *Synth. Commun.* **2001**, *31*, 39−45.

[30] The hydrogenation of **8** in methanol resulted in a mixture of **14, 15** and 2-benzyltetraline, the latter arising from hydrogenolysis of **14** and **15**. For comparison, see a description of the heterogeneous hydrogenation of tetralone derivatives in: R. G. Melton, E. J. Eisenbraun, P. W. K. Flanagan, M. C. Hamming, *Org. Prep. Proc.* **1970**, *2*, 37−43.

[31] After the submission of this article, the enantioselective reduction of compound **1** in the presence of supported palladium modified by proline was reported; *ee* values were not higher than 20%: G. Fogassy, A. Tungler, A. Lévai, G. Tóth, *J. Mol. Catal. A: Chem.* **2002**, *179*, 101−106.

[32] [32a] W. Oppolzer, R. J. Mills, M. Réglier, *Tetrahedron Lett.* **1986**, *27*, 183−186. [32b] T. Honda, N. Kimura, *J. Chem. Soc., Chem. Commun.* **1994**, 77−78.

[33] T. Ohta, T. Miyake, N. Seido, H. Kumobayashi, H. Takaya, *J. Org. Chem.* **1995**, *60*, 357−363.

[34] Different rates for the hydrogenation of geometrical isomers have been reported: [34a] M. J. Burk, F. Bienewald, M. Harris, A. Zanotti-Gerosa, *Angew. Chem. Int. Ed.* **1998**, *37*, 1931−1933.

[35] J. Yu, J. B. Spencer, *Tetrahedron* **1998**, *54*, 15821−15832.

[36] A. G. M. Barrett, W. Tam, *J. Org. Chem.* **1997**, *62*, 7673−7678.

[37] M. Studer, H.-U. Blaser, *J. Mol. Catal. A: Chem.* **1996**, *112*, 437−445.

[38] O. Roy, M. Diekmann, A. Riahi, F. Hénin, J. Muzart, *Chem. Commun.* **2001**, 533−534, Corrections p. 1418.

[39] S. Létinois, F. Hénin, J. Muzart, *Tetrahedron: Asymmetry* **2000**, *11*, 2037−2044.

[40] L. Duhamel, P. Duhamel, *C. R. Acad. Sci. Paris, Série II* **1995**, *320*, 689−694.

[41] Reviews: [41a] J. S. Mc Callum, L. S. Liebeskind, *Methoden Org. Chem. (Houben-Weyl)* **1996**, vol. II ("Stereoselective Synthesis"), p. 916−968. [41b] P. Fey, W. Hartwig, *Methoden Org.*

Chem. (Houben-Weyl) **1996**, vol. II ("Stereoselective Synthesis"), p. 969−1029. [41c] P. Duhamel, *Methoden Org. Chem. (Houben-Weyl)* **1996**, vol. II ("Stereoselective Synthesis"), p. 1101−1118.
[42] C. Thorey, A. Riahi, F. Hénin, J. Muzart, *Synth. Commun.* **1998**, *28*, 4339−4344.
[43] J. L. Gras, *Tetrahedron Lett.* **1978**, 2111−2114.
[44] A. M'Boungou-M'Passi, F. Hénin, J. Muzart, J. P. Pète, *Bull. Soc. Chim. Fr.* **1993**, *130*, 214−217.
[45] G. Wilken, C. Thorey, H. Gröger, D. Haase, W. Saak, S. Pohl, J. Muzart, J. Martens, *Ann. Chem./Recueil* **1997**, 2133−2146.
[46] Gift from L. Duhamel and P. Duhamel.
[47] C.-D. Graf, C. Malan, K. Harms, P. Knochel, *J. Org. Chem.* **1999**, *64*, 5581−5588.
[48] A. Chatterjee, L. N. Dutta, S. K. Chatterjee, *Indian J. Chem.* **1980**, *19B*, 955−960.
[49] T. J. H. M. Cuppenest, N. Berendsen, W. H. Laarhoven, *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 168−171.

Received December 21, 2001
[O01599]