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Synthesis of a *trans*-benzo-[*f*]-heterodecalin by catalytic hydrogenation. The important parameters for high stereo- and chemoselectivity

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Abstract

Racemic *trans*-**1A** (*trans*-10-methoxy-1,3,4,4a,5,10b-hexahydro-2*H*-[1]benzopyrano[3,4-*b*]pyridine, see Scheme 1) was obtained in high chemical yield (up to 89%) and with excellent stereoselectivity (95% *trans*) by catalytic hydrogenation–dehalogenation of 7-chloro-10-methoxy-3,4,4a,5-tetrahydro-2*H*-[1]benzopyrano[3,4-*b*]pyridine **2A**. The best results were obtained using Pd/C catalysts in dimethyl formamide (DMF) in presence of *N,N*-diisopropylethylamine (DIPEA) with high amounts of catalyst at low hydrogen pressure and low initial temperature. At higher initial temperatures, partial aromatization of the N-heterocycle occurred, leading on further hydrogenation to increased levels of *cis*-**1A**. Under these conditions, partial demethoxylation at the 10-position was observed as a side reaction as well. In presence of organic bases, the C=C bond was hydrogenated faster than the C–Cl bond. Inorganic bases in protic solvents favored dehalogenation over double bond reduction. Interestingly, the rate of dehalogenation decreased when the hydrogen pressure was increased. Reaction schemes are presented to rationalize these results and a comparison of our catalytic system with other methods described in the literature is made.

Keywords: Aromatization; *trans*-Benzo-[*f*]-heterodecalins; Dehalogenation; Diastereoselective hydrogenation; Heterocycle; Hydrogen pressure; Palladium

1. Introduction

trans-Benzo-[*f*]-heterodecalins of type **1** are of considerable interest as drugs that bind selectively to receptors in mammalian brain cells [1–8]. In most cases, the *trans*-stereochemistry is achieved via diastereoselective reduction of intermediates such as **2** or **3**. Since many of the known reduction procedures preferentially give the inactive *cis*-stereoisomer, considerable efforts were devoted to the development of *trans*-selective methods [1,2,4,6,9–11]. However, only few of these studies were of a systematic nature [6,10]. Moreover, some published results could not be reproduced by other investigators [4,11].

This paper describes the systematic investigation and optimization of the catalytic hydrogenation of **2A**. This is the key step of the synthesis of *trans*-10-methoxy-4-propyl-1,3,4,4a,5,10b-hexahydro-2*H*-[1]benzopyrano[3,4-*b*]pyridine **1B**. **1B** was developed by Hutchison et al. as a combined $5HT_2$ antagonist/$5HT_{1A}$ receptor agonist [1,2].

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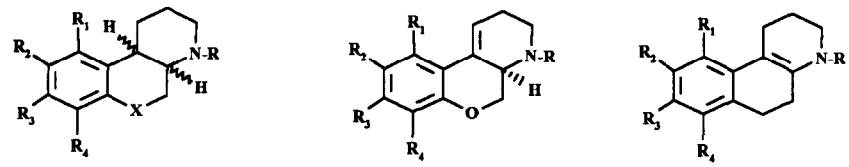


1: X = O or CH_2 2 3

1A: R_1=O-CH_3, R_2=R_3=R_4=H X=O, R=H

2A: R_1=O-CH_3, R_2=R_3=H, R_4=Cl X=O, R=H

1B: R_1 - R_4 like 1A, R=Pr

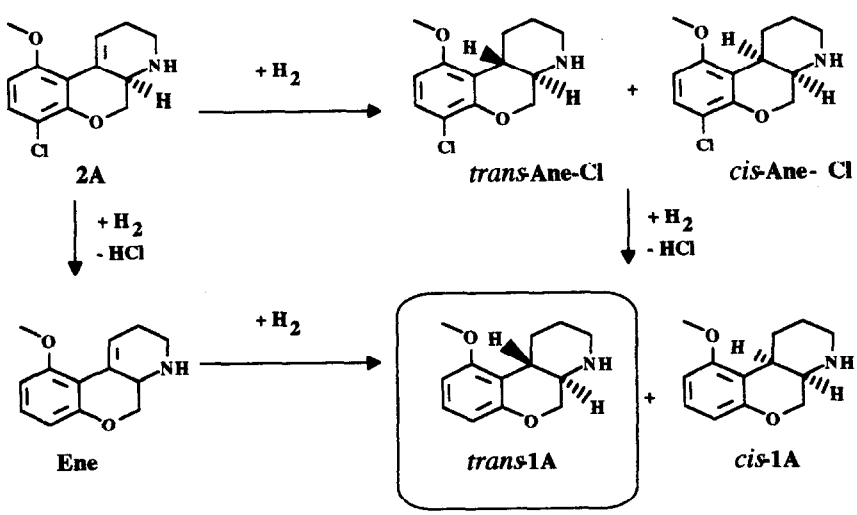
Scheme 1. Structures of starting materials and products. All starting materials and products are racemates. For clarity, only one enantiomer is depicted in the drawings.

In the synthetic sequence leading to **1B**, **2A** was the favored intermediate. The Cl atom in the R_4 position was used as a protective group for the cyclization in an earlier step. For the transformation of **2A** to **1B**, a diastereoselective hydrogenation of the C=C bond, a hydrogenolytic cleavage of the C–Cl bond and an alkylation of the amine are necessary. In preliminary tests, Pd catalyst showed the best stereoselectivity. Because of this, we decided to optimize the simultaneous hydrogenation of the double bond and the dehalogenation (see Scheme 2). The influence of the catalyst type, the nature of the solvent and the base, as well as the effects of the reaction conditions were investigated. We found a suitable catalytic system and optimal conditions that give high chemical yield (up to 89%) and an excellent stereoselectivity (trans/cis > 16). To the best of our knowledge, this is the highest trans/cis ratio ever obtained by catalytic hydrogenation of compounds similar to **2** or **3**. In addition, a reaction scheme was developed that allows to rationalize the observed effect of different reaction conditions on the stereo- and chemoselectivity.

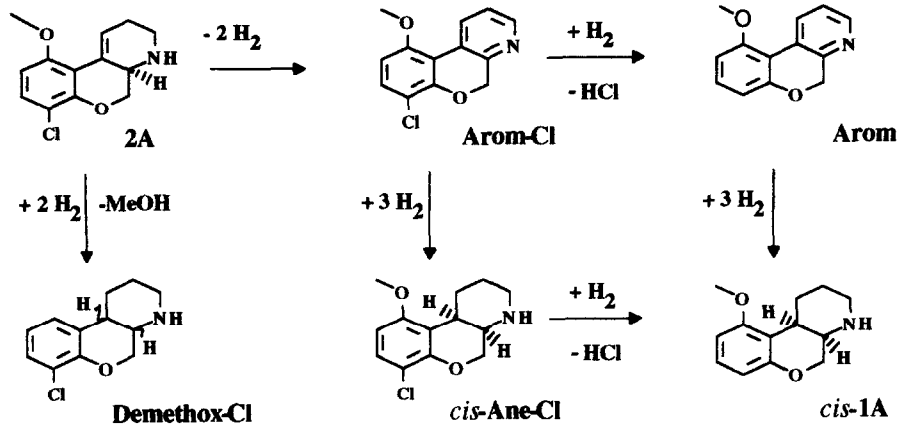
2. Results

2.1. Products and intermediates

Schemes 2 and 3 show the products and reaction intermediates that were identified in the reaction



Scheme 2. Main reaction pathways.



Scheme 3. Side reactions.

mixtures by GLC–MS. The starting material **2A**, *cis*-**1A** and *trans*-**1A** were characterized by NMR and elemental analysis as well.

2.2. Catalyst screening

A preliminary catalyst screening with Pd/C, Pt/C, Rh/C and Raney-Ni had shown that Pd/C gave the best results in terms of selectivity and activity for the simultaneous hydrogenation and dehalogenation of **2A** [12]. These results were confirmed in the present study where some additional catalyst types were investigated. Table 1 displays typical screening results obtained with Pd/C (T1-1), with the mixed metal catalysts Pd–Rh/C (T1-2), Pd–Pt/C (T1-3) and Pd–Ru/C (T1-4), and with a soluble Rh(I)–phosphine complex (T1-5). A rather high catalyst concentration was needed in all cases to get a reasonable reaction time. Purification of the starting material did not improve the activity of the catalyst significantly. In the reaction medium chosen for these tests (EtOH with KOH as base), none of the tested catalysts gave a *trans*/*cis* ratio higher than about 6. Pd/C and Pd–Rh/C showed the best stereoselectivity whereas the Pd–Pt/C system was the most active. For different Pd/C catalysts, neither the charcoal type nor the metal concentration or metal location affected the stereoselectivity noticeably (results not shown). The Rh(I)–phosphine complex gave no dehalogenation and a very slow reaction of the C=C bond and a *trans*/*cis* ratio of 0.7.

On the basis of these results, all further experiments were carried out with a 5% Pd/C catalyst (Type 4522 from Engelhard).

2.3. Effect of solvent and base

These effects were dependent on the hydrogen pressure. At 4 bar hydrogen pressure, the stereoselectivity did not depend much on the solvent and base. After a reaction time of 22 h, all combinations investigated (T2-1 to T2-4 in Table 2) showed a *trans*/*cis* ratio between 9 and 12. The most active systems were those in EtOH with complete dehalogenation after 22 h. The least active was DIPEA/DMF with 39.9% *trans*-**Ane–Cl** and 1.7% *cis*-**Ane–Cl** after 22 h. In order to achieve complete conversion with very slow systems, we had to filter the catalyst off and finish the hydrogenation with a new portion of catalyst. Under these conditions, the hydrogenation of the double bond was significantly faster than the dechlorination, and no demethoxylation or aromatization was observed.

At a hydrogen pressure of < 1 bar, the solvent systems Et_3N/EtOH (T2-5), DIPEA/DMF (T2-6) and aqueous KOH/Toluene (T2-7) showed marked differences. At low conversion, very high initial stereoselectivities were observed for all systems but they decreased during the course of the

Table 1
Product distribution and *trans/cis* ratios for the catalyst screening (GLC area %, 4 bar H_2, 50°C)

Exp.	**2A***HCl (g)	KOH 50% (g)	EtOH (ml)	Catalyst	Amount (g)	Time (h)	**2A**	*t/c* [b] total	*trans*-**1A**	*cis*-**1A**	*t/c* **1A**	*trans*-**Ane-Cl**	*cis*-**Ane-Cl**	*t/c* **Ane-Cl**
T1-1	1.44	1.61	18	5% Pd/C	0.29	20	0	**6.0**	80.8	13.9	5.8	2.5	0.0	–
T1-2	0.50	0.57	15	4.5% Pd/0.5% Rh/C	0.20	16	0	**6.3**	79.0	13.5	5.9	6.5	0.0	–
T1-3	0.50	0.57	15	4.0% Pd/1.0% Pt/C	0.37	16	0	**5.2**	83.4	16.1	5.2	0.0	0.0	–
T1-4	0.50	0.57	15	2.5% Pd/2.5% Ru/C	0.39	24	0	**4.9**	65.0	14.5	4.5	5.5	0.0	–
T1-5 [a]	0.25	–	10 ml MeOH	$Rh(NBD)_2BF_4$ Diphos-4	[a]	19	78	**0.7**	0.0	0.0	–	3.7	5.5	0.7

[a] 6.8 mg bis(norbornadiene)rhodium(I) tetrafluoroborate and 6.8 mg 1,4-bis(diphenylphosphine)butane.
[b] *trans/cis* ratio (total = (*trans*-**1A** + *trans*-**Ane–Cl**)/(*cis*-**1A** + *cis*-**Ane–Cl**)).

reaction from a trans/cis ratio of 19 to 6 in Et_3N/EtOH, from 14 to 9 in KOH/toluene and from 21 to 13 in DIPEA/DMF. In contrast to the reactions with organic bases, dehalogenation in aqueous KOH/toluene was faster than the hydrogenation of the C=C bond. At low hydrogen pressure, some demethoxylation and aromatization was observed. With KOH/toluene, the final mixture contained 19% **Arom**, with DIPEA/DMF 7% **Arom** and also 1% of **Demethox–Cl**.

On the basis of these results, all further experiments were carried out with the Pd/C catalyst 4522 in DIPEA/DMF.

2.4. *Effect of hydrogen pressure and catalyst concentration*

As described above, the hydrogen pressure has an important effect on the stereoselectivity. While the *trans/cis* ratio for **1A** was always below 12 at 4 bar H_2 (T2-3 and T2-8), it could be increased to 20 or higher (T2-9, T2-10, and T2-11) by lowering the hydrogen partial pressure from 4 to <1 bar and working at low initial temperatures. An increase in the amount of catalyst from an S/C ratio of 1/0.25 to 1/0.5 also increased the *trans*-selectivity (T2-10 and T2-9).

The hydrogen pressure influenced the rate of the dehalogenation too. To our surprise, this rate did not increase with increasing hydrogen pressure but rather decreased. Therefore, r ($r = \Sigma$ chlorinated/Σ dechlorinated compounds) was lower at low pressure than at high pressure. Under comparable conditions, $r = 0.21$ at <1 bar (T2-11) and $r = 0.71$ at 4 bar (T2-3) was observed after about 20 h. Another set of similar experiments showed $r = 1.63$ at <1 bar (T2-9) and $r = 2.86$ at 4 bar (T2-8).

2.5. *Influence of temperature*

Because of the rather low activity of the selective catalysts, the reaction temperature was sometimes increased during the course of the reaction. The results of experiments T2-11, T2-12 and T2-13 in Table 2 demonstrate the effect of both the initial and the final temperature. At low temperature (e.g. ≤ 30°C), the *trans/cis* ratio remained constant during the whole reaction and no or only little side products were formed. With $T \geq 50$°C at low hydrogen pressure and with high amounts of catalyst, the initially high *trans/cis* ratio decreased significantly during the reaction (for instance from 24 to 13 in T2-13).

With $T \geq 50$°C, we also observed more side products. The most important ones were **Arom–Cl** and **Arom** (see Scheme 3), formed by dehydrogenation of the N-containing heterocycle. Another side reaction cleaved the methoxy group of the starting material. Again, this was favored by high temperatures, high amounts of catalyst and low hydrogen pressure (T2-11 to T2-14). The

Table 2
Product distribution and *trans*/*cis* ratios for different reaction conditions (GLC area %) using 5% Pd/C (Engelhard 4522). The first line of every entry gives the results obtained from the analysis of a sample taken after t_1 hours at T_1°C. The reaction was then continued until after another t_2 hours at T_2°C the mixture was analyzed again (second line)

Exp.	S/C [a] ratio	p_{H_2} (bar)	t_1 [b], t_2	T_1 [b], T_2	Solvent and base	**2A**	**Ene**	**Arom Cl**	**Arom**	**Demeth-ox-Cl**	*t/c* [d] total	*trans*-**1A**	*cis*-**1A**	*t/c* **1A**	*trans*-**Ane–Cl**	*cis*-**Ane–Cl**	*t/c* **Ane–Cl**
T2-1	1/1.3	4	3	30	EtOH	0	0	0	0	0	9	76.4	9.8	9	13.0	0.6	20
			20	30	DIPEA	0	0	0	0	0	9	87.6	9.4	9	0.0	0.0	–
T2-2	1/1.3	4	4	30	EtOH	0	0	0	0	0	10	68.5	8.3	8	22.3	0.8	28
			18	30	Et_3N	0	0	0	0	0	12	91.3	7.9	12	0.0	0.0	–
T2-3	1/1.3	4	3	20	DMF	0	0	0	0	0	12	28.3	3.9	7	63.9	4.0	16
			19	30	DIPEA	0	0	0	0	0	10	50.9	7.5	7	39.9	1.7	23
T2-4	1/1.3	4	4	30	DMF	0	0	0	0	0	15	48.0	4.2	12	45.4	2.2	20
			18	30	Et_3N	0	0	0	0	0	12	80.6	7.8	10	11.6	0.0	–
T2-5	1/0.50	< 1 [c]	3	30	EtOH	42	18	1	1	0	19	11.7	0.6	19	23.7	1.2	19
			19	60	Et_3N	0	0	0	1	0	6	85.6	13.8	6	0.0	0.0	–
T2-6	1/0.50	< 1 [c]	2	30	DMF	57	13	1	1	1	21	5.0	0.3	18	19.4	0.9	22
			20	60	DIPEA	0	0	0	7	1	13	70.1	5.3	13	13.7	0.9	15
T2-7	1/0.50	< 1 [c]	3	30	Toluene	53	36	1	2	0	14	3.1	0.3	12	3.6	0.2	16
			16	60	KOH	0	0	2	19	0	9	70.5	8.2	9	0.0	0.0	–
T2-8	1/0.50	4	3	30	DMF	0	0	0	0	0	12	6.6	1.2	5.7	85.6	6.7	13
			16	30	DIPEA	0	0	0	0	0	11	22.3	3.4	6.5	68.8	4.9	14
T2-9	1/0.50	< 1 [c]	3	30	DMF	45	11	1	2	0	28	8.0	0.3	24	31.3	1.1	30
			20	30	DIPEA	0	0	0	3	0	31	33.6	1.4	24	60.2	1.6	37
T2-10	1/0.25	< 1 [c]	3	30	DMF	57	5	0	0	0	22	3.1	0.1	35	30.5	1.5	21
	0		19	60	DIPEA	0	0	0	1	0	19	79.4	4.4	18	13.1	0.4	33
T2-11	1/1.3	< 1 [c]	2	20	DMF	27	9	1	1	0	22	12.3	0.6	21	46.0	2.1	22
			16	26	DIPEA	0	0	0	2	0	23	76.1	4.0	19	17.5	0.0	–
T2-12	1/1.3	< 1 [c]	2	20	DMF	28	11	1	1	0	21	13.0	0.6	21	43.1	1.9	22
			20	50	DIPEA	0	0	0	2	1	17	92.0	5.5	17	0.0	0.0	–
T2-13	1/1.3	< 1 [c]	2	50	DMF	18	13	5	11	2	23	20.8	1.0	21	26.7	1.0	27
			17	50	DIPEA	0	0	0	16	0	14	76.3	5.4	14	0.0	0.0	–
T2-14	1/1.2	0	3	100	DMF DIPEA	0	0	14	50	5	35	21.5	0.8	27	5.9	0.0	–

[a] S/C: ratio substrate to catalyst (w/w).
[b] T_1 and T_2: temperature in °C; t_1 and t_2: time in hours.
[c] H_2 flow controller.
[d] *t/c*: *trans*/*cis* ratio (total = (*trans*-**1A** + *trans*-**Ane–Cl**)/(*cis*-**1A** + *cis*-**Ane–Cl**)).

maximum of **Demethox–Cl** (5% of the reaction mixture) was observed in T2-14.

In order to investigate the side product formation and the change in the *trans*/*cis* ratio during the course of the reaction, the following experiment was carried out (see Fig. 1): **2A** was heated for 2 h under Argon to 100°C followed by hydrogenation at 20 bar hydrogen pressure and elevated temperature. The first sample was taken after 2 h (Table 2, T2-14). The starting material had disappeared completely and a mixture of hydrogenated and dehydrogenated species was formed. The most abundant component was **Arom** (50%).

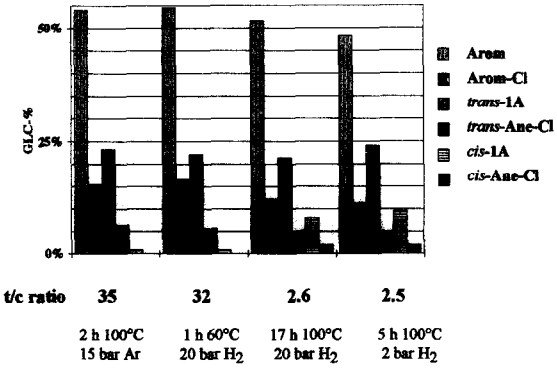


Fig. 1. Product distribution and *trans*/*cis* ratios in the aromatization/hydrogenation experiment (for details see text).

Calculation of the hydrogen balance (hydrogenated and dehydrogenated species) revealed a deficit of 0.22 moles H_2 per mol **2A**. Most likely this hydrogen was taken up by the Pd/C catalyst. A GLC–MS analysis of this sample indicated that also small amounts of tetrahydro pyridine derivatives ($\leq 1.0\%$) were formed. During the subsequent hydrogenation with H_2, the initially high *trans*/*cis* ratio of 35 decreased in the course of the reaction to 2.5 (see Fig. 1). With the appearance of the *cis* compounds, the amount of **Arom** and **Arom–Cl** decreased.

3. Discussion

While developing a synthetic procedure for the desired *trans*-**1A**, we also tried to gain insight into the reaction pathways in order to explain the influence of the different reaction parameters on the stereo- and chemoselectivity. In this section we will discuss our results and develop a reaction model to explain some of the observations. In the discussion we will include a literature overview and a comparison with other reduction methods as well.

3.1. Comparison of our preparative results with the literature

Under optimized condition we are able to obtain *trans*-**1A** (*trans*-10-methoxy-1,3,4,4a,5,10b-hexahydro-2*H*-[1]benzopyrano[3,4-*b*]pyridine, see Scheme 1) in high chemical yield (up to 89%) and with excellent stereoselectivity (95% trans). We used a Pd/C catalyst in DMF with DIPEA at low hydrogen pressure and low initial temperature. A base like DIPEA was necessary for the removal of the HCl formed during the reaction. Considering the additional difficulty of the simultaneous removal of a chlorine atom, this is a quite satisfactory result. However, it has to be pointed out that very high catalysts concentration was needed to achieve complete conversion. This is of little consequence for preparative applications on a laboratory scale. For a technical process, further optimization of the catalytic activity would be necessary.

Hutchison et al. described the hydrogenation of type **2** compounds (R = H, Me, Pr, R_1–R_4 = three H and one O–Me substituent) with 10% Pd/C at 3–4 bar H_2 in aqueous ethanol [1,2]. With R = H, they always found a *trans*/*cis* ratio of ≤ 3, regardless of the position of the O–Me substituent. They also investigated the hydrogenation of the N–Me and the N–Pr analogs of **2A**. A *trans*/*cis* ratio of about 1 was observed and the hydrogenation of the double bond was considerably slower [12]. If the corresponding lactam was used, then the *cis* isomer was favored (*trans*/*cis* ratio 0.1), and the rate of reaction decreased at least by a factor of 10 [12]. These results show that it is difficult to get high stereo- and chemoselectivity in the catalytic hydrogenation of type **2** compounds and that the type of nitrogen influences both rate and stereoselectivity.

Cannon et al. did much work on compounds related to **3** (R = H, R_1–R_4 three H and one O–Me substituent [3,5,6,9,11]). They screened a wide variety of hydrogenation and reduction methods for the stereoselective conversion of the double bond (e.g., $NaCNBH_3$ [3,8], B_2H_6 in THF [6], Li/NH_3 [6], and PtO_2/H_2 in AcOH or EtOH [6]). None of the described methods yielded a better *trans*/*cis* ratio than ≈ 1, and in most cases, considerably more *cis* than *trans* product was formed. The same authors also reduced the lactam derivative of **3** with $HSiEt_3$/TFA [9,11] or 5% Pd/C and H_2 [11]. They claimed that with the silane/acid reagent 100% of the corresponding *trans*-derivatives could be obtained. Other authors were not able to reproduce the results with the same [4] or similar compounds [12], in the former case probably due to a mixture of isomers in the starting material [9]. With Pd/C and H_2, Cannon et al. isolated exclusively the undesired *cis*-isomer [11].

3.2. Rationalization of the stereoselectivity

Here, we shall first present the generally accepted model for the stereochemical outcome

of olefin hydrogenation (Horiuti–Polanyi or H.–P. mechanism [21], see also [13] and Scheme 4). In the following paragraphs, we will try to rationalize the influence of some reaction parameters on the basis of this model.

In the H.–P. mechanism, the less hindered side of the olefin is adsorbed on the catalyst surface. Two adsorbed hydrogen atoms then react via the half-hydrogenated state to the saturated compound. To obtain the usually observed *cis*-addition, both hydrogens have to be added from the same (metal) side to the olefin. For the hydrogenation of **2A**, this means that *trans*-stereochemistry results either when the face anti to the hydrogen atom is adsorbed preferentially or when the irreversible hydrogen addition to *Pro-trans*-**2A**–* is faster. From the data discussed in the results and in the literature section, it can be concluded that there is no strong bias for either the *cis*- or the *trans*-geometry. This indicates that both isomers can be formed preferentially under suitable condition because the two sides of the olefin are similar in steric hindrance. It also means that small changes in reaction conditions can have major effects but are difficult to explain.

3.3. Rationalization of the effects of the important reaction parameters

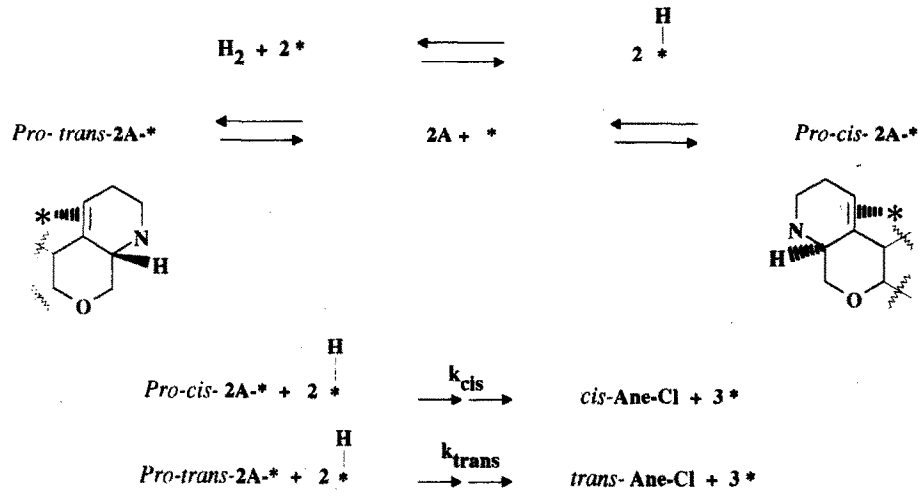
In order to get high *trans*-selectivity, large amounts of catalyst had to be used at low T and low p_{H_2}. Most of our results can be explained plausibly assuming classical hydrogenation reactivities (see Schemes 2 and 3 for the major reaction pathways). However, a few points need special consideration.

Hydrogen pressure and catalyst loading. There are few reports in the literature where an influence of the amount of catalyst on the stereochemistry has been observed [22–24]. Nevertheless, our results can be explained in the framework of the H.–P. model assuming that *Pro-trans*-**2A**–* and *Pro-cis*-**2A**–* are in equilibrium (Scheme 4) and that *Pro-trans*-**2A**–* is thermodynamically more stable. Under hydrogen-deficient conditions (low pressure, large amounts of catalyst), there is time to equilibrate the two species before an irreversible H-addition step can take place. If k_{cis} and k_{trans} are of the same order of magnitude, then our results can be explained. Under hydrogen-rich conditions, the rate of the formation of the surface species determines stereoselectivity because equilibration is not possible.

We were afraid of C=C bond isomerization on Pd/C similar to the ones described for instance by Siegel et al. [25] for the hydrogenation of substituted cyclohexenes over Pd. However, we observed double bond isomerized products of **2A** in less than 1%, even under conditions that should favor such a process (T2-14).

Effect of temperature. Because of the low activity of the most selective system, we tried to increase the rate by raising the temperature. At low conversion, the stereoselectivity did not depend on the temperature but was determined by the other reaction parameters. Fig. 1 illustrates that even at 100°C very high initial *trans*/*cis* ratios could be obtained. In the course of the reaction however, the *trans*/*cis* ratio always decreased drastically if the temperature in the beginning of the reaction was $\geq$50°C (cf. T2-11–14). This indicates either epimerization of the products or slow formation of the *cis*-products through another reaction pathway. Since pure **1A** was found to be stable under reaction conditions, epimerization was ruled out. Changing *trans*/*cis* ratios were always paralleled by the formation of some **Arom–Cl** and **Arom** which slowly disappeared in the course of the reaction. Therefore, we suggest that the change in the *trans*/*cis* ratio was brought about by the formation and subsequent hydrogenation of **Arom** and **Arom–Cl** (Scheme 3, Fig. 1). As expected and described in the literature [13], hydrogenation of fused aromatic rings formed almost exclusively the *cis*-fused rings and very little *trans*-isomer.

To sum up: Initial low temperature is necessary to avoid aromatization and consecutive hydrogenation of **Arom** to *cis*-**1A**. When the hydrogenation of the double bond is complete, the temperature can be raised to accelerate the dehalogenation of



Scheme 4. Horiuti–Polanyi mechanism for the hydrogenation of the C=C bond. Note that an analogous pathway can be formulated for the dehalogenated **Ene** and a direct interconversion between the *Pro-trans* and the *Pro-cis* species is also possible. * represents an active center on the metal surface.

Ane–Cl, which is no longer susceptible to dehydrogenation.

Dehalogenation versus C=C bond hydrogenation. As mentioned above, the removal of the Cl atom in the R_4 position and the hydrogenation of the double bond took place in a one-pot reaction. We could therefore study the influence of the reaction parameters and compare the rates of the two reactions.

It is well known that strong bases like aqueous KOH accelerate the hydrogenolysis of C–Cl bonds whereas the rate of double bond hydrogenations is less affected by the solvent and the base [17]. **2A** showed the same behavior: With the 5% Pd/C catalyst, the double bond hydrogenation was always faster than the dehalogenation if a week organic base was used. KOH on the other hand increased the relative rate of dehalogenation.

The rate of dehalogenation showed an unexpected hydrogen pressure dependence. In some cases, increased hydrogen pressure decreased the rate of dehalogenation (see results section). Inhibition of the adsorption of the C–Cl group by adsorbed hydrogen at high H_2 pressure would explain such a finding but there is not enough known on the mechanism if C–Cl hydrogenolysis to substantiate such a proposal. There are only few reports that connect hydrogen pressure with the rate of dechlorination. LaPierre et al. investigated the dechlorination/hydrogenation of 1,1-bis-(*p*-chlorophenyl)-2,2-dichloroethylene over 10% Pd/C in the liquid [15] and in the vapor phase [16]. In both cases they found that the removal of the first aromatic chlorine had a higher rate constant at low hydrogen pressure than at high pressure. The hydrogenation of the olefinic double bond had a higher order in hydrogen than the hydrodechlorination.

Side product formation. The formation of the undesired **Arom**, **Arom–Cl** and **Demethox–Cl** was promoted by high temperature, low hydrogen pressure, and high amounts of catalyst. Both aromatization and demethoxylation have literature precedence. Under the conditions mentioned above, **2A** partially disproportionated to form mainly **1A**, **Ane–Cl**, **Arom**, and **Arom–Cl** (Scheme 3). Dehydrogenation of 1,2,5,6-tetrahydropyridines substructures over Pd/C or Pd-black is well known [18–20]. It is promoted by hydrogen acceptor groups like N-benzyl [19] or Ar–Cl that in our case are present in the same molecule.

We also found small amounts of **Demethox–Cl** in our reaction mixtures at high T and low p_{H_2}.

Even though a hydrogenolysis of an aromatic methoxy group is very unusual, we found an example in the literature where demethoxylation occurred on PtO_2 at 1 bar H_2 and room temperature [14].

Catalyst activity. Up to now it remains unclear why the catalysts we employed showed such a low hydrogenation activity. Since impurities are unlikely, the deactivation was obviously caused by strongly adsorbed **2A** and reaction products, or by the amines we used as bases. Both Freifelder [26] and Zymalkowski [27] describe poisoning of platinum-group metals by organic amines.

4. Experimental

The starting material **2A**·HCl was prepared according to [2]. It was converted to the free base with 20% aqueous KOH and extracted with toluene. The toluene extracts were pooled, dried over Na_2SO_4, and evaporated to dryness. The resulting brown oil was used without further purification for the hydrogenation. The 5% Pd/C catalyst used for most of the experiments was purchased from Engelhard (Code 4522), and the mixed metal catalyst from Degussa. The solvents and organic bases were purchased from Fluka (p.a. grade).

GLC analysis. All samples were N-acetylated by adding equal amounts of Ac_2O (v/v) to the sample solution and keeping the vial at 50°C for 1 hour. A 30 m DB17 W30 capillary column with a diameter of 0.316 mm was used for the separation (1 min at 200°C, 10°C/min → 250°C, 30 min at 250°C). The results given are GLC area-% (FID detector); no correction for the response factors was made. In all experiments, >95% of the peaks observed were known compounds. Retention times (min): **Arom** (6.6), **Arom–Cl** (9.6), *trans*-**1A** (12.4), *cis*-**1A** (13.2), **Demethox–Cl** (14.2), **Ene** (15.8), *trans*-**Ane–Cl** (21.8), *cis*-**Ane–Cl** (23.3), **2A** (28.2).

The mass of all compounds was confirmed by a GLC–MS experiment (TSQ 45 mass spectrometer coupled to a Carlo Erba 4160 GLC). To obtain mainly the MH^+ ion, chemical ionization with ammonia was used. Masses obtained (Molecular formula of MH^+, mass): **Arom** ($C_{13}H_{12}NO_2$, 214), **Arom–Cl** ($C_{13}H_{11}ClNO_2$, 248), *trans*-**1A** ($C_{15}H_{20}NO_3$, 262), *cis*-**1A** ($C_{15}H_{20}NO_3$, 262), **Demethox–Cl** ($C_{14}H_{17}ClNO_2$, 266), **Ene** ($C_{15}H_{19}NO_3$, 260), *trans*-**Ane–Cl** ($C_{15}H_{19}ClNO_3$, 296), *cis*-**Ane–Cl** ($C_{15}H_{19}ClNO_3$, 296), **2A** ($C_{15}H_{17}ClNO_3$, 294). **2A**, *trans*-**1A**, and *cis*-**1A** were identified by the comparison of their NMR spectra to reference compounds [2]. **1A** was also characterized by elemental analysis ($C_{13}H_{17}NO_2$): Calc C: 71.2%, H: 7.8%, N: 6.4%, O: 14.6%. Found: C: 71.0%, H: 7.8% N: 6.4%, O: 14.8%.

Hydrogenation experiments were either carried out in a 200 ml Parr bottle on a Parr shaker or in a 100 ml stainless steel autoclave with a magnetic stirrer. In some experiments the H_2 flow was controlled with a Brooks Series 5850 mass flow controller (see Table 2).

In a typical experiment, 4.00 g **2A** (free base, 15.9 mmol) were dissolved in 20 g DMF and transferred into a 100 ml steel autoclave. 4.11 g *N,N*-diisopropylethylamine (31.8 mmol) was added to the solution. 1.00 g 5% Pd/C (Engelhard 4522) was suspended in 12.7 g DMF and added to the mixture. The autoclave was closed and purged with N_2 (3 times, 5 bar). After checking the system for leaks (20 bar H_2), the initial N_2 pressure was set to 1 bar. The system was stirred with 1500 rpm and heated to 30°C at a rate of ≈2°C/min. H_2 was then allowed to flow into the system at a rate of 70–100 ml H_2/h (1.013 bar, 0°C, 14% theoretical amount H_2/h) with the maximum H_2 pressure set to 1.5 bar. After 2.5 and 4.5 hours, the autoclave was opened and samples of 0.5–1.0 ml were removed. After the sampling, the purging was repeated and the H_2 flow was set as described above. After 5 h of reaction time (usually uptake of ≈1 equivalent H_2), the temperature was raised to 60°C at a rate of ≈2°C/min. The total reaction time was 21.5 h. The autoclave was then cooled to room temperature, purged with N_2 and discharged. The catalyst was filtered off and a 0.5 ml sample of the final solution was removed for analytical purposes. If conversion was incom-

plete, then the above solution was charged with 1.00 g fresh 5% Pd/C catalyst and hydrogenated at 60°C and an H_2 pressure at <1 bar for 19 h. Solid **1A** with a satisfactory elemental analysis (see above) was obtained by filtering the catalyst off and evaporating the DMF solution to dryness. If no samples were removed for analytical purposes, yields of up to 89% could be obtained.

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References

[1] A. Hutchison, M. Williams, R. de Jesus, G.A. Stone, L. Sylvester, F.H. Clarke and M.A. Sills, J. Med. Chem., 32 (1989) 720.
[2] A.J. Hutchison, Eur. Pat. 161218, (1985).
[3] J.G. Cannon, V.E.D. Amoo, J.P. Long, R.K. Bhatnagar and J.R. Flynn, J. Med. Chem., 29 (1986) 2529.
[4] C. Mellin, J. Vallgårda, D.L. Nelson, L. Björk, H. Yu, N.E. Andén, I. Csöregh, L.E. Arvidsson and U. Hacksell, J. Med. Chem., 34 (1991) 497.
[5] J.G. Cannon, C. Suarez-Gutierrez, T. Lee, J.P. Long, B. Costall, D.H. Fortune and R.J. Naylor, J. Med. Chem., 22 (1979) 341.
[6] J.G. Cannon, G.J. Hatheway, J.P. Long and F.M. Sharabi, J. Med. Chem., 19 (1976) 987.
[7] H. Wikström, D. Sanchez, P. Lindberg, L.E. Arvidsson, U. Hacksell, A. Johansson, J.L.G. Nilsson, S. Hjorth and A. Carlsson, J. Med. Chem., 25 (1982) 925.
[8] J.G. Cannon, R.L. Hamer, M. Ilhan, R.K. Bhatnagar and J.P. Long, J. Med. Chem., 27 (1984) 190.
[9] J.G. Cannon and K.S. Kirschbaum, Synthesis, (1993) 1151.
[10] H.W. Thompson, E. McPherson and B.L. Lences, J. Org. Chem., 41 (1976) 2903.
[11] J.G. Cannon, Y. Chang, V.E. Amoo and K.A. Walker, Synthesis Commun., (1986) 494.
[12] J. Bach, unpublished results.
[13] M. Bartók, Stereochemistry of Heterogeneous Metal Catalysis, John Wiley and Sons Ltd., Chichester, 1985, p. 94.
[14] J. Cohen and W.I. Taylor, J. Org. Chem., 28 (1963) 3567.
[15] R.B. LaPierre, L. Guczi, W.L. Kranich and A.H. Weiss, J. Catal., 52 (1978) 218.
[16] R.B. LaPierre, D. Wu, W.L. Kranich and A.H. Weiss, J. Catal., 52 (1978) 59.
[17] P.N. Rylander, Hydrogenation Methods, Academic Press, London, 1985, p. 149.
[18] J. McNulty and I.W.J. Still, Tetrahedron Lett., 32 (1991) 4875.
[19] G. Cordonnier and H. Sliwa, J. Heterocyclic Chem., 24 (1987) 111.
[20] I. Huber, F. Fülöp, J. Lázár, G. Bernáth and G. Thót, J. Chem. Soc., Perkin Trans. I (1992) 157.
[21] I. Horiuti and M. Polanyi, Trans. Faraday Soc., 30 (1934) 1164.
[22] R.L. Augustine, J. Org. Chem., 28 (1963) 152.
[23] H.O. House, R.G. Carlson, H. Müller, A.W. Noltes and C.D. Slater, J. Am. Chem. Soc., 84 (1962) 2614.
[24] S. Mitsui, H. Saito, S. Sekiguchi, Y. Kumagai and Y. Senda, Tetrahedron, 28 (1972) 4751.
[25] S. Siegel and G.V. Smith, J. Am. Chem. Soc., 82 (1960) 6087.
[26] M. Freifelder, Practical Catalytic Hydrogenation, Wiley-Interscience, New York, 1971, p. 39.
[27] F. Zymalkowski, Katalystische Hydrierungen im Organisch-Chemischen Laboratorium, F. Enke Verlag, Stuttart, 1965, p. 35.