Functional-Group-Directed Diastereoselective Hydrogenation of Aromatic Compounds. 2[1]

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Diastereoselective liquid-phase hydrogenation of a series of monosubstituted indan substrates was studied on supported rhodium catalysts. Predominantly the *cis*−*cis* diastereomer, obtained by hydrogenation from the diastereoface opposite the substituent at the stereogenic center, and the *cis*−*trans* diastereomer, obtained by hydrogenation from the diastereoface on the same side as the substituent, were formed. The diastereoselectivity depends on the balance between steric repulsion and electronic attraction of the substituent with the surface of the catalyst. For alkoxy and carboxyl groups (acid, methyl ester, and amide), the steric repulsion dominated and the *cis*−*cis* diastereomer was obtained with moderately high selectivity. The diastereoselectivity obtained in the hydrogenation was influenced by the addition of bases to the reaction mixture. Addition of triethylamine caused a small increase in the selectivity to the *cis*−*cis* diastereomer in some substrates, whereas the addition of NaOH significantly increased the selectivity toward the *cis*−*trans* isomer in all substrates.

Introduction

Stereoselective syntheses of cyclic compounds by diasteroselective hydrogenation of the corresponding substituted aromatic compounds on heterogeneous catalysts has received growing attention in recent years.[2−5] The mechanism of face selection during hydrogenation of modified aromatic compounds is, however, not well understood. It is of interest therefore to study interactions (or directing effects) of nonreducible functional groups individually to obtain an insight into the mechanism of diastereoselection. To this end, we initiated a study into the hydrogenation of a series of aromatic substrates differing only in the functional group substituent at the same stereogenic center. In part 1 of this series[1] we investigated the hydrogenation of racemic indan substrates substituted at the benzylic position with hydroxyl, amino, and methyl groups (**1**, Figure 1). In the present paper we report the results of hydrogenation of indan substrates having alkoxy and carboxyl groups at the benzylic position. The choice of the class of substrates was dictated by two considerations: the selected molecules had to be flat so that the interaction of substituents is well expressed during their adsorption on the catalyst surface, and they had to be conformationally rigid. The choice of the benzylic-substituted indans was advantageous in one more respect in that the relative configuration of the fully hydrogenated products can be determined relatively easily. Supported rhodium catalysts were used for hydrogenation because of their high activity under relatively mild reaction conditions.[6,7] We also continued our investigations into the influence of the addition of inorganic and organic bases during reaction on the diastereoselectivity as in part 1.

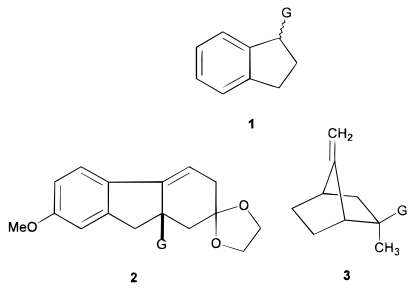

Figure 1. Substrates investigated by Thompson and co-workers (**2** and **3**)[8,9] and substituted indan substrates (**1**) investigated in part 1 and the present study.

Although a systematic study of the directing effects of different functional groups had not been conducted in aromatic hydrogenation prior to our investigation, a corresponding study had been conducted in olefin hydrogenation.[8,9] In their study, Thompson and co-workers hydrogenated a series of substituted tetrahydrofluorenes[8] (**2**, Figure 1) and 2-exo-substituted 7-methylenenorbornanes[9] (**3**, Figure 1), differing only in the functional group substituent at one stereocenter, over supported palladium catalysts. Since the two faces of the olefinic substrates are not identical, hydrogenation from either of the two faces results in different products. Hydrogenation proceeds mainly from the side of the functional group (proximofacial) if the electronic interaction between this

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group and the metal surface dominates, whereas it proceeds predominantly from the side opposite the functional group (distofacial) if steric repulsion dominates. The relative magnitude of repulsion and attraction of the substituents with a particular catalyst was gauged by hydrogenating under identical conditions a series of olefinic compounds differing only in the substituent. In principle, the facial selectivity in the hydrogenation of substituted aromatic compounds should similarly depend on the attractive or repulsive properties of the substituent(s) with the catalyst. However, palladium is generally preferred for olefinic hydrogenation, whereas rhodium is extensively used for aromatic hydrogenation.[6,7] It is therefore of interest to compare the effect of substituents in the hydrogenation of olefinic and aromatic substrates.

To the best of our knowledge, nothing has been published on substituent-directed hydrogenation of aromatic compounds with homogeneous catalysts, probably because these catalysts lack activity. The influence of substituents has been exploited, however, in the hydrogenation of a variety of olefinic substrates, particularly with soluble rhodium and iridium complexes. Excellent selectivities have been achieved for many substrates utilizing the attractive interaction of polar substitutents such as the hydroxyl and carboxyl groups with the metal center in homogeneous catalysts.[10,11] Some comparative data are available for the application of heterogeneous and homogeneous catalysts in directed hydrogenation reactions.[12−14] It indicates that in general heterogeneous catalysts lag well behind their homogeneous counterparts in terms of selectivities, even under comparable reaction conditions.

Results

Hydrogenation of all substrates yielded predominantly *cis* (*cis*−*cis* + *cis*−*trans*) diastereomers (usually *cis* to *trans* ratio >10) with respect to the two substituents on the six-membered ring (Scheme 1). Different methods were employed for the identification of the relative configuration of the *cis*−*cis* and *cis*−*trans* diastereomers, depending on the substrate hydrogenated as described in the Experimental Section. The diastereoselectivity to the two *cis* isomers is expressed as the diastereomeric ratio (dr) at 100% conversion of the substrate and intermediates and is defined as dr = [*cis*−*cis*]/[*cis*−*trans*]. For clarity, the dr is presented as a ratio in which the sum of the yields of the two diastereomers is normalized to 100. To demonstrate the variation of diastereoselectivity with reaction time, selectivity and incremental selectivity to the *cis*−*cis* diastereomer are presented for a few experiments. Selectivity is defined as [*cis*−*cis*]/[cis], and the incremental selectivity is defined as ([*cis*−*cis*]$_2$ − [*cis*−*cis*]$_1$)/([cis]$_2$ − [cis]$_1$), where subscript 2 refers to the point of kinetic analysis at which the incremental dr is calculated and subscript 1 refers to the previous point of kinetic analysis, and [*cis*] = [*cis*−*cis*] + [*cis*−*trans*].

Scheme 1

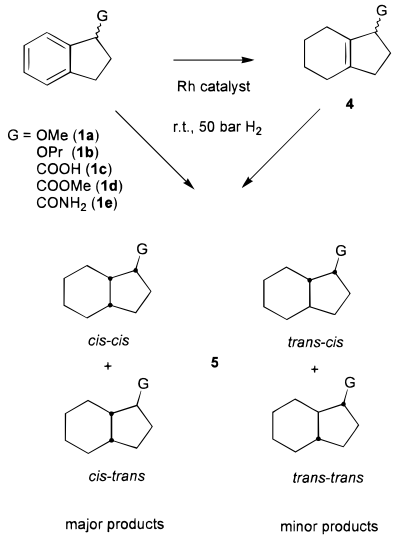

Table 1. Hydrogenation of 1-Alkoxyindans

1, G =	catalyst[a]	solvent	yield of *cis*- and *trans*-perhydroindan[b] (%)	yield of *cis* perhydro products[b] (%)	dr[b]
OMe	Rh/C	EtOH	74	21	79:21
OMe	Rh/C	hexane	36	60	75:25
OMe	Rh/Al_2O_3	EtOH	4	91	88:12
OMe	Rh/Al_2O_3	hexane	5	85	82:18
OPr	Rh/C	EtOH	78	19	81:19
OPr	Rh/Al_2O_3	EtOH	7	88	92:8

[a] The substrate-to-metal molar ratio for 1-methoxyindan is 128, and that for 1-propoxyindan is 117. [b] Determined by analyses over a HP-1 capillary column.

Small to significant amounts of cyclohexene intermediates were observed (identified by GC−MS analysis) depending on the substrate hydrogenated and the reaction conditions. For most substrates the hydrogenation of the cyclohexene intermediate proceeded slower than that of the substrate, and it caused a change in the diastereoselectivity, the magnitude of which depended on the substrate. The cyclohexene intermediate hydrogenated slower than the corresponding aromatic substrate probably because of its higher steric hindrance (attributed to its nonplanar structure) during its adsorption on the catalyst. The position of the double bond in the cyclohexene intermediates was identified by NMR analyses to be between the junction carbon atoms, only in the case of the ester **1d**.

Results of the hydrogenation of 1-methoxyindan (**1a**) are reported in Table 1. Substantial amounts of the hydrogenolysis−hydrogenation byproducts *cis*- and *trans*-perhydroindan were obtained in addition to the fully hydrogenated products on the Rh/C catalyst, especially in ethanol. The fractional yield of these products is also reported in Table 1 at 100% conversion of the substrates. Less hydrogenolysis occurred on the Rh/C catalyst in hexane and very little on the Rh/Al_2O_3 catalyst. In general, a high diastereoselectivity to the *cis*−*cis* isomer was obtained over both catalysts, Rh/Al_2O_3 being more stereoselective than Rh/C, and reactions in ethanol being more stereoselective than those in hexane. Hydrogenation of 1-propoxyindan (**1b**) in ethanol was studied to investigate the effect of the size of the alkoxy substituent on the diastereoselectivity. Like in the case of 1-meth-

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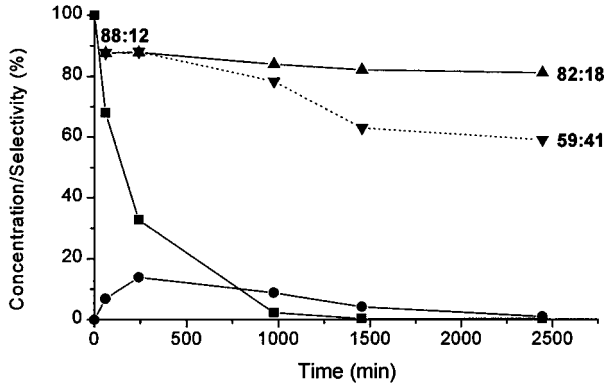

Figure 2. Kinetics of the hydrogenation of 1-methoxyindan in hexane over Rh/Al_2O_3 under standard reaction conditions: concentration of 1-methoxyindan (■) and its cyclohexene intermediate (●) and selectivity (▲) and incremental selectivity (▼) to the *cis*−*cis* diastereomer.

oxyindan, the Rh/C catalyst showed a lower chemoselectivity as well as diastereoselectivity than the Rh/Al_2O_3 catalyst (Table 1). The diastereoselectivity in the hydrogenation of 1-propoxyindan was slightly higher than in that of 1-methoxyindane. In 1-methoxyindan as well as 1-propoxyindan the diastereoselectivity to the *cis*−*cis* isomer decreased as the reaction proceeded to completion. The decrease in selectivity and incremental selectivity to the *cis*−*cis* diastereomer with conversion in the hydrogenation of 1-methoxyindan (and its intermediate) in hexane over the Rh/Al_2O_3 catalyst are shown in Figure 2. The dr values corresponding to the initial and final selectivity and incremental selectivity are also indicated in the figure. The substrate concentration decreases continuously, whereas the concentration of the intermediate goes through a maximum. Toward the end of the reaction, the fully hydrogenated *cis* products are formed primarily due to hydrogenation of the intermediate and not of the substrate. The selectivity and incremental selectivity stay constant during the initial period in which the cyclohexene intermediate is being formed and decrease with the conversion of the intermediate to the products. This indicates that the decrease in the selectivity to the *cis*−*cis* diastereomer and hence the dr with time is primarily due to the fact that the cyclohexene intermediate hydrogenates with a much lower selectivity to the *cis*−*cis* diastereomer than 1-methoxyindan.[15]

Results of hydrogenation of the carboxyl substrates, viz., indan-1-carboxylic acid (**1c**), the methyl ester of indan-1-carboxylic acid (**1d**), and indan-1-carboxamide (**1e**) (Scheme 2), are presented in Table 2. All substrates yielded predominantly (92−95%) the *cis*−*cis* and *cis*−*trans* diastereomers, with a comparable and relatively high selectivity to the *cis*−*cis* diastereomer. The selectivity is higher with Rh/Al_2O_3 than with Rh/C. For the ester, the selectivity is hardly affected by the change in the solvent from ethanol to hexane. Reactions of the other substrates were conducted only in ethanol because of their limited solubility in hexane. The diastereoselectivity of all substrates was unaffected by changing the substrate-to-catalyst ratio. The diastereoselectivity to the *cis*−*cis*

Scheme 2

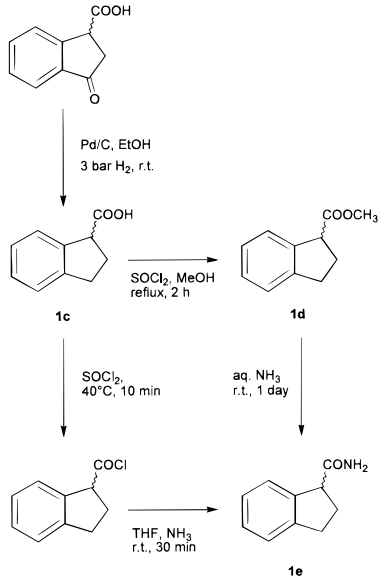

Table 2. Hydrogenation of Carboxyl Substrates

1, G =	catalyst[a]	solvent	dr[b]
COOH	Rh/C	EtOH	77:23
$CONH_2$	Rh/C	EtOH	71:28
COOMe	Rh/C	EtOH	80:20
COOMe	Rh/C	hexane	80:20
COOH	Rh/Al_2O_3	EtOH	84:16
$CONH_2$	Rh/Al_2O_3	EtOH	81:19
COOMe	Rh/Al_2O_3	EtOH	85:15
COOMe	Rh/Al_2O_3	hexane	82:18

[a] The substrate-to-metal molar ratio for acid and amide is 127, and that for ester is 117. [b] Yield of the *cis* diastereomers (>92%) and dr determined by analyses over a RTX-200 capillary column.

diastereomer decreased significantly, however, in the ester hydrogenation especially toward the end of the reaction. For example, in the hydrogenation of the ester over the Rh/Al_2O_3 catalyst in ethanol, the dr decreased from 89:11 at the beginning to 83:17 at the end of the reaction. In one experiment, the hydrogenation of the ester was interrupted at an intermediate conversion, and a mixture of the unconverted substrate, its cyclohexene intermediate, and fully hydrogenated products was isolated, by removing the catalyst and the solvent. Column chromatography over silica gel (hexane:ethyl acetate = 9:1) enabled separation of a mixture of the cyclohexene intermediate and the fully hydrogenated products from the unconverted substrate. A normal and a DEPT ^{13}C NMR spectrum of the mixture enabled us to assign the position of the double bond between the two junction carbon atoms (see the Supporting Information). The cyclohexene intermediate in this mixture was hydrogenated further over the Rh/Al_2O_3 catalyst in ethanol under standard reaction conditions. A dr value of 71:29 was obtained in this experiment, and the value changed very little with increasing conversion of the cyclohexene intermediate. Thus, hydrogenation of the cyclohexene intermediate takes place with a constant but different selectivity than that of the parent aromatic substrate. The change in diastereoselectivity during the reaction could not be determined in the case of the acid substrate **1c** because of insufficient chromatographic resolution and in the case of the amide substrate **1e** because of the precipitation of the *cis*−*cis* diastereomer.

(15) It could be argued that the change in diastereoselectivity is related to a change in the catalyst with time. We have eliminated this possibility, at least in the case of 1-methoxyindan, by conducting an experiment in which a fresh batch of catalyst was added, after removal of the original catalyst, to a half-converted reaction mixture. The diastereoselectivity obtained in this experiment was the same as that obtained in the normal experiment.

Scheme 3

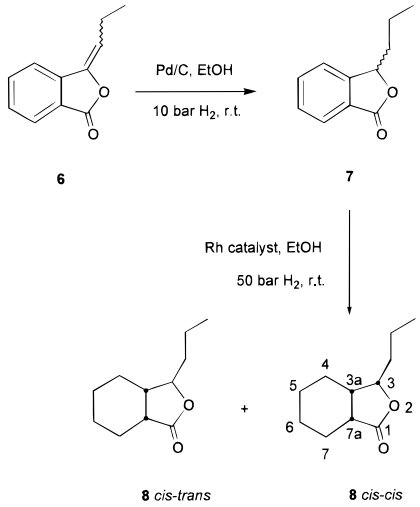

Table 3. Hydrogenation of 3-Propyl-3*H*-isobenzofuran-1-one in Ethanol

catalyst	hydrogen pressure (bar)	dr[b]	catalyst	hydrogen pressure (bar)	dr[b]
Rh/C[a]	50	94:6	Rh/C[c]	10	95:5
Rh/C[a,d]	50	92:8	Rh/Al_2O_3[a]	50	94:6
Rh/C[a]	20	95:5			

[a] The substrate to metal molar ratio is 115. [b] Yield of the cis diastereomers (~99%) and dr determined by ^1H analyses over a γ-DEX capillary column. [c] The catalyst-to-substrate molar ratio is 60. [d] Reaction conducted at 50 °C.

Results of hydrogenation of 3-propyl-3*H*-isobenzofuran-1-one (**7**, Scheme 3) in ethanol are shown in Table 3. In all experiments, a very high chemoselectivity (~99%) toward the fully hydrogenated *cis* products (**8**, Scheme 3) and a very high diastereoselectivity toward the *cis*−*cis* diastereomer was obtained. Rh/C and Rh/Al_2O_3 were equally selective. A cyclohexene intermediate was formed during the hydrogenation, and its maximum concentration reached exceptionally high values of 20−40% of the initial substrate concentration, depending on the reaction conditions. The diastereoselectivity to the *cis*−*cis* isomer increased very slightly as the reaction proceeded to completion, implying that the intermediate was hydrogenated with a greater selectivity to the *cis*−*cis* isomer than the parent substrate. Changing the reaction temperature from ambient temperature to 50 °C and the pressure from 50 to 10 bar and halving the substrate-to-rhodium ratio had a small effect on the dr with the Rh/C catalyst.

The influence of the addition of triethylamine (TEA) during hydrogenation was investigated for all substrates. In line with previous observations,[1] the addition of amine decreased the activity in all reactions and led to almost complete suppression of the hydrogenolysis of the 1-alkoxyindan substrates. With all the substrates but 1-methoxyindan and 3-propyl-3*H*-isobenzofuran-1-one, the TEA-to-Rh and substrate-to-catalyst ratios were halved (by doubling the catalyst amount) because of very low activity. Results in Table 4 show that the diastereoselectivity increased in the case of 1-propoxyindan from 81:19 to 93:7 and in the case of indan-1-carboxamide from 71:28 to 82:18, whereas in all other substrates it remained almost unaffected. The dr value changed with the conversion for all substrates; typically the initial dr value was higher than the corresponding values in the reactions without additive, but the dr value decreased as the reaction proceeded to completion.

Table 4. Hydrogenation in Ethanol over Rh/C with Triethylamine and NaOH additives

substrate	substrate-to-rhodium molar ratio	dr without additive	dr TEA additive	dr NaOH additive
1−OMe[a]	128	79:21	81:19	49:51
1−OMe[b]	64	79:21		55:45
1−OPr[b]	59	81:19	93:7	67:33
1−COOMe[b]	59	80:20	79:21	61:39
1−$CONH_2$[b]	64	71:28	82:18	59:41
3-propyl-3*H*-isobenzofuran-1-one[a]	115	94:6	95:5	

[a] The triethylamine to rhodium molar ratio is 10, and the Na-to-rhodium molar ratio is 6. [b] The triethylamine to rhodium molar ratio is 5, and Na-to-rhodium molar ratio is 3.

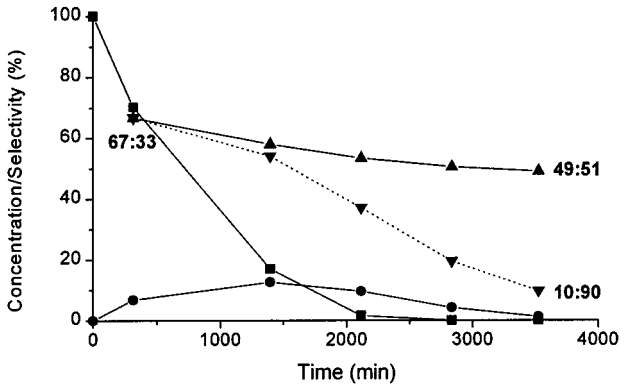

Figure 3. Kinetics of the hydrogenation of 1-methoxyindan in ethanol over Rh/C with NaOH additive, under standard reaction conditions: concentration of 1-methoxyindan (■) and its cyclohexene intermediate (●) and selectivity (▲) and incremental selectivity (▼) to the *cis*−*cis* diastereomer.

As in the case of TEA, addition of an aqueous solution of NaOH (0.3 mL of strength 0.5 N) resulted in a decrease in the activity accompanied by almost complete suppression of hydrogenolysis of the 1-alkoxyindan substrates. Because of the low activity, the substrate-to-catalyst and Na-to-Rh ratios were halved by doubling the amount of the catalyst. The dr was significantly reduced in all cases (Table 4). In the case of 1-methoxyindan, a substantial reduction is obtained in dr and the value of dr reached unity in the experiment with higher Na-to-Rh ratio. For all substrates the value of dr decreased as the reaction proceeded, probably because of the hydrogenation of the cyclohexene intermediate. The decrease in dr during reaction was largest for 1-methoxyindan. Figure 3 shows the kinetics of hydrogenation of 1-methoxyindan in ethanol with NaOH additive over the Rh/C catalyst. Analogous to Figure 2, the selectivity and incremental selectivity to the *cis*−*cis* diastereomer are plotted as a function of reaction time along with the concentrations of 1-methoxyindan and its intermediate, and the initial and final dr values are also indicated. As in the case of reactions without additives, toward the end of the reaction, the fully hydrogenated *cis* products are formed predominantly by the hydrogenation of the intermediate and not of the substrate. It is evident from Figures 2 and 3 that the addition of NaOH leads to a lower activity and a substantial reduction in the initial as well as the final dr value. The drop in incremental dr is substantial, especially during the hydrogenation of the intermediate,

indicating that the cyclohexene intermediate is much less hydrogenated in a distofacial fashion than the parent substrate.

Discussion

The substrates are hydrogenated distofacially when the steric repulsion of the substituent dominates, yielding predominantly the *cis*−*cis* diastereomer, whereas they are hydrogenated proximofacially when the electronic attraction dominates, yielding predominantly the *cis*−*trans* diastereomer (Scheme 1). The ratio of the *cis*−*cis* to *cis*−*trans* diastereomers of substrates with a different substituent gives an estimate of the relative repulsive or attractive interaction between the substituent and rhodium surface. Results in part 1 indicated that only the amino group in 1-aminoindan interacted very strongly with the catalyst surface, giving almost exclusively the *cis*−*trans* diastereomeric product. The yield of the *cis*−*trans* diastereomer is thus a measure of the attraction of the functional group, in the aromatic substrates hydrogenated, to the catalyst, also termed the haptophilicity of the functional group. The hydroxyl group had a very small haptophilic effect, if at all, because the *cis*−*cis* diastereomer was obtained as the major product. The methyl group by virtue of its small size produced the *cis*−*cis* diastereomer in moderate excess. We expected the alkoxy group to have little or no interaction with the metal surface because of its low polarity. However, the carboxyl group can in principle interact with the metal surface on account of its high polarity. This interaction has often been successfully exploited in homogeneous catalysis to obtain high selectivities to the proximofacial products in olefin hydrogenations.[10,11]

The results for the hydrogenation of 1-methoxyindan (Table 1) indicate that the *cis*−*cis* diastereomer is obtained with a high selectivity. As observed in the case of indanol,[1] substantial hydrogenolysis takes place over the Rh/C catalyst with spillover hydrogen.[16] The extent of hydrogenolysis is smaller with hexane as solvent for both catalysts. 1-Propoxyindan shows the same trends as 1-methoxyindan. The Rh/Al_2O_3 catalyst gives a slightly higher selectivity to the *cis*−*cis* isomer with 1-propoxyindan than with 1-methoxyindan, in line with the larger steric hindrance of the propyl group than the methyl group.

Results reported for the substrates with carboxylic acid and ester substituents (Table 2) indicate that these groups show little attraction to the catalyst surface since the *cis*−*cis* diastereomer is produced with a relatively high selectivity. Indan-1-carboxamide is also hydrogenated with a moderately high selectivity to the *cis*−*cis* diastereomer. The low electronic interaction exhibited by the relatively polar carboxyl groups is surprising. For all substrates, higher selectivity is obtained over the Rh/Al_2O_3 catalyst than over Rh/C, in line with the results for the other substrates. Hydrogenation of 3-propyl-3*H*-isobenzofuran-1-one proceeds with a very high selectivity as expected due to the substantial steric hindrance offered by the propyl group (Table 3). The selectivity is comparable to the one obtained in the hydrogenation of 1-propoxyindan. As expected in the hydrogenation of all substrates, a change in the process conditions or the metal-to-substrate ratio has a very small influence on the selectivity because the directing information is carried individually by each molecule.

Cyclohexene intermediates were observed in the hydrogenation of all substrates over the rhodium catalysts. These intermediates underwent hydrogenation when the concentration of the parent aromatic substrate was sufficiently low. The position of the double bond in the cyclohexene intermediate was identified as between the junction carbon atoms only for the ester. It is likely, however, that the double bond is located between the two junction carbon atoms for other substrates too, this position being favored from a steric point of view since the junction carbon atoms of the aromatic substrate stay farther away from the surface during adsorption than the other carbon atoms in the six-membered ring. This position of the double bond is also likely from a thermodynamic point of view (Zaitsev's rule). In addition, chromatographic analyses during the reaction showed only one peak for the intermediate on achiral as well as chiral columns. The intermediates were hydrogenated with a lower selectivity to the *cis*−*cis* diastereomer than the parent aromatic substrate in all substrates (except for 3-propyl-3*H*-isobenzofuran-1-one), where the cyclohexene intermediate concentration was followed as a function of time, as can be seen in the kinetics of the hydrogenation of 1-methoxyindan in Figure 2. The diastereoselectivity values reported for different substrates are thus contaminated by the results of hydrogenation of the corresponding cyclohexene intermediates. Separating the two effects would be possible if an independent study of the hydrogenation of the cyclohexene intermediates is conducted. This is of little practical interest, however, considering that the formation of the intermediates seems unavoidable during aromatic hydrogenation. Nevertheless, the hydrogenation of the cyclohexene intermediate of the ester substrate **1d** was studied to clarify the role of the cyclohexene intermediates in the hydrogenation of the aromatic substrates. This study enabled us to calculate the dr values of 89:11 and 71:29 in the direct hydrogenation of the aromatic ring and the hydrogenation of the cyclohexene intermediate in the case of the ester. Also, from the first and last points in the kinetic analysis in Figure 2, the dr values of 88:12 and 59:41 were obtained in the direct hydrogenation of the aromatic ring and the hydrogenation of the cyclohexene intermediate, respectively, in the case of 1-methoxyindan. Unfortunately, the dr values for the cyclohexene intermediates in the hydrogenation of other aromatic substrates could not be similarly calculated because the intermediates underwent hydrogenation together with the substrate when the concentration of the substrate was sufficiently low. The lower dr obtained in the hydrogenation of the cyclohexene intermediate could be due to the spatial arrangement of the adsorbed cyclohexene intermediate, resulting in a weaker expression of the steric influence of the functional group. However, it might also be due to the weaker adsorption of the olefinic bond as compared to an aromatic ring, resulting in a stronger expression of the electronic influence of the group.

Addition of triethylamine increases the yield of the *cis*−*cis* isomer in some substrates, whereas in other substrates it has no effect on the selectivity (Table 4). The aromatic molecules undergoing hydrogenation occupy more space on the metal surface when they are adsorbed in the proximofacial fashion than in the distofacial

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Table 5. Comparison of Haptophilicities (Expressed as the Selectivity to the Proximofacial Diastereomer in the Hydrogenation Product) of Various Functional Groups in Substrates 1, 2, and 3

G =	1	2[a]	3[b]
NH_2	98[c]		
CH_2NH_2			63
CH_2OH	55[c]	95	19
OH	41[c]		
Me	37[c]		
$CONH_2$	28[d]	10	0
COOH	23[d]	18	0
OMe	21[d]		
COOMe	20[d]	15	0
OPr	19[d]		

[a] After Thompson and Naipawer,[8] Pd/C catalyst, solvent 2-methoxyethanol. [b] After Thompson and Wong,[9] Pd/C catalyst, solvent ethanol. [c] Part 1, Rh/C catalyst, solvent ethanol. [d] Present study, Rh/C catalyst, solvent ethanol.

fashion. Addition of amine increases the crowding even more, thus favoring the formation of the *cis*−*cis* isomer. This is not observed in the case of all substrates, probably because of an opposing selectivity obtained in the hydrogenation of the corresponding cyclohexene intermediates. On addition of NaOH the dr reduces drastically for the 1-alkoxyindan substrates and approaches unity especially for 1-methoxyindan (Table 4), suggesting the interaction of the etheric oxygen with the Na cations adsorbed on the rhodium surface. The reduction in dr is accentuated by the fact that the cyclohexene intermediates produce the *cis*−*trans* diastereomer with a much higher selectivity than the parent benzylic ether as shown in Figure 3. The dr values obtained in the direct hydrogenation of the aromatic ring and the hydrogenation of the cyclohexene intermediate were 67:33 and 10:90, respectively. The selectivity is also reduced in the carboxyl substrates, probably because of similar interactions of the carbonyl oxygen in carboxyl substrates and their intermediates with the Na cations. Thus, results of the addition of bases suggest that the amine influences the facial selectivity by a steric mechanism while NaOH acts primarily by an electronic mechanism.

The results presented in part 1 and in the present study encompass directing effects of several nonreducible substituents encountered in aromatic hydrogenation. Table 5 summarizes the haptophilicity of substituents expressed in terms of the selectivity to the proximofacial product. For comparison we have included the selectivities to proximofacial products reported by Thompson and co-workers for substrates **2** and **3** obtained over a Pd/C catalyst. It is seen that despite differences in substrates, reaction conditions, and catalysts, the trends in the haptophilicity are the same. The amino group, the hydroxymethylene group, and the carboxyl groups exhibit a high, moderate, and low haptophilicity, respectively. In addition, in our investigations, the haptophilicities of the hydroxyl and methyl groups lie between those of the hydroxymethylene and carboxyl groups, whereas the haptophilicities of the methoxy and propoxy groups are comparable to those of the carboxyl groups.

It is noteworthy that the directing effects of the hydroxyl and carboxyl substituents in many substrates are quite strong in the case of hydrogenation with homogeneous catalysts. From the results presented in part 1 and here, as well as in the work of Thompson and co-workers, it is concluded that these effects are much too weak (especially for the carboxyl substituents) to have a comparable influence in the case of heterogeneous catalysts. In fact, in complete contrast to the results with homogeneous catalysts, the distofacial product is obtained predominantly in the hydrogenation of the aromatic compounds directed by carboxyl substituents. This can be explained in terms of the higher Lewis acidity and the lower steric hindrance around the metal atom in the case of homogeneous catalysts as compared to their heterogeneous counterparts. The coordination sphere of a metal atom embedded in a surface in heterogeneous catalysts is less flexible than that of a metal center in homogeneous catalysts. Therefore, unlike in the case of homogeneous catalysts, an increase in electronic attraction due to a substituent is accompanied by an increase in steric hindrance in the case of heterogeneous catalysts.

Conclusions

The alkoxy groups in benzylic ethers do not interact significantly with the surface of the catalyst. The interaction is low irrespective of the catalyst support or the solvent. The same result holds true for all carboxyl (acid, ester, and amide) substrates, contrary to the intuitive expectation that these polar groups would interact with the rhodium surface. The diastereoselectivity is slightly affected by changing either the substrate-to-catalyst ratio or the reaction conditions.

The benzylic ethers undergo severe hydrogenolysis over Rh/C catalysts as observed for 1-indanol, especially in ethanol. Hydrogenolysis is retarded on addition of organic or inorganic bases. The addition of triethylamine has a relatively small influence on the diastereoselectivity obtained in substrates with either the alkoxy or the carboxyl substituent. Addition of NaOH reduces the diastereoselectivity to the *cis*−*cis* isomer drastically for the alkoxy substrates due to interaction of the etheric oxygen with Na cations on the rhodium surface. The diastereoselectivity to the *cis*−*cis* isomer also reduces significantly in the case of carboxyl substrates presumably due to the interaction of the carbonyl oxygen with the Na cations.

The main implication of the results presented in the two parts of this series is that the facial selection in diastereoselective hydrogenation of aromatics on heterogeneous catalysts is primarily determined by the sterical requirements of the molecule. The electronic interaction plays an important role only when the molecule bears an amino group or when the hydrogenation is conducted in the presence of inorganic basic additives.

Experimental Section

Hydrogenation Experiments. Hydrogenation reactions were conducted in a 60 mL stainless steel autoclave equipped with a gas-inducing impeller at a stirring speed of 1100 rpm under efficient mass transport conditions. In a typical experiment, a solution of 0.5 g of substrate in 15 mL of ethanol or hexane (and basic additive, if any) was added to 50 mg of catalyst in the autoclave. Rh/Al_2O_3 (Fluka) and Rh/C (Aldrich) catalysts (metal loading 5 wt %) were used as supplied. The autoclave was closed, flushed three times successively with nitrogen and hydrogen, and then pressurized to 50 bar with hydrogen. All reactions were conducted at room temperature. Samples could be taken with a sample tube during the reaction to detect the completion of the reaction (typically less than 48 h in experiments without base addition). Analyses of samples for determination of conversion and selectivity were done using a gas chromatograph equipped with a FID detector and various

capillary columns depending on the substrate hydrogenated. Some hydrogenation experiments were continued overnight, even after complete conversion of the substrate and the intermediate. The diastereoselectivity remained unchanged over this additional period.

Preparation of the Substrates. Racemic 1-methoxyindan (**1a**) was prepared from racemic 1-indanol. To a solution of 1-indanol in dry tetrahydrofuran was added NaH, and the mixture was heated to 60 °C and maintained under argon for 30 min at the same temperature. Methyl iodide was added to the mixture, and it was maintained at 60 °C for 4 h. Excess NaH was hydrolyzed with water, and the mixture was extracted with ether twice. The ether extracts were pooled together and washed with water. The ether was removed in vacuo, and the yellow liquid product was purified by Kugelrohr distillation. The resulting colorless distillate of 1-methoxyindan was stored under argon, since it was air-sensitive and was directly used in hydrogenation experiments. Racemic 1-propoxyindan (**1b**) was prepared in exactly the same way with propyl iodide instead of methyl iodide. The yellow liquid product contained the product as well as the unconverted adduct in a ratio of about 1:3. Separation was affected by column chromatography (hexane:ethyl acetate = 19:1) to yield pure (>99%) 1-propoxyindan as a colorless liquid. The identity of 1-methoxyindan was established by comparing its NMR spectrum to that reported in the literature.[17] The identity of 1-propoxyindan was established from its NMR and MS analyses.

Racemic indan-1-carboxylic acid (**1c**) was prepared by hydrogenolysis of racemic 3-oxoindan-1-carboxylic acid over 10 wt % Pd/C catalyst (Fluka) in ethanol under 3 bar of hydrogen pressure (Scheme 2). The resulting product was isolated by removal of the solvent in vacuo after the catalyst was filtered off. A quantitative yield of indan-1-carboxylic acid (white solid) was obtained, and the acid was stored under argon because it was air-sensitive and used directly without any purification in further reactions/hydrogenations. The racemic methyl ester of indan-1-carboxylic acid (**1d**) was prepared by refluxing a solution of the acid in methanol after addition of excess of thionyl chloride for 2 h (Scheme 2). The solvent was removed in vacuo, and the yellow liquid product was distilled under vacuum in a Kugelrohr distillation apparatus. The resulting colorless liquid was used in the hydrogenation experiments.

Racemic indan-1-carboxamide (**1e**) was prepared by two methods (Scheme 2). In one method, a suspension of the methyl ester of indan-1-carboxylic acid was stirred vigorously in an aqueous ammonia solution, giving a slightly green-white precipitate, which was isolated by filtration and washed successively with water. In the second method, indan-1-carboxylic acid was converted to the acid chloride by being heated with thionyl chloride for 20 min at about 40 °C. The acid chloride was isolated by removing the excess thionyl chloride in vacuo. It was dissolved in tetrahydrofuran, and ammonia gas was bubbled through to get a slightly green-white precipitate. The solvent was removed in vacuo and the resulting solid washed with water. The crude indan-1-carboxamide was recrystallized from water.

Commercially available propylidene phthalide (**6**, Lancaster, *cis*:*trans* = 6.7, total purity 96.6%) was hydrogenated on the Pd/C catalyst at ambient temperature and 10 bar of hydrogen pressure in ethanol (Scheme 3). The catalyst hydrogenated the olefinic bond exclusively, and a quantitative yield of pure racemic 3-propyl-3*H*-isobenzofuran-1-one (**7**, >99.6% pure, identified by NMR[18]) was obtained as a colorless liquid after removal of the solvent in vacuo. This was used further in hydrogenation experiments.

Identification of *cis*−*cis* and *cis*−*trans* Product Diastereomers. Perhydro-1-methoxyindan (5a) and Perhydro-1-propoxyindan (5b). A reference mixture of the *cis*−*cis* and *cis*−*trans* diastereomers was prepared starting from perhydro-1-indanol using the same method as used in the preparation of 1-methoxyindan.[19] Comparison of the ^{1}H and ^{13}C NMR spectra of the reference mixture with the product of hydrogenation was used to identify the relative configuration. For 1-propoxyindan it was assumed that the major product had the *cis*−*cis* configuration, in analogy to the results of 1-methoxyindan.

Perhydroindan-1-carboxylic Acid (5c) and Perhydroindan-1-carboxylic Acid Methyl Ester (5d). The product of hydrogenation of indan-1-carboxylic acid consisted primarily of two diastereomers as observed by NMR analysis. The ^{1}H and ^{13}C NMR spectral data of the product mixture did not fit the NMR spectral data reported for the *trans* isomers by Galteri et al.[20] For the identification of the relative configuration of the *cis* diastereomers, the hydrogenated carboxylic acid was converted to its methyl ester by treatment with diazomethane in ether (prepared using the method of Black[21]). The mixture of hydrogenated indan-1-carboxylic acid methyl esters was then injected into a gas chromatograph equipped with an HP-1 capillary column. Comparison of the order of elution of the two diastereomers to that reported by Granger et al.[22] was used to identify the absolute configuration. The *cis*−*trans* diastereomer elutes before the *cis*−*cis* diastereomer.

Perhydroindan-1-carboxamide (5e). For identification of the *cis* diastereomeric products obtained in the hydrogenation of indan-1-carboxamide, a reference mixture was prepared from perhydroindan-1-carboxylic acid in a two-step procedure via the acid chloride as reported for indan-1-carboxamide. The reference products were isolated, and comparison of their ^{1}H and ^{13}C NMR spectra and chromatogram in an RTX-200 column with the products of hydrogenation enabled the assignment of the *cis*−*cis* and *cis*−*trans* configurations to the major and the minor products, respectively.

3-Propyl-3*H*-hexahydroisobenzofuran-1-one (8). The absolute configuration was identified by a two-dimensional NOESY analysis of the isolated product mixture (see the Supporting Information). In the two-dimensional ^{1}H NMR spectrum of the product mixture, a NOE was observed between the protons at the 3a and 7a positions on the cyclohexanediyl ring for both the major and the minor diastereomers, indicating that the *cis* diastereomers were formed exclusively. A NOE was observed between the proton at position 3 and the protons at positions 3a and 7a on the cyclohexanediyl ring, however only for the major diastereomer. Thus, the *cis*−*cis* and *cis*−*trans* configurations were assigned to the major and minor products, respectively.

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Supporting Information Available: NMR and MS data of 1-propoxyindan (**1b**), 3-propyl-3*H*-isobenzofuran-1-one (**7**), 2,3,4,5,6,7-hexahydro-1*H*-indene-1-carboxylic acid methyl ester (**4d**), and the *cis*−*cis* and *cis*−*trans* diastereomers of all perhydro products (**5a**−**e** and **8**) and two-dimensional ^{1}H NMR NOE spectrum of a mixture of the *cis*−*cis* and *cis*−*trans* diastereomers of 3-propyl-3*H*-hexahydroisobenzofuran-1-one (**8**). This material is available free of charge via the Internet at http://pubs.acs.org.

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