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Diastereoselective reductive amination reactions using novel metal–carbon catalysts prepared from inorganic Grignard reagents

G. Siedlaczek, M. Schwickardi, U. Kolb, B. Bogdanovic* and D.G. Blackmond*

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr, Germany

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A novel class of heterogeneous catalysts prepared from inorganic Grignard reagents is shown to provide finely divided transition metal–carbon nanostructures with potential advantages as selective hydrogenation catalysts under mild liquid-phase conditions. Preliminary investigations of the catalytic behavior of these materials in diastereoselective reductive amination reactions are described.

Keywords: reductive amination, diastereoselectivity, diastereoselective catalysis, inorganic Grignard reagents

1. Introduction

Organic molecules possessing one or more chiral centers find use as pharmaceuticals, fine chemicals, or agrochemicals, and often the production of a high excess of one enantiomer or diastereomer is required for these applications. A number of recently commercialized processes [1] serve to highlight the economic and environmental advantages of selective catalysis as a practical means to the production of these complex organic molecules. The study of heterogeneous catalysts in stereoselective reactions has most often focused on the preparation of a catalyst which itself contains the chiral information needed to impart a bias towards formation of one stereoisomer in the catalytic reaction of interest. A separate strategy common in organic synthesis involves achiral catalysts and the use of a chiral auxiliary which is temporarily bound to the substrate, where it directs a reaction toward the preferential formation of one diastereomer, and then is cleaved at the end of the reaction [2–4].

This diastereoselective approach is made even more straightforward when the chiral directing component is itself one of the substrates. In this case the cleavage and recycling of the chiral auxiliary are avoided since it remains as part of the desired diastereomeric product molecule. However, flexibility in choice of the chiral component is then limited by the nature of the required product. In this case the characteristics of the achiral catalyst itself may play a more important role in determining diastereoselectivity. For example, the commercial production of angiotensin-converting enzyme (ACE) inhibitors enalapril and lysinopril (for treatment of high blood pressure) involves the reductive coupling of an (S,S) dipeptide with an α-keto ester to form a C–N bond with a new stereogenic carbon center. In that case, Raney nickel was found to afford high (S,S,S) diastereoselectivity while Pt, Rh, and Ru were almost completely unselective [5]. Elucidation of the origin of this substrate-directed selectivity and its metal-specific characteristics, including a rationale for understanding *a priori* under what conditions which metal/substrate combinations may be effective, remains a goal of further research.

A novel class of heterogeneous catalysts based on inorganic Grignard reagents (IGR) [6,7] shows potential for practical application in this type of selective organic reaction. As reported by Bogdanovic and coworkers [7], the preparation of IGR reagents of a wide variety of early and late transition metals has been carried out from diethyl magnesium or Mg and transition metal dichlorides, as shown in the examples below for Pd and Ru:

$$\mathrm{PdCl_2 + 2Et_2Mg \xrightarrow[-78\ \text{to}\ 20\,^\circ\mathrm{C}]{\mathrm{THF}} \left[Pd(MgCl)_2\right] + 2(C_2H_4 + C_2H_6)\uparrow} \quad (1)$$

$$\mathrm{RuCl_3 + 3Mg \xrightarrow[20\,^\circ\mathrm{C}]{\mathrm{THF}} \left[Ru(MgCl)_3\right]} \quad (2)$$

These reagents have been shown to have a broad potential for the formation of metal–metal and metal–carbon bonds and may be used as analogues to organic Grignard reagents for the controlled preparation of highly reactive, nanoparticulate intermetallics, alloys and metals. It has also been demonstrated that they can be used as precursors for very finely divided metal in a carbon matrix for a variety of transition metals as well as for bimetallic reagents. This is accomplished by reaction of the IGR with organohalogen compounds, as shown below for Ru:

$$\mathrm{4\left[Ru(MgCl)_3\right] + 3Cl_2C{=}CCl_2 \xrightarrow{THF} \left[Ru_4C_6(MgCl_2)_{\mathit{p}}(THF)_{\mathit{q}}\right]\downarrow + (12-\mathit{p})MgCl_2} \quad (3)$$

EXAFS measurements [8] for this Ru–C system confirmed that this preparation yielded stable Ru–C particles containing Ru in a high state of dispersion. Since carbon is the

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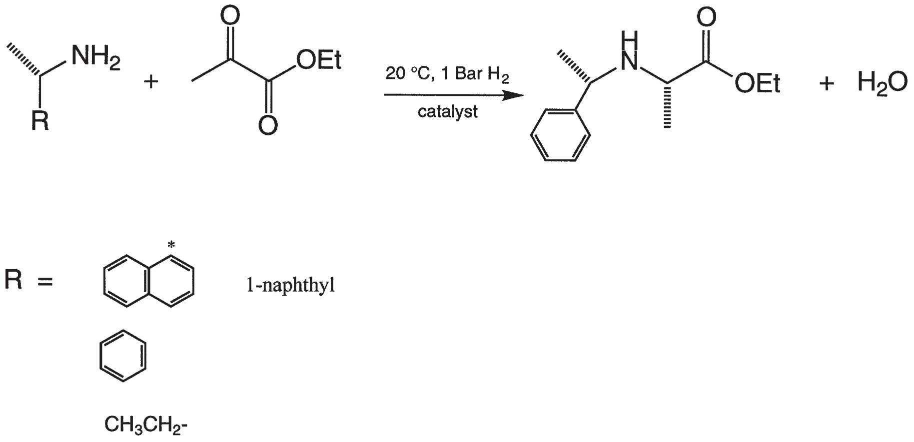
* To whom correspondence should be addressed.

Table 1
Properties of catalysts prepared from inorganic Grignard reagents (IGR).

Entry No.	Metal	Empirical formula[a]	Metal : carbon formula	Metal particle size[b] (nm)
1	Pd	$PdC_{0.9}(THF)_{0.3}(MgCl_2)_{0.1}Mg_{0.2}$	PdC	1.2
2	Pt	$PtC_{0.9}(THF)_{0.3}(MgCl_2)_{0.04}Cl_{0.02}$	PtC	12.2
3	Ru	$RuC_{1.39}(THF)_{0.4}(MgCl_2)_{0.12}Cl_{0.2}$	Ru_4C_6	3.2
4	Rh	$RhC_{1.2}(THF)_{0.4}(MgCl_2)_{0.19}Mg_{0.17}$	RhC	3.2
5	Pd	Pd/C (commercial catalyst)	–	2.0
6	Pt	Pt/C (commercial catalyst)	–	10.4

[a] From elemental analysis.
[b] From transmission electron microscopy.



Scheme 1.

preferred catalyst support for the organic reactions common in the pharmaceutical industry[1], these new materials exhibiting high metal dispersions in metal–carbon nanostructures offer potential as novel catalysts for these applications. This paper reports preliminary investigations of the behavior of metal–carbon catalysts prepared from inorganic Grignard reagents in diastereoselective reductive amination reactions.

2. Experimental

2.1. Catalyst preparation

Inorganic Grignard reagents $Me(MgCl)_x$ (with Me = Pd, Pt, Ru, or Rh, $x = 1$ for Rh, $x = 2$ for Pd and Pt, and $x = 3$ for Ru) were prepared as shown above in equations (1) or (2) and described in detail in [7,8]. The reagents were then reacted with tetrachloroethylene in THF, as shown above in equation (3), to produce metal–carbon reagents. Elemental analysis (Kolbe Microanalytisches Laboratorium) gave the results shown in table 1.

2.2. Catalyst characterization

High-resolution electron micrographs were obtained by field emission transmission electron microscopy (Hitachi HF 2000, 200 keV) coupled with EDX analysis. X-ray diffraction line-broadening measurements (STOE, STAD/2/PL powder diffractometer) were carried out using a Cu $K\alpha_1$ source.

2.3. Catalytic reactions

Reductive amination of ethyl pyruvate with enantiopure amines $R(CH_3)CHNH_2$ (where R = naphthyl, phenyl or ethyl) to produce the coupled secondary amine product (scheme 1) were carried out at 20 °C (293 K) and 1 bar (100 kPa) in 2-propanol in a stirred (2000 rpm) autoclave. Substrate concentrations between 0.08 and 0.16 M were used, and the ratio amine : ethyl pyruvate varied from 1 : 0.5 to 1 : 2. The catalyst loading of 1 mol% metal based on amine substrate was treated and loaded into the reactor under Ar. Total reaction volume was 100 ml. The reactor was held at constant hydrogen pressure and the gas was metered into the reactor through a valve connected to a high-pressure reservoir. Reaction rates were measured by monitoring hydrogen uptake via a pressure transducer in the reservoir. Measurements of the gas–liquid mass transfer coefficient confirmed that the rate of hydrogen mass transfer was more than 25 times greater than the highest

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[1] The preference for carbon supports is due to the ease of precious metal recovery for Pd and Pt catalysts by simple collection of the metal oxide after burning away the support. Direct recycling of the intact catalyst is usually avoided due to strict FDA requirements concerning the potential for residual adsorbed impurities.

observed reaction rate. Prior to use, ethyl pyruvate was distilled and 2-propanol was dried over Na and distilled. The amine substrates were used as received. GC analysis (HP 6890) of the reductive amination product was carried out with a 15 m RTX column and FID detector using a temperature program between 20 and 320 °C. Conversions are given as % of amine substrate reacted. Hydrogenation of ethyl pyruvate as a side reaction accounted for less than 2.5% conversion of ethyl pyruvate. Up to 2% hydrogenolysis products (e.g., ethyl benzene, ethyl anthracene) were observed. A small amount of unidentifed side products of the amine substrate were formed.

3. Results and discussion

3.1. Catalyst characterization

Table 1 shows the elemental analysis and average metal particle sizes from TEM for the metal–carbon species prepared from the inorganic Grignard reagents and indicates the incorporation of some magnesium chloride and THF in the IGR catalysts. For Pd, Pt, and Rh, the metal : carbon ratio was unity; for the Ru : C system, the formula was Ru_4C_6. Figure 1 reveals a fairly homogeneous preparation for the PdC catalyst, with metal particle sizes averaging 1.2 nm. The PtC preparation exhibited a significantly larger metal particle size and broader product distribution, while RhC and Ru_4C_6 were intermediate in size. XRD line-broadening measurements showed that all four of the IGR catalyst preparations had metal particle sizes less than 5 nm, in agreement with TEM for all catalysts except PtC. The reason for the discrepancy for the PtC catalyst is unclear and may imply unconventional particle shape.

3.2. Reductive amination

Reductive amination of 1-substituted-(S)-1-ethylamines with ethyl pyruvate resulted in the formation of a coupled product with a new stereogenic center at the former keto-carbon of the α-keto ester, as shown in scheme 1. Table 2 shows the (S, S) diastereoselectivities achieved for a variety of IGR catalysts and R-groups in the directing amine substrate. No significant change in diastereoselectivity was observed as a function of different relative initial substrate concentrations (table 2, entries 2 and 7–9), or with conversion of substrate as monitored by samples taken over the course of a single reaction.

Control of the ultimate regio- or stereoselectivity of the product in substrate-directed diastereoselective reactions comes about through interactions between the two components resulting in a distinct bias in their approach to or association with one another and with the catalyst. Substituents on the substrate can play a large role in the stereochemical outcome of the reaction [2,3]. As can be seen for PdC in this study, the steric bulk of the substituent on the chiral amine substrate had a strong effect on the observed diastereoselectivity (table 1, entries 1–3). The bulky naphthyl group afforded the highest selectivity, while the linear ethyl group as a substituent gave a very low selectivity, yielding approximately 54% (S, S) and 45% (S, R) products.

The rate of reaction was slowest for the naphthyl-substituted amine, which exhibited an induction period, but was faster for the phenyl- compared to the ethyl-substituted amine (figure 2). This suggests that both steric and adsorptive considerations of the chiral amine are factors in determining both reaction rate and diastereoselectivity. Without significant steric direction from the substituent near the chiral center on the amine, the achiral catalyst is inefficient at choosing between the two enantiofaces for approach to the adsorbed α-keto ester substrate, as was found with the ethyl-substituted amine. Directed adsorption through the ring system may help to direct the selectivity for the phenyl- and the naphthyl-substituted amines, but the bulkiness of the naphthyl group may slow down the overall reaction.

For substrates efficient at directing the stereochemistry of the reaction, the selectivity was found to depend further on the type of metal. Diastereoselectivities decreased in the following order for the phenyl-substituted amine (table 1, entries 4–7):

$$\mathrm{Pt} \approx \mathrm{Pd} > \mathrm{Rh} > \mathrm{Ru}.$$

An intrinsic difference in product selectivity for different metals was thus confirmed as has been noted previously for other reductive aminations [4], although the fundamental reason for this difference remains unclear and is the subject of further study.

Reaction rate on a total metal basis decreased in the same order for these four catalysts, as seen in figure 3. The significantly larger metal particle size exhibited by PtC implies that its site-specific rate may exceed that of Pd. It was noted above in the case where different substrates were compared for a given metal that the slowest reaction gave the highest selectivity; however, when a given substrate is compared over a series of different catalysts, it appears that catalytic and chiral efficiency increased in parallel, that is, faster rates corresponded to higher diastereoselectivities. Thus the key to the different selectivities offered by the different metals may be partly kinetic in origin.

Elemental analysis (table 1) reveals that the IGR catalysts retained residual $MgCl_2$ in the metal–carbon nanostructures. The Lewis acidity of $MgCl_2$ might influence rate or selectivity, or both, in the reductive amination reaction. Acidity of the support may also play a role in the very high diastereoselectivity obtained previously in this reductive amination reaction (R = naphthyl) by Pfaltz and coworkers [9] using a commercial Pt/Al_2O_3 catalyst.

Choice of solvent also influences diastereoselectivity (table 2, entries 10 and 11). The PdC catalyst gave a similar performance in the non-polar solvent toluene as in the polar solvent i-propanol. Diastereoselectivity was much poorer in

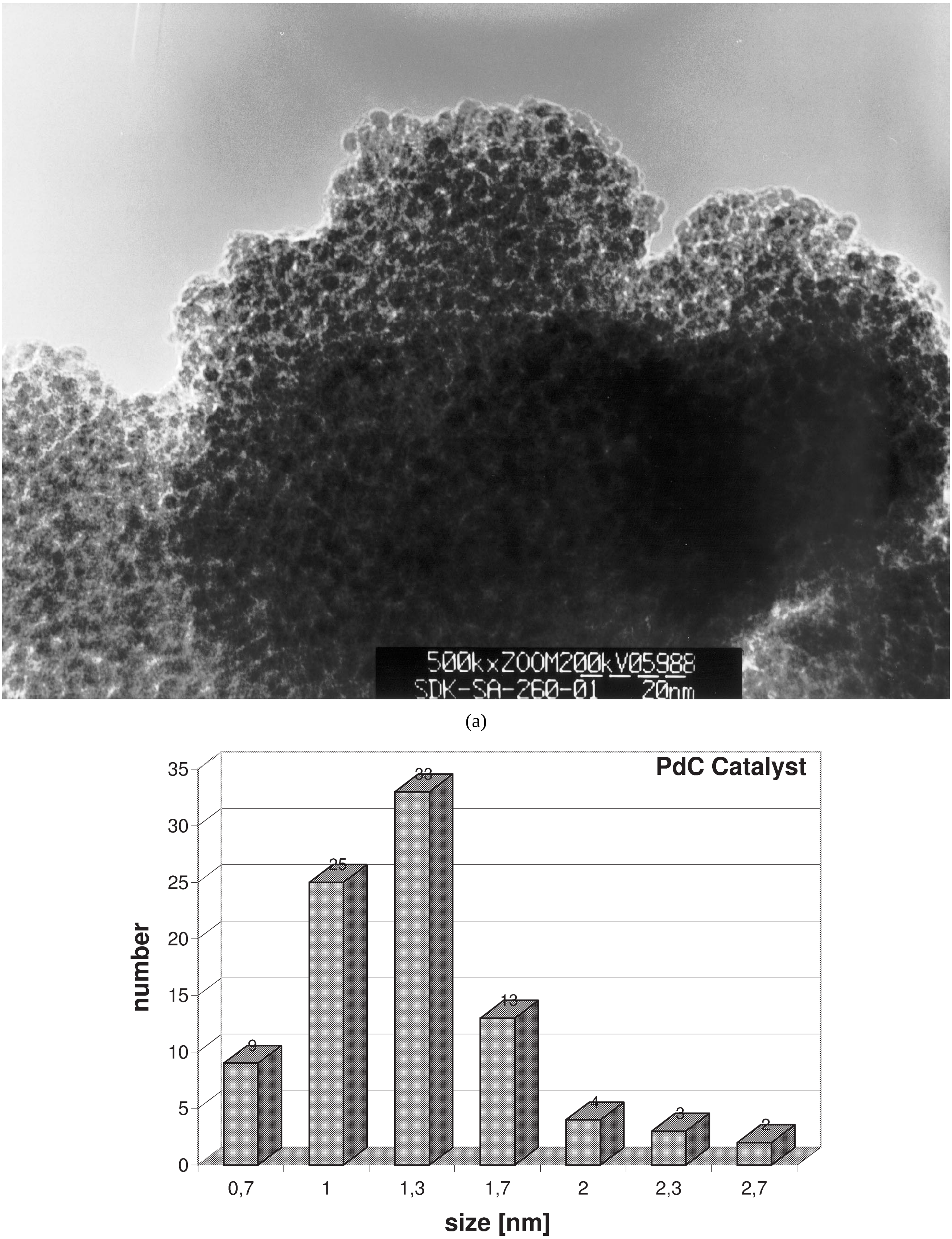


Figure 1. (a) Transmission electron micrograph distribution for the Pd IGR catalyst preparation (entry 1, table 1); scale is given at the bottom of the micrograph, with the length of the four bars (----) equal to 20 nm; (b) histogram based on ca. 100 particle count.

Table 2
Catalytic properties of IGR catalysts and commercial carbon-supported catalysts in the reductive amination of amines with ethyl pyruvate.

Entry No.	Catalyst	Amine : ester (mmol : mmol)	R-group in amine substrate	Solvent	Amine conversion (%)	Diastereoselectivity (%de)
1	PdC	9 : 9	naphthyl	*i*-propanol	88	87.4
2	PdC	9 : 9	phenyl	*i*-propanol	72	78.8
3	PdC	9 : 9	ethyl	*i*-propanol	66	9.0
4	RuC	9 : 9	phenyl	*i*-propanol	60	53.9
5	RhC	16 : 16	phenyl	*i*-propanol	63	64.8
6	PtC	16 : 16	phenyl	*i*-propanol	59	79.8
7	PdC	16 : 16	phenyl	*i*-propanol	84	77.0
8	PdC	16 : 8	phenyl	*i*-propanol	38 (72)[a]	78.8
9	PdC	8 : 16	phenyl	*i*-propanol	100	74.5
10	PdC	16 : 16	phenyl	toluene	64	78.3
11	PdC	16 : 16	phenyl	acetic acid	53	26.7
12	Pd/C (commercial)	16 : 16	phenyl	*i*-propanol	66	54.6
13	Pt/C (commercial)	16 : 16	phenyl	*i*-propanol	61	46.2

[a] Amine substrate used in 2× excess; conversion based on ethyl pyruvate concentration is given in parentheses.

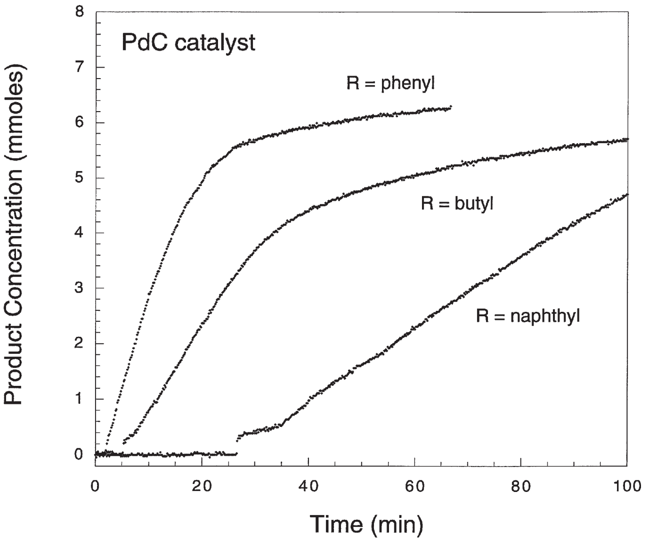


Figure 2. Reaction rate for the reductive amination of ethyl pyruvate with chiral amines as a function of the substituent on the amine. Pd IGR catalyst (table 1, entry 1); reaction conditions given in table 2, entries 1–3.

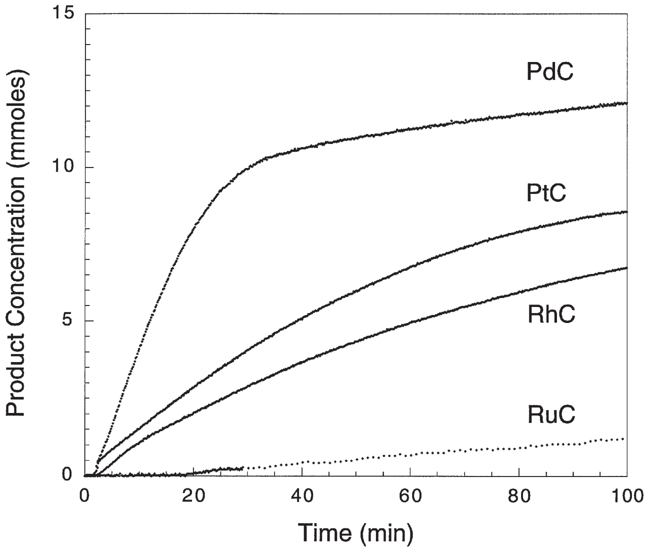
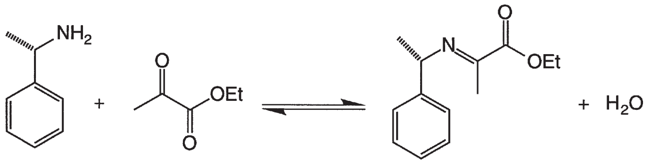


Figure 3. Reaction rate for the reductive amination of ethyl pyruvate with chiral amines as a function of the type of metal using IGR catalysts (table 1, entries 1–4); reaction conditions given in table 2, entries 4–7.

acetic acid, although this solvent generally gives the highest enantioselectivities in the hydrogenation of ethyl pyruvate using amine-based chiral modifiers.

IGR catalysts were also compared with commercial supported metal catalysts commonly used in pharmaceutical hydrogenation reactions. Standard carbon-supported Pt and Pd of metal particle sizes similar to the IGR preparations (table 2, entries 12 and 13) gave poorer diastereoselectivities compared to the IGR catalysts. The IGR and commercial catalysts possess a range of particle sizes from 1.2 to 12 nm, and no correlation between the metal particle size and diastereoselectivity was possible to observe, although this variable was not studied in a systematic manner for a given metal.

Reaction rate was found to have a similar positive order dependence on the concentration of both amine and ester substrates, as seen in figure 4. Decreasing the concentration of either substrate by 50% resulted in a similar decrease in rate. Total conversion of the amine was achieved only when ethyl pyruvate was used in excess, with most reactions leveling off between 60 and 88% conversion of amine. This suggests the reversible formation of an imine intermediate species [4] and the concomitant formation of water, with the reverse reaction slowing the formation of the coupled product if water is not removed from the system (equation (4)):



(4)

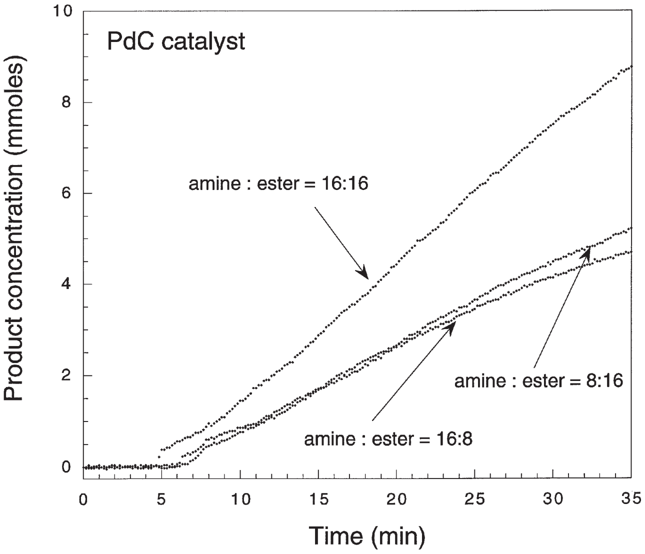


Figure 4. Reaction rate for the reductive amination of ethyl pyruvate with chiral amines as a function of the initial relative substrate concentrations. Pd IGR catalyst (table 1, entry 1); reaction conditions given in table 2, entries 7–9.

4. Conclusions

Novel catalysts consisting of finely divided transition metals in carbon nanostructures are shown to be active and selective catalysts for the reductive amination of α-keto esters with chiral amines. The substituent group on the amine substrate, which is the chiral directing component, plays the biggest role in determining product diastereoselectivity. The nature of the metal also has a strong influence on catalytic behavior, with Pd and Pt exhibiting the highest reaction rates and diastereoselectivities. The higher diastereoselectivities exhibited by the Pd and Pt catalysts prepared from inorganic Grignard reagents show their promise as efficient alternatives to carbon-supported selective hydrogenation catalysts. The possibility of producing well-defined catalysts of high dispersion with these materials makes them useful for further fundamental studies of the catalytic properties of nanostructural materials, including intrinsic differences between different metals in selective reactions.

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