CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200600899

Palladium Catalysts on Alkaline-Earth Supports for Racemization and Dynamic Kinetic Resolution of Benzylic Amines

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Abstract: Palladium catalysts on alkaline-earth supports were studied as new heterogeneous catalysts for racemization of chiral benzylic amines such as 1-phenylethylamine. Particularly 5% $Pd/BaSO_4$ and 5% $Pd/CaCO_3$ were able to selectively racemize amines, with minimal formation of secondary amines or hydrogenolysis to ethylbenzene. In contrast, these side reactions were pronounced on Pd/C. A reaction mechanism is proposed that is consistent with the reaction kinetics. The catalyst activity was found to depend on the number of available surface Pd atoms, determined by titration with CO. The selectivity crucially depends on the rate of condensation of the amine and the primary imine, which is highest on Pd/C. The racemization catalysts were combined in one pot with an immobilized lipase to perform dynamic kinetic resolution of chiral amines. High yields (up to 88%) of essentially enantiopure amides were obtained in a single step. The chemo-enzymatic catalyst system proved to be stable and could be reused without losing the initial activity.

Keywords: amides · amines · heterogeneous catalysis · kinetic resolution · palladium

Introduction

Enantiomerically pure amines find many applications in the pharmaceutical and agrochemical industries. They are used as active intermediates, chemical building blocks, and chiral auxiliaries.[1] Usually, they are obtained by separation, for example, diastereomeric crystallization or chiral chromatography; by asymmetric hydrogenation of imines, enamines, or oximes; or by kinetic resolution.[1,2] A large number of resolution methods have been described that use enzymes as catalysts,[3] but the resolution process is generally limited to a maximum yield of 50%. Continuous racemization of the remaining enantiomer combined with kinetic resolution, called dynamic kinetic resolution (DKR), is an option to overcome this problem. Like kinetic resolution, DKR starts from the racemic mixture, but now the desired product enantiomer can be obtained with a theoretical yield of 100%. While kinetic resolution is performed by an enzyme, the racemization requires chemocatalysts. The DKR of secondary alcohols is now well established and uses chemocatalysts such as homogeneous transition-metal catalysts, supported metal catalysts, or solid acids.[4] For amines reports on selective racemization or DKR are much more scarce. Homogeneous Ru-based catalysts were reported as being active in racemization of chiral amines. Bäckvall et al.[5] used the Shvo complex catalyst, which showed good activity in racemization of a broad range of amines, with very few side reactions. In initial experiments, even with 5 mol% of the binuclear complex, a reaction temperature of 110°C was required, which impeded combination with an enzyme.[5] Changing the substituents on the cyclopentadienone ligand allowed the reaction temperature to be decreased to 90°C and enabled one-pot combination with enzymatic resolution,[6] but the long reaction time of three days is still disadvantageous.

In an alternative strategy for amine racemization, the residual amine enantiomer is treated at high temperature with a mixture of hydrogen, ammonia, and the corresponding ketone over solid metal oxide catalysts.[7] As this process is a gas-phase reaction, it is incompatible with enzymatic kinetic resolution. Using a heterogeneous racemization catalyst in a one-pot process is definitely more convenient, and such a reported process uses Pd on charcoal as racemization catalytst in DKR of 1-phenethylamine in Et_3N. Unfortunately, the reaction was quite slow (8 days) and side reactions decrease the eventual yield of enantiopure amide.[8] In a modified approach ketoximes are the starting materials, and the amines

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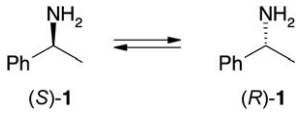
that are formed are resolved in situ by using an enzyme in combination with a Pd/C racemization catalyst. The reaction is still slow (5 days) and additives are required to prevent the formation of large amounts of secondary products.[9]

The activity of Pd in racemization of amines was first suggested by Murahashi et al. as a side reaction when Pd black was used for catalytic alkyl-group exchange between primary and secondary amines.[10] After screening different types of heterogeneous hydrogenation catalysts in the racemization of (*S*)-1-phenylethylamine, we were drawn to the possible use of Pd on alkaline-earth supports as racemization catalyst. These catalysts are known to be selective for the hydrogenation of alkynes to alkenes, of dienes to monoolefins, for the synthesis of hydroxamic acids,[11] and for diastereoselective hydrogenation of imines.[12] However, their activity was not yet investigated in the racemization of optically active amines.

Herein we explore the potential of Pd on alkaline-earth supports as catalysts for racemization of optically active amines. Based on a detailed analysis of the reaction kinetics, a sound mechanism was elucidated, and the parameters that steer the racemization activity and selectivity were revealed. By using an immobilized lipase, racemization and kinetic resolution were combined in a one-pot DKR process. Reuse of the chemocatalyst/enzyme system was also investigated. A preliminary report on some aspects of this work appeared recently.[13]

Results and Discussion

Selection of a racemization catalyst and optimization of conditions: Racemization of (*S*)-1-phenylethylamine was chosen as test reaction (Scheme 1). The optimum catalyst should



Scheme 1. Racemization of (*S*)-1-phenylethylamine

effect a 50% conversion of the starting enantiomer with 100% selectivity to the opposite stereoisomer, and thus result in an *ee* of 0%. From the library of heterogeneous catalysts screened in Table 1, Pd appears indeed to be active in the racemization of chiral benzylic amines. The performance obtained with 5% $Pd/BaSO_4$ most closely approaches the ideal behavior (Table 1, entry 2). Clearly, Pd is more suitable for the racemization of amines than other noble metals such as Ir, Pt, Rh, and Ru (Table 1, entries 4–7). The basicity of the support also seems important. Without any optimization of the reaction conditions, 5% $Pd/BaSO_4$ gave an acceptable selectivity of 73%, while 5% Pd/C exhibited no selectivity at all. Beside the *R* enantiomer, ethylbenzene and some amine condensation products were identified as side products. Table 2 compiles results obtained by deposition of Pd on different alkaline-earth supports, and includes 5% Pd/C as a reference. These data confirm that the best combination comprises Pd as active noble metal, and a salt of an alkaline-earth metal as basic support.

Table 1. Screening results with various heterogeneous hydrogenation catalysts in racemization of (*S*)-1-phenylethylamine.[a]

Entry	Catalyst	Conv. [%]	$Yield_{R\text{-amine}}$ [%]	$Sel._{R\text{-amine}}$ [%]	$ee_{S\text{-amine}}$ [%]
1	*ideal catalyst*	*50*	*50*	*100*	*0*
2	5% $Pd/BaSO_4$	41	30	73	34
3	5% Pd/C	100	0	0	–
4	5% Ru/C	64	6	9	70
5	5% Rh/C	100	0	0	–
6	5% $Ir/CaCO_3$	92	2	2	55
7	5% Pt/C	10	0	0	100
8	8% Pd/C(+2% Pt)	100	0	0	–
9	5% Ir/C	3	1	33	98
10	1% Pd/ZSM-5	0	–	–	100
11	30% Ni+1.26% Pd/SiO_2	87	6	7	37
12	5% $Ru/BaSO_4$	29	0	0	100

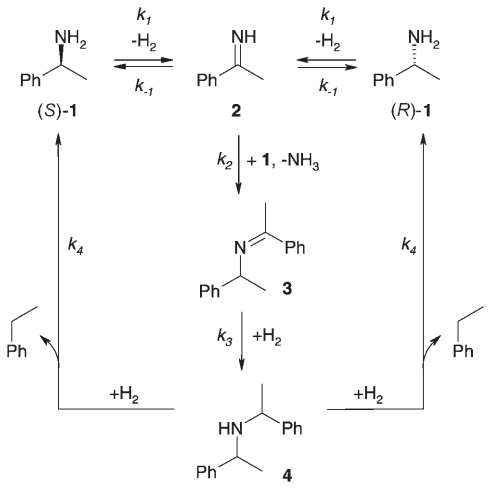
[a] Reaction conditions: 0.2 MPa H_2 pressure, 40 mg catalyst, 0.33 mmol (*S*)-1-phenylethylamine, 4 mL toluene, three days, 70 °C.

Table 2. Pd on alkaline-earth supports versus Pd/C in racemization of (*S*)-1-phenylethylamine.[a]

Entry	Catalyst	Conv. [%]	$Yield_{R\text{-amine}}$ [%]	$Sel._{R\text{-amine}}$ [%]	$ee_{S\text{-amine}}$ [%]
1	5% $Pd/BaSO_4$	41	30	73	34
2	5% $Pd/CaCO_3$	59	21	36	33
3	5% $Pd/SrCO_3$	58	35	60	10
4	5% $Pd/BaCO_3$	65	35	53	0
5	5% Pd/C	100	–	–	–

[a] Reaction conditions: 0.2 MPa H_2 pressure, 40 mg catalyst, 0.33 mmol (*S*)-1-phenylethylamine, 4 mL toluene, three days, 70 °C.

Based on this knowledge, we attempted to improve the catalytic performance by tuning the reaction conditions, such as hydrogen pressure. The racemization likely occurs by dehydrogenation/hydrogenation (Scheme 2),[5,8,9,10] and



Scheme 2. Reaction mechanism and kinetic constants for racemization of (*S*)-1-phenylethylamine.

the hydrogen pressure will strongly affect the equilibrium between amine and imine. Experiments at hydrogen pressures between 0 and 0.2 MPa proved indeed that an optimum hydrogen pressure exists that affords superior racemization selectivity and yield. The absence of hydrogen led to a high *ee* because the imine cannot be hydrogenated back to the amine. On the contrary, a high hydrogen pressure suppresses imine formation (Figure 1). A hydrogen pressure of

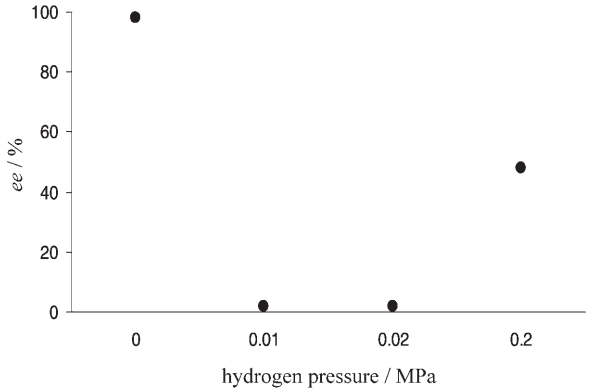


Figure 1. Relation between enantiomeric excess and hydrogen pressure in racemization of (*S*)-1-phenylethylamine; 24 h reaction time and standard reaction conditions.

0.01 MPa appears to be optimal. Correspondingly, the reaction time was reduced from three days to one day, irrespective of the alkaline-earth support used (Table 3).

Table 3. Activity of 5% Pd on alkaline-earth supports versus 5% Pd/C under optimized hydrogen pressure.[a]

Entry	Catalyst	Conv. [%]	Sel.$_{R\text{-amine}}$ [%]	Sel.$_{ETB}$ [%]	$ee_{S\text{-amine}}$ [%]
1	5% Pd/$BaSO_4$	56	81	19	2
	5% Pd/$BaSO_4$[b]	35	91	8	25
2	5% Pd/$CaCO_3$	56	80	18	2
3	5% Pd/$SrCO_3$	60	67	26	1
4	5% Pd/$BaCO_3$	58	69	31	2
5	5% Pd/C	98	2	41	6
	5% Pd/C[c]	40	38	11	60

[a] Standard reaction conditions, 0.01 MPa H_2, 24 h, ETB = ethylbenzene. [b] Reaction time 5 h. [c] Reaction time 1 h.

Selectivity is a key issue in this racemization. The major side product in these reactions was ethylbenzene. Data presented in Table 3 indicate that the selectivity is crucially affected by the support: 5% Pd/$BaSO_4$ and 5% Pd/$CaCO_3$ led to the highest selectivities for the desired *R*-amine. On these catalysts the amount of secondary amine was less than 1%, and even less than 0.5% for 5% Pd/$BaSO_4$.

Apparently, the alkaline-earth supports preserve the primary amine much better than charcoal. Literature shows that the hydrogenolysis of C–N bonds on Pd is promoted by acid sites.[14] Charcoal usually contains phenolic and carboxylic acid groups. Moreover, Pd/C is known as a hydrogenolysis catalyst for secondary amines at low hydrogen pressure.[12,14] However, pretreatment of Pd/C by washing with a base or use of a basic solvent such as triethylamine did not improve the selectivity to the (*R*)-amine (Table 4, entries 2 and 3). In contrast, pretreatment of Pd/$CaCO_3$ with NaOH increased the selectivity of racemization, which is indeed an indication that a basic support is more suitable for racemization of chiral amines (Table 4, entries 4 and 5). The data for

Table 4. Influence of pretreatment with a base of Pd catalysts in racemization of (*S*)-1-phenylethylamine.[a]

Entry	Catalyst	Conv. [%]	Sel.$_{R\text{-amine}}$ [%]	Sel.$_{ETB}$ [%]	$ee_{S\text{-amine}}$ [%]
1	5% Pd/C[b]	40	38	11	60
2	5% Pd/C[c]	44	39	20	53
3	5% Pd/C[d]	94	7	12	1
4	5% Pd/$CaCO_3$	56	80	18	2
5	5% Pd/$CaCO_3$[e]	50	99	0	1

[a] Standard reaction conditions. [b] 1 h. [c] Washed with NaOH solution. 1 h. [d] 4 mL Et_3N used as solvent. 1 h. [e] Washed with NaOH solution; 24 h.

the 5% Pd/$CaCO_3$ catalyst washed with NaOH perfectly reflect the expected behavior of an ideal catalyst (compare Table 4, entry 5 with Table 1, entry 1).

Racemization kinetics and mechanistic proposal: The racemization kinetics of the can be approached in several ways. First, one may simply assume Equation (1).

$$(S)\text{-amine} \underset{k_{inv}}{\overset{k_{inv}}{\rightleftharpoons}} (R)\text{-amine} \quad (1)$$

Assuming (pseudo)first-order in both amine enantiomers, the rate equations can be integrated between time 0 and t [Eq. (2)], where $[S]_0$ and $[S]_t$ are the concentrations of *S* enantiomer at times 0 and t.

$$\ln\left(\frac{[S]_0}{2[S]_t - [S]_0}\right) = 2\,k_{inv}t \quad (2)$$

As can be seen from Figure 2, the initial kinetics of racemization, for example, on Pd/$BaSO_4$, can be adequately fitted by using Equation (2), that is, the (pseudo)first-order assumption of Equation (1) is valid. However, when secondary reactions become important, for example, at higher conversions, or when Pd/C is used as the catalyst, a more detailed kinetic scheme is necessary (Scheme 2). In this scheme, prochiral imine **2** can be hydrogenated back with formation of the two amine enantiomers, or it can be attacked by another molecule of amine **1**. Rapid elimination of NH_3 from the aminal[10] results in α-methyl-*N*-(1-phenethylidene)benzylamine **3**. This imine is readily hydrogenated to the two diastereoisomers of bis(1-phenylethyl)amine (**4**), which were identified by GC-MS. Rate equations (3)–(7) can be written for the reactions shown in Scheme 2.

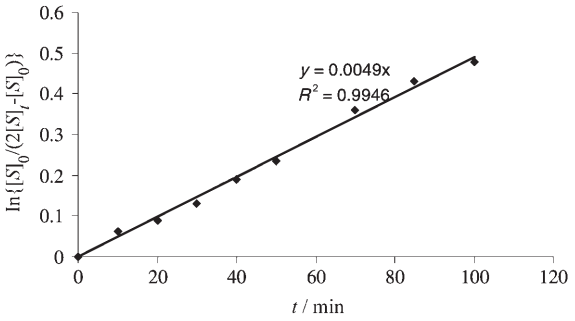


Figure 2. Linearization of kinetic data (standard conditions), by using Equation (2), for 5%Pd/$BaSO_4$ in racemization of (*S*)-1-phenylethylamine.

$$\frac{d[S]}{dt} = -k_1[S] + 0.5k_{-1}[\text{imine}] - k_2[\text{imine}][S] + 0.5\,k_4[\textit{sec}\text{-amine}] \quad (3)$$

$$\frac{d[R]}{dt} = -k_1[R] + 0.5k_{-1}[\text{imine}] - k_2[\text{imine}][R] + 0.5\,k_4[\textit{sec}\text{-amine}] \quad (4)$$

$$\frac{d[\text{imine}]}{dt} = k_1\{[R] + [S]\} - k_{-1}[\text{imine}] - k_2[\text{imine}]\{[R] + [S]\} \quad (5)$$

$$\frac{d[\textit{sec}\text{-imine}]}{dt} = k_2[\text{imine}]\{[R] + [S]\} - k_3[\textit{sec}\text{-imine}]\{[R] + [S]\} \quad (6)$$

$$\frac{d[\textit{sec}\text{-amine}]}{dt} = k_3[\textit{sec}\text{-imine}] - k_4[\textit{sec}\text{-amine}]\{[R] + [S]\} \quad (7)$$

In the steady-state approximation of constant imine concentration (d[imine]/dt=0), both approaches are equivalent, with $2k_{inv}=k_1$. Hence, Equation (2) remains a useful tool to evaluate k_1 when the initial data points are considered. In the initial phase of the reaction, when only racemization occurs, dehydrogenation (k_1) can be considered the rate-limiting step, since the primary imine intermediate **2** is not detected at all.

Based on the values of k_1, calculated using Equation (2) and $2k_{inv}=k_1$, and knowing that the typical Pd concentration varies between 9.4×10^{-4} and 4.7×10^{-3} M, initial Pd turnover frequencies can be obtained for the dehydrogenation of the *S*-amine to the imine. For different catalysts, these values are compared in Table 5 and Figure 3 with the amount of CO adsorbed on Pd at room temperature. Titration of the surface of a solid noble metal catalyst with carbon monoxide is a well-known method to determine the number of available atoms at the surface of the clusters, and hence the dispersion of the catalyst. The validity of these dispersion measurements was also confirmed by TEM imaging (not shown). For instance, for two samples of 1% Pd/$BaSO_4$, CO/Pd ratios of 0.017 and 0.021 were recorded; in TEM the same samples gave typical Pd particle sizes of 9–14 nm [1% Pd/$BaSO_4$(A)] and 6–10 nm [1% Pd/$BaSO_4$(B)] (Table 5, entries 1 and 2).

Table 5. Relation between molar CO/Pd ratio and activity in racemization of (*S*)-1-phenylethylamine at 70°C.[a]

Entry	Catalyst	CO/Pd	TOF [s^{-1}]×10^4 (calcd for total Pd)	TOF [s^{-1}]×10^2 (per available Pd)
1	1% Pd/$BaSO_4$ (A)	0.017	7.3	4.3
2	1% Pd/$BaSO_4$ (B)	0.021	10.6	5.0
3	5% Pd/$BaSO_4$	0.021	13.2	6.3
4	5% Pd/$CaCO_3$	0.048	17.6	3.7
5	5% Pd/C	0.081	32.2	4.0

[a] Pd particle sizes: 9–14 nm (A), 6–10 nm (B); TOF calculated based on conversions <10%. Reactions under standard conditions.

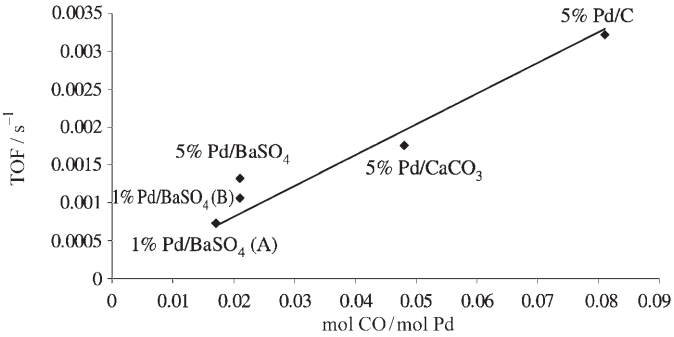


Figure 3. Relationship between Pd TOF and molar CO/Pd ratio. Data for reactions under standard conditions.

As can be seen from Figure 3, a fairly linear relationship is found between the Pd TOF and the CO/Pd ratio, even for Pd catalysts with different supports. In general, Pd/$BaSO_4$ catalysts have lower dispersion and hence lower TOF. Dispersion and TOF are highest for Pd/C, while intermediate values are found for Pd/$CaCO_3$. The Pd activity is primarily determined by the number of accessible Pd atoms, that is, by the dispersion. There is no evidence for a direct relation between Pd dispersion and selectivity of the reaction. Equations (3)–(7) were used to fit the data points up to higher conversions (e.g., 40%). Recall that a racemization reaction is complete at 50% conversion of the initial enantiomer. Figure 4 plots the experimental results collected for 5% Pd/$BaSO_4$, 5% Pd/$CaCO_3$, and 5% Pd/C (as dots), and the fitted curves. Excellent agreement between model and experimental data was achieved with the rate constants of Table 6. Large values were assumed for the hydrogenations of the primary and secondary imines, which are fast steps (k_{-1} and k_3). Values of k_1 correspond to the initial Pd TOF values, as discussed previously. Most critical for the fits are the values of k_2. These values prove that the bimolecular condensation, which decreases the selectivity, is most pronounced on Pd/C.

Overall, the fits indicate that the reactions of Scheme 2 adequately describe the complex reaction network. For simplicity, (pseudo)first-order kinetics in all reagents was assumed in all reactions. This does not necessarily mean that the surface is only partially covered with the amine reagent.

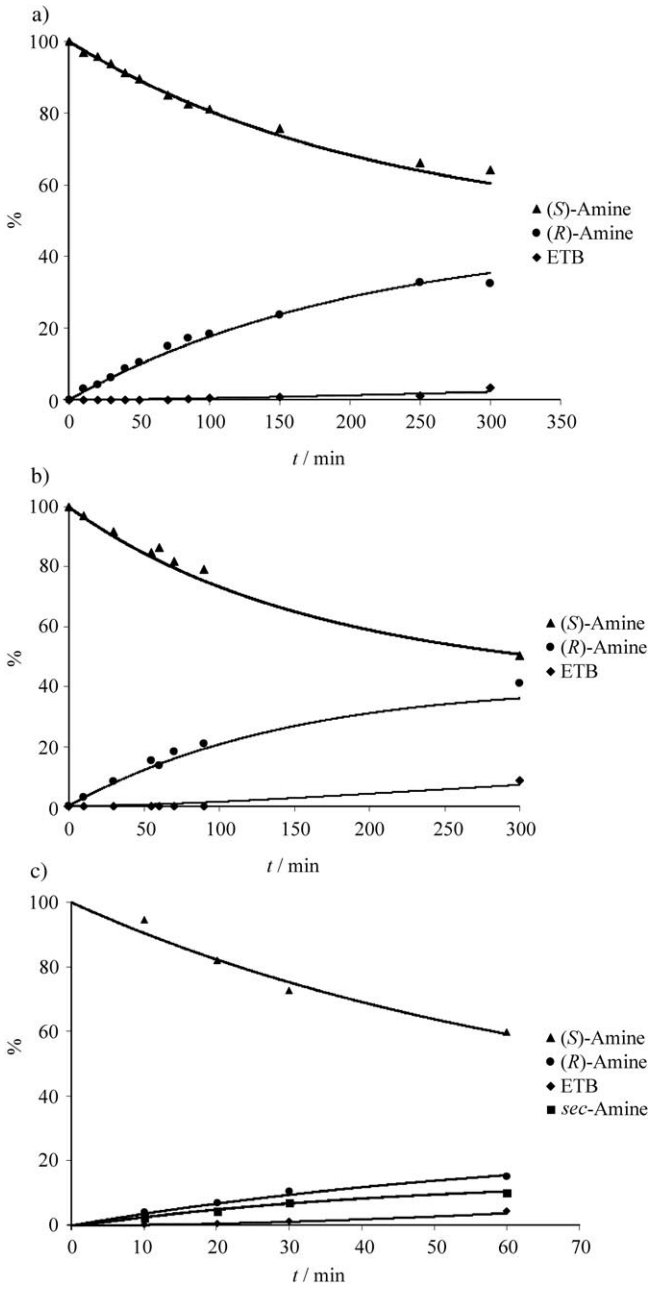


Figure 4. Fitting of experimental data to kinetic model in racemization of (*S*)-1-phenylethylamine for a) 5% Pd/$BaSO_4$, b) 5% Pd/$CaCO_3$, and c) 5% Pd/C. Standard reaction conditions; symbols: experimental values, curves: fitted curves. ETB = ethylbenzene.

For the specific case of racemization, the partial coverage by (*S*)- and (*R*)-amines will be proportional to the fractions of the two enantiomers in solution, and this will lead to very similar kinetics as in Equations (3)–(5). Importantly, the fitting explains why ethylbenzene formation only becomes considerable well after the start of racemization. This excludes the possibility that ethylbenzene could be formed in a parallel reaction, by direct hydrogenolysis of 1-phenylethylamine; rather it results from hydrogenolysis of the secondary product bis(1-phenylethyl)amine **4**. The consecutive formation of the secondary amine and ethylbenzene was clearly observed in the case of 5% Pd/C (Figure 4c).

Table 6. Rate constants for reactions under standard conditions.

k	5% Pd/$BaSO_4$	5% Pd/$CaCO_3$	5% Pd/C
k_1 [min^{-1}]	0.0045	0.006	0.011
k_{-1} [min^{-1}]	2	2	2
k_2 [$M^{-1} min^{-1}$]	150	420	2400
k_3 [min^{-1}]	1	1	1
k_4 [min^{-1}]	0.01	0.01	0.01

Based on these kinetics, the temperature dependence of the racemization of (*S*)-1-phenylethylamine was investigated for 5% Pd/$BaSO_4$ at three different temperatures (Figure 5). The activation energy of $E_a = 120 \pm 10\ kJ\,mol^{-1}$ indicates that the reaction is not subject to any diffusion limitation, but under a kinetic regime.

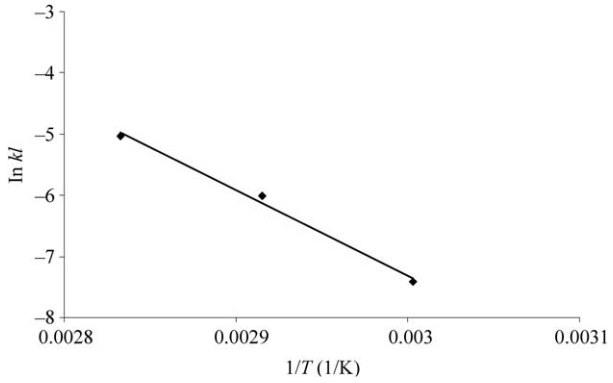
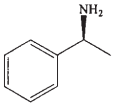
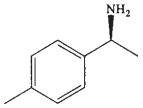
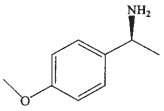
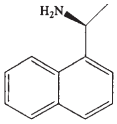
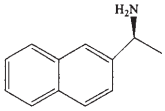
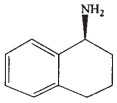
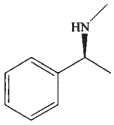
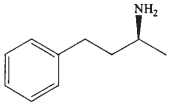


Figure 5. Arrhenius plot for racemization of (*S*)-1-phenylethylamine over 5% Pd/$BaSO_4$.

Scope of the racemization: Pd on alkaline-earth catalysts were also tested in racemization of other optically active amines. Table 7 lists the racemization activity of 5% Pd/$BaSO_4$ with eight substrates. Usually, reaction times of 24 h were sufficient, except for (*S*)-1-methyl-3-phenylpropylamine, which needs 96 h, and (*S*)-1-(4-methoxyphenyl)ethylamine, which needs 72 h. The only byproducts identified were the hydrogenolysis products. The initial rates of racemization were studied for some substituted benzylic amines in the same way as for (*S*)-1-phenylethylamine (Figure 6). With increasing electron-donating character of the substituent, the selectivity at the same conversion clearly increases, but the racemization rate decreases. The opposite trend, that is, higher racemization rate for electron-rich substituents, was observed for homogeneous Ru catalysts.[5] This seems to indicate that different elementary steps are involved in the dehydrogenation of the amine with homogeneous Ru or heterogeneous Pd catalysts; the mechanistic details of this process are currently under investigation. When (*S*)-1-(4-chlorophenyl)ethylamine was used as substrate, a large amount of 1-phenylethylamine was obtained by Pd-catalyzed C–Cl hydrogenolysis. In the racemization of the

Table 7. Racemization activity of 5% $Pd/BaSO_4$ for different chiral amines.[a]

Entry	Amine	Conv. [%]	Sel.$_{R\text{-amine}}$ [%]	*ee* [%]
1		56	81	2
2		50	91	5
3		53	96[b]	3
4		20	77	68
5		46	81	19
6		50	91	4
7		59	64	3
8		57	62[c]	10

[a] Standard racemization conditions, 0.01 MPa H_2, 24 h. [b] 72 h. [c] 90 °C, four days, 0.20 mmol amine.

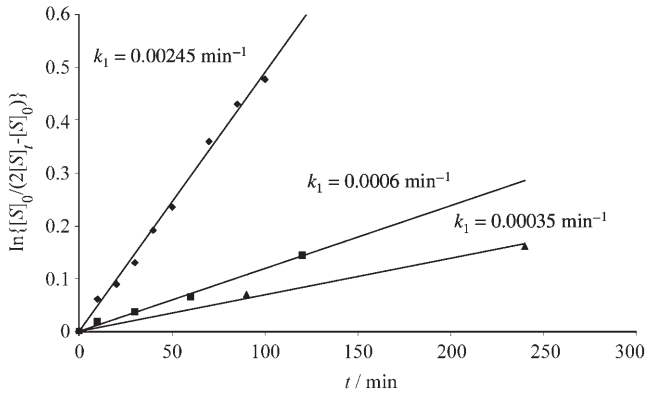


Figure 6. Linearization of kinetic data (standard conditions) for racemization of (*S*)-1-phenylethylamine (◆), (*S*)-1-(4-tolyl)ethylamine (■), and (*S*)-1-(4-methoxyphenyl)ethylamine (▲).

naphthylethylamines, lower selectivities were observed than for the phenylethylamines. This might be due to increased stabilization of the imine intermediate by the naphthyl ring. If the imine is more stable, its concentration is higher, the probability for bimolecular reactions, such as attack of the amine, increases, and a lower selectivity results.

As expected, substantial amounts of hydrogenolysis products were formed in the racemization of the secondary amine (*S*)-*N*-methyl(1-phenylethyl)amine. This is in line with the idea that secondary amines are more prone to hydrogenolysis than primary amines. When the amino group is not in the benzylic position, but linked via an aliphatic chain to the aromatic ring, a higher reaction temperature is required. For (*S*)-1-methyl-3-phenylpropylamine, racemization on $Pd/BaSO_4$ requires 4 d at 90 °C. Chiral aliphatic amines were even unreactive towards racemization under these reaction conditions with Pd on alkaline earth supports. Clearly, for racemization of chiral aliphatic amines, future work must focus on finding better reaction conditions or other catalysts.

Effect of dopants on the racemization: It is well known that Lindlar Pd catalysts, that is, $Pd/CaCO_3$ doped with various loadings of Pb, display improved selectivity, for example, in partial hydrogenation of alkynes to alkenes.[15] Figure 7 presents the effect of different Pb loadings on amine racemization. Increasing Pb loadings gradually decrease the catalytic activity, even though the Pb doping does not decrease the number of accessible Pd atoms, as measured by CO chemisorption on catalysts with 5% Pd and 0, 1, or 2.5% Pb. The selectivity increase at higher Pb contents is merely the effect of lower conversion.

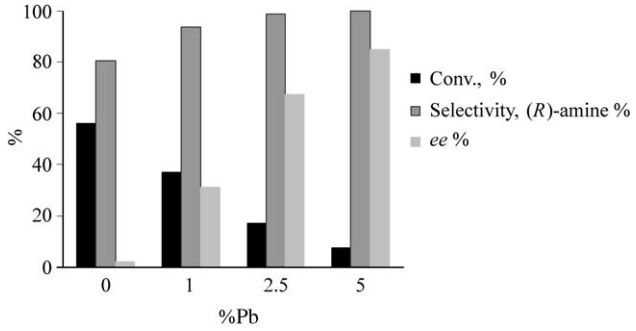


Figure 7. Effect of Pb loading in the racemization of (*S*)-1-phenylethylamine over 5% $Pd/CaCO_3$ under standard racemization conditions for 24 h.

Alternatively, addition of Pt or Bi to Pd/C catalysts was investigated. These dopants caused a tenfold activity decrease in comparison with the undoped catalyst (Table 8). Pt

Table 8. Effect of dopants in 5% Pd/C versus TOF.[a]

Catalyst	TOF [s^{-1}] $\times 10^4$
5% Pd/C	32.2
8% Pd (+2% Pt)/C	2.8
5% Pd (+2% Bi)/C	2.9

[a] Standard racemization conditions.

slightly enhanced the selectivity in (*R*)-amine, while doping with Bi led to an almost unselective catalyst.

Kinetic resolution of benzylic amines: For resolution of the amines, *Candida antarctica* lipase B (CalB) was used in immobilized form. In commercial Novozyme 435 this lipase is entrapped in an acrylic matrix. While the nature of the carrier has been shown to affect the enantioselectivity of resolution reactions, for example, in the esterification of 4-methyloctanoic acid with EtOH,[16] such effects are not expected for acyl transfer reactions such as transesterification or amide formation using an ester as an acylating agent. A typical time profile of the acylation of racemic 1-phenylethylamine by isopropyl acetate is shown in Figure 8.

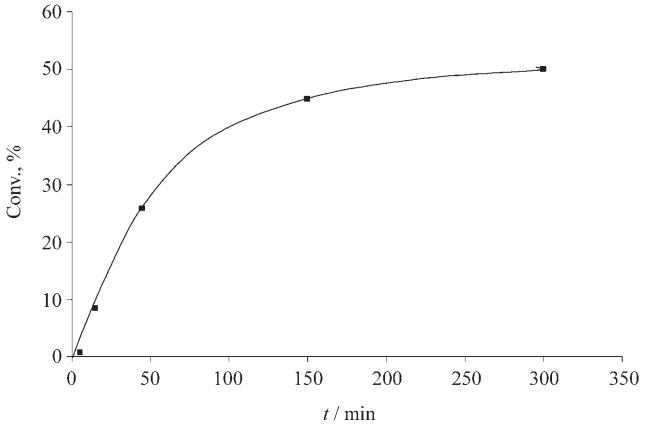


Figure 8. Conversion profile for kinetic resolution of 1-phenylethylamine with 100 mg Novozyme 435 and 0.35 mmol *i*PrOAc at 70 °C (0.33 mmol of substrate in 4 mL of toluene).

A first observation is that the (*S*)-amine is not acylated at all by the enzyme. At an amine conversion very close to 50 %, the product *ee* (ee_P) is superior to 99.5 %, while the *ee* of the residual amine substrate (ee_S) is 99 %. Based on the approach of Rakels et al.,[17] it can be calculated that the enantioselectivity of the enzyme is very high, with an *E* value theoretically exceeding 2000. This high enantioselectivity is in agreement with earlier work on CalB-catalyzed acylation of aryl ethyl amines, in which *E* values larger than 100 have frequently been observed.[3] Secondly, Figure 8 allows the acylation rate to be evaluated under conditions similar to those for the dynamic kinetic resolution. At 70 °C in toluene, and at 0.083 M of racemic amine, the specific activity of the enzyme, as calculated from the initial rates, is 0.038 μmol substrate converted per minute and per milligram immobilized enzyme, or 0.038 IU mg^{-1}. Figure 8 shows that the acylation rate decreases as the reaction progresses. In the relevant concentration domain of the acylating agent isopropyl acetate (0.02–0.2 M), the initial acylation rate is hardly dependent on the concentration of the acylating agent. Hence, the decrease in acylation rate during the kinetic resolution is ascribed to the order of the enzymatic reaction in the amine substrate. In a first-order linearization of the data in Figure 8, a straight line is obtained for ln[*R*] versus time. This indicates that in the concentration domain considered ([*R*] = 0.01–0.08 M), the acylation is pseudo-first-order in [*R*]. In terms of the Michaelis–Menten formalism, this implies that $K_M > [R]$, or the enzyme is used at substrate concentrations well below those of its maximal rate.

Combined bio- and chemocatalytic dynamic kinetic resolution: The dynamic kinetic resolution (DKR) of racemic amines was performed in a one-pot process by adding an immobilized lipase and an acyl donor to the reaction suspension (Table 9). Generally, the selectivity for by-products

Table 9. DKR of 1-phenylethylamine.[a]

Entry	Catalyst	Conv. [%]	Sel.$_{R\text{-amide}}$ [%]	Sel.$_{ETB}$ [%]	ee$_{R\text{-amide}}$ [%]
1	5 % Pd/$BaSO_4$	89	90	10	>99
2	5 % Pd/$CaCO_3$	89	84	16	>99
3	5 % Pd/$SrCO_3$	83	85	15	>99
4	5 % Pd/$BaCO_3$	89	75	9	>99
5	5 % Pd/C	100	30	25	>99

[a] Standard DKR conditions, 0.01 MPa H_2, 24 h, 0.35 mmol ethyl acetate.

in the DKR of 1-phenylethylamine is equal to, or even lower than, that in the racemization, since the amine is acylated to the amide before it can be irreversibly lost by hydrogenolysis. In the coupled reactions, the relative selectivities of Pd/C and Pd supported on alkaline earth compounds remained similar, with Pd/C still producing large amounts of coupling products and ethylbenzene. Pd on $BaSO_4$ proved again to be the most selective catalyst. When Pd on an alkaline earth support is used as the racemization catalyst, the amide yield is always far above the 50 % limit and the product *ee* exceeds 99 % in all cases. This proves that there are no parallel unselective routes to the amide. While it was previously shown that washing the racemization catalyst with NaOH increased the selectivity of racemization (Table 4), the NaOH-treated catalysts were not used further in DKR because traces of NaOH decreased the enzyme activity.

In a DKR process, the rates of racemization and kinetic resolution should be of the same order of magnitude. If the racemization is too slow, ee_S quickly rises, and this might entail enzyme-catalyzed formation of the wrong product isomer, particularly with less enantioselective enzymes. The theoretical framework of DKR has been outlined in detail by Kitamura et al.[18] In their model, it is assumed that not only the racemization, but also the resolution, is first-order in the substrate. As proven previously, the latter assumption can reasonably be made for the Novozyme 435-catalyzed acylation of 1-phenylethylamine. Hence, kinetic data of the DKR can be modeled by replacing rate equation (4) by Equation (8) and by adding Equation (9).

$$\frac{d[R]}{dt} = -k_1[R] + 0.5\,k_{-1}[\text{imine}] - k_2[\text{imine}][R] + 0.5\,k_4[\textit{sec}\text{-amine}] - k_R[R] \quad (8)$$

$$\frac{d[R\text{-amide}]}{dt} = k_R[R] \quad (9)$$

Herein [*R*] refers to the concentration of *R*-amine substrate, and [*R*-amide] is the concentration of enantiopure amide product. An exemplary fit is shown in Figure 9. De-

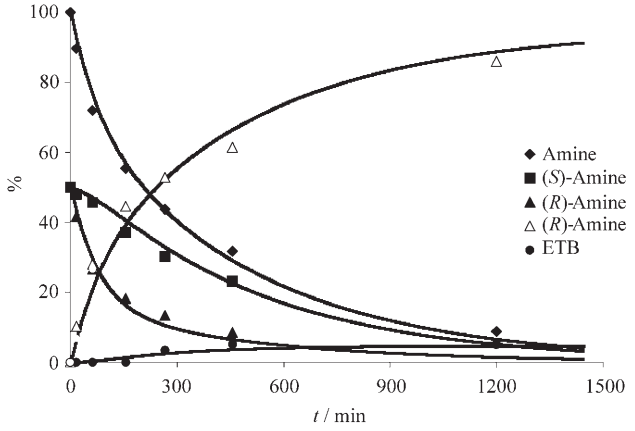


Figure 9. Fitting of experimental data to kinetic model in DKR of 1-phenylethylamine over 5% Pd/$BaSO_4$ and 100 mg of Novozyme 435. Standard DKR conditions.

spite the assumptions and simplifications made, such as the pseudo-first-order dependence of acylation on (*R*)-amine, the concentrations of (*R*)-amide, total amine, (*S*)-amine, and (*R*)-amine can be fitted adequately. Exactly the same constants were employed as in Figure 4a and Table 6, except for the k_2 value. The use of the same k_1 and k_{-1} values means that the activity of the racemization catalyst is unaffected by the presence of the enzyme. For k_2, a higher value (330 M^{-1} min^{-1}) was employed to obtain a good fit. This is not surprising, as even a minute amount of undesired hydrolysis of the acyl donor results in the presence of acetic acid, which could favor acid-catalyzed bimolecular condensation of **1** and **2**. The value for k_R of 0.009 min^{-1} is of comparable magnitude to that of k_1 (0.0045 min^{-1}) which described the rate-limiting step of the racemization. In classical DKR kinetics as described by Kitamura et al.,[18] one obtains a ratio $k_{inv}/k_R = 0.25$. With such a ratio, ee_P is expected to decrease only to a limited extent during DKR, especially if the enzyme is highly enantioselective.

Additional improvements can be made by varying the type of acylating agent. Even if the literature abounds with reports regarding kinetic resolution of optically active amines using different acylating agents, some of these are incompatible with the racemization process. Acylating agents with C=C bonds, such as vinyl acetate,[3] are unsuitable because they are hydrogenated on the Pd catalysts. Moreover, the alcohol that is released should be less nucleophilic than the amine, since it might otherwise cause undesired reactions with the amide reaction product.[19] Testing various acylating agents for DKR of 1-phenylethylamine showed that conversions and selectivities were highest with EtOAc, *i*PrOAc, and ethyl methoxyacetate. The performances of the last two acylating agents are even slightly better than those of EtOAc. A superior selectivity for (*R*)-amide (98%) is obtained with methyl decanoate, but the reaction is slower (Table 10). With methyl formate, a lower *ee* was obtained, because of uncatalyzed formation of the (*S*)-amide.

As expected, the hydrogen pressure has a subtle influence on the DKR via the racemization. For 5% Pd/$BaSO_4$ in DKR of 1-phenylethylamine (Table 11), a maximum yield of chiral amide is found at an H_2 pressure of 0.02 MPa. Increasing the reaction time from 24 to 72 h slightly increases the conversion while preserving the same selectivity. The activity of 5% Pd/$BaSO_4$ in the DKR of other amines was also tested (Table 12); DKR was successful with at least seven substrates. The enzyme was not able to acylate *N*-methyl(1-phenylethyl)amine. Like in the case of racemization, benzylic amines with electron-donating substituents are the best substrates; they exhibit excellent amide selectivity with high product *ee* and high yield. The conditions employed in the DKR process, such as type and amount of acylating donor and reaction time, depend on the nature of the amine. As in racemization, lower yields were obtained with 1-naphthylethylamine. For resolving 1-methyl-3-phenylpropylamine,

Table 10. Influence of acyl donor type in DKR of 1-phenylethylamine on 5% Pd/$BaSO_4$ and 5% Pd/$CaCO_3$.[a]

Entry	Catalyst	Acyl donor, mmol	Conv. [%]	Sel.$_{R\text{-amide}}$ [%]	Sel.$_{ETB}$ [%]	$ee_{R\text{-amide}}$ [%]
1	5% Pd/$BaSO_4$	methyl formate, 0.83	94	57	0	14
2	5% Pd/$BaSO_4$	MeOAc, 0.41	72	97	3	99
3	5% Pd/$BaSO_4$	EtOAc, 0.35	89	90	10	>99
4	5% Pd/$BaSO_4$	*i*PrOAc, 0.35	91	94	6	>99
5	5% Pd/$BaSO_4$	ethyl methoxyacetate, 0.35	91	96	4	99
6	5% Pd/$BaSO_4$	methyl butyrate, 0.34	67	93	6	97
7	5% Pd/$BaSO_4$	methyl decanoate, 0.34	72	98	2	>99
8	5% Pd/$CaCO_3$	MeOAc, 0.41	85	90	9	>99
9	5% Pd/$CaCO_3$	EtOAc, 0.35	89	84	16	>99
10	5% Pd/$CaCO_3$	*i*PrOAc, 0.35	93	87	7	>99

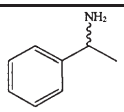
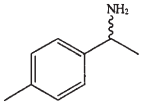
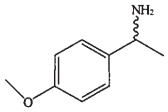
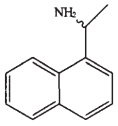
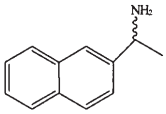
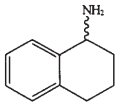
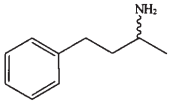
[a] Standard DKR conditions, 0.01 MPa H_2, 24 h.

Table 11. Influence of H_2 pressure and time in DKR of 1-phenethylamine on 5% Pd/$BaSO_4$.[a]

p_{H_2} [MPa]	Conv. [%]	Sel.$_{R\text{-amide}}$ [%]	Sel.$_{ETB}$ [%]	$ee_{R\text{-amide}}$ [%]
0.01[b]	95	90	10	>99
0.02[b]	98	90	10	>99
0.2[b]	99	85	15	>99
0.01[c]	89	90	10	>99

[a] Standard DKR conditions, 0.35 mmol acylating agent, EtOAc. [b] 72 h. [c] 24 h.

Table 12. DKR of benzylic amines with Pd on alkaline-earth supports.[a]

Entry	Amine	Time [h]	Conv. [%]	Sel.$_{R\text{-amide}}$ [%]	$ee_{R\text{-amide}}$ [%]
1		24	91	94	>99[b]
2		48	92	97	>99[c]
3		48	90	98	>99[d]
4		48	64	87	>99[e]
5		48	89	87	>99[e]
6		72	84	90	>99[c]
7		96	98	91	>99[f]

[a] Standard DKR conditions, 0.01 MPa H_2, 5% Pd/$BaSO_4$. [b] 0.33 mmol *i*PrOAc. [c] 0.35 mmol EtOAc. [d] 0.60 mmol EtOAc, [e] 0.60 mmol *i*PrOAc. [f] 5% Pd/$CaCO_3$, 90°C, 0.33 mmol ethyl methoxyacetate, 15 mg Na_2CO_3, 15 mg Novozyme 435.

special reactions conditions were employed, since at 70°C only kinetic resolution and no racemization was observed. Better results (98% conversion, 91% amine selectivity, 90% *ee*) were obtained by raising the temperature to 90°C, extending the reaction time to four days, and adding less enzyme and some Na_2CO_3, which seems to prevent uncatalyzed formation of *S*-amide. Especially this reaction shows that side product formation is limited in a DKR compared to racemization (compare Table 12, entry 7 with Table 7, entry 8).

To evaluate the heterogeneity of the system and to increase the productivity of the catalysts, reuse of both catalysts was attempted. In the DKR of 1-phenylethylamine a sample was taken for analysis after the first run and the liquid was removed by centrifugation. The physical mixture of the two solid catalysts was washed several times with solvent, dried under nitrogen flow, and a fresh solution of substrate (4 mL toluene and 0.33 mmol of 1-phenethylamine) was added together with the acylating agent. After three consecutive runs no appreciable loss of conversion was observed and the selectivity remained higher than 90%, with an *ee* of the resulting (*R*)-amide higher than 99% (Figure 10). This result proves the robustness of the system.

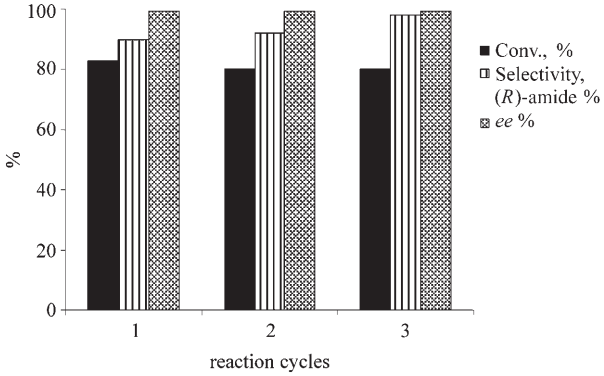


Figure 10. Reuse of the enzyme and 5% Pd/$BaSO_4$ catalysts in DKR of 1-phenylethylamine. Standard DKR conditions, 0.01 MPa H_2, 24 h, and 0.35 mmol acylating agent.

Conclusion

In summary, Pd immobilized on supports such as $BaSO_4$, $CaCO_3$, $SrCO_3$, or $BaCO_3$ is an efficient heterogeneous catalyst for the racemization of benzylic amines. The racemization proceeds via dehydrogenation and hydrogenation, and is first-order in the amine substrate. The by-products arise via formation of a secondary amine and its subsequent hydrogenolysis. Side product formation is strongly suppressed when $BaSO_4$ or $CaCO_3$ is used as support for Pd. The racemization can be combined with enzymatic kinetic resolution in a one-pot process leading to enantiomerically pure amides from racemic amines with good yields. Particulary Pd on $BaSO_4$ showed a satisfactory activity combined with high selectivity in the racemization and DKR of benzylic amines. The catalytic system formed by the chemocatalyst and the immobilized enzyme can be recovered and reused several times without any loss of activity. Although very good results were obtained for benzylic chiral amines, the design of a better heterogeneous chemocatalyst for the DKR of saturated amines still represents a future objective.

Experimental Section

Materials: All reactants were obtained from commercial sources and used as received.

Catalysts: Literature procedures were followed for the preparation of 5% Pd/$BaSO_4$,[20a] 5% Pd/$BaCO_3$,[20a] and 5% Pd/$SrCO_3$.[20b] In these procedures (B), Pd was reduced with an alkaline solution of formaldehyde at a formaldehyde/Pd molar ratio of 10/1, and $PdCl_2$ was used as metal source. 1% Pd/$BaSO_4$ (B) was prepared using the same source of metal and the same molar formaldehyde/Pd ratio as for 5% samples. For the preparation of 1% Pd/$BaSO_4$ (A), Pd$(OAc)_2$ was used as metal source, with a formaldehyde/Pd ratio of 50/1. 5% Pd/$CaCO_3$, 5% Pd/$CaCO_3$ (+2.5% Pb), 5% Pd/$CaCO_3$ (+1% Pb), 5% Pd/C, 5% Pd/C (+2% Bi) were gifts from Johnson Matthey; 8% Pd/C (+2% Pt), 5% Pd/$CaCO_3$ (+5% Pb) were purchased from Heraeus; all catalysts were used without any further pretreatment. *Candida antarctica* lipase B immobilized in acrylic resin (Novozyme 435) was purchased from Aldrich.

Racemization reactions: Reactions were performed in 10 mL stainless steel autoclaves at 70°C under a hydrogen pressure of 0.01–0.2 MPa. To

easily obtain H_2 pressures below 0.1 MPa, 5% H_2 in N_2 was used as reactive gas. For the standard racemization 0.33 mmol of (*S*)-1-phenylethylamine, 4 mL of toluene, and 40 mg of catalyst were used.

Dynamic kinetic resolution: Reactions were performed under similar conditions with 0.33 mmol of racemic 1-phenylethylamine, 4 mL toluene, 100 mg of immobilized *Candida Antarctica* lipase B (Novozyme 435) as resolution catalyst, 40 mg of racemization catalyst, and 0.35 mmol of acylating agent. At the end of the reaction the autoclave was cooled to room temperature, the catalyst was separated by centrifugation and a sample was taken for further analysis.

Instrumentation: XRD measurements were made on a Stoe StudiP diffractometer with $Cu_{K\alpha 1}$ radiation ($\lambda = 1.54$ Å). For all catalysts, the XRD pattern was the same as that of the pure supports; in the case of $BaSO_4$ traces of $Ba(OH)_2{\cdot}8H_2O$ were also observed. No traces of PdO or $PdCl_2$ were detected. HRTEM and EDX measurements were respectively performed with a JEOL 4000EX and a Philips CM20 operated at 400 kV. The EDX measurement confirmed for all samples that Pd catalysts did not contain any traces of Cl^- ions. Pd particle size was measured by averaging over 100 individual particles. ICP measurements were made on a Jobin Yvon Ultima instrument. The metal loadings found for $Pd/BaSO_4$, $Pd/SrCO_3$, and $Pd/BaCO_3$ were 4.7, 5, and 5 wt%, respectively. All catalysts are denoted as 5% Pd/support. Yields and enantiomeric purities of substrate and reaction products were determined by GC (HP 6890) on a CP-CHIRASIL-DEX CB chiral column (25 m) with FID detector and tetradecane as internal standard. The temperature program was as follows: 25 min at 70 °C, heating at 15 °C min^{-1} to 150 °C, and finally 10 min at 150 °C. Under these conditions, typical retention times are: ethylbenzene, 2.07 min; (*R*)-1-phenylethylamine, 13.35 min; (*S*)-1-phenylethylamine, 14.3 min; (*S*)-*N*-1-phenylethyl acetamide, 30.5 min; (*R*)-*N*-1-phenylethyl acetamide, 30.9 min. Ethylbenzene and the secondary amines were identified by using a GC-MS Agilent 6890-N with an Agilent 5973-MSD on a silica column HP-5MS (30 m). MS data for bis(1-phenethyl)amine (**4**): *m*/*z* (%): 225 (1), 210 (43), 120 (8), 106 (75), 105 (100), 79 (16), 77 (28), 51 (6).

CO chemisorption measurements: CO chemisorption measurements were made using an Omnistar TM mass spectrometer coupled to a Pfeiffer Vacuum pump and an oven with automatic temperature control. The pretreatment procedure comprised heating in 10 mL min^{-1} H_2 flow at 10 °C min^{-1} up to 70 °C, 1 h under flowing H_2 at 70 °C, cooling to 25 °C under He flow (10 mL min^{-1}), and 30 min at 25 °C. The measurements were made at room temperature by giving 5 µL pulses of CO at regular time intervals.

Acknowledgements

We are grateful to the Bilateral program Flanders-Romania BIL 04/42, to the IAP program Supramolecular Chemistry and Catalysis of the Belgian Federal Government, to F.W.O. Vlaanderen for a grant, and to Cost action D24.

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Received: June 23, 2006
Published online: December 7, 2006

