Efficient dynamic kinetic resolution of secondary amines with Pd on alkaline earth salts and a lipase

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Combination of Pd, supported on alkaline earth type supports with a lipase results in a selective catalytic system for dynamic kinetic resolution of benzylic amines.

Enantiomerically pure amines have found many applications in pharmaceutical and agrochemistry. For their preparation, separation by diastereomeric crystallization or chiral chromatography, asymmetric hydrogenation of imines, enamines or oximes, and kinetic resolution are the most popular methods.[1] Resolution by enzymatic acylation of racemic amines plays an increasingly important role.[2] In order to surpass the 50% yield limit, dynamic kinetic resolutions (DKR) combine kinetic resolution with *in situ* racemization of the undesired enantiomer. Like the kinetic resolution, DKR starts from a racemic compound, but now a 100% yield can theoretically be achieved in a single step. While the resolution is usually performed by an enzyme, the racemization requires chemocatalysts. DKR of secondary alcohols is now well established, and uses chemocatalysts such as homogeneous Ru transition metal catalysts, supported metal catalysts or solid acids.[3–5] Reports on selective racemization or DKR of amines are much more scarce. A Ru–cyclopentadienone complex catalyzes racemization of a broad range of amines. Even if there are hardly side reactions, 5 mol% of the dinuclear complex needs to be used, and the reaction temperature of 110 °C impedes combination with an enzyme.[6] With Pd on charcoal as a racemization catalyst for DKR of 1-phenylethylamine in Et_3N, the reaction was quite slow (8 days) and side reactions decreased the eventual yield of enantiopure amide.[7] In a modified approach, ketoximes are the starting products, but this obviously necessitates a supplementary synthesis effort.[8] We report here on racemization reactions catalyzed by Pd metal on $BaSO_4$, $CaCO_3$, $BaCO_3$ and $SrCO_3$. These catalysts, combined with an immobilized enzyme proved to be very active in the dynamic kinetic resolution of chiral aromatic amines. Comparison with the 5% Pd/C catalyst confirms that the alkaline earth supports are essential for a successful DKR.

The activity of Pd as a racemization catalyst was first suggested by Murahashi, who used Pd black for catalytic alkyl group exchange between primary and secondary amines.[9] We first screened various Pd catalysts in the racemization of (*S*)-1-phenethylamine under 0.1 bar H_2 pressure. Besides activity, the selectivity for the (*R*)-amine is crucial. Potential side products are ethylbenzene, and amine or imine condensation products. Ideally, a racemization should stop at 50% conversion of the (*S*)-amine, with a 100% (*R*)-amine selectivity, implying 0% *ee* of the amine. After a 24 h reaction, *ee*'s are very low for all Pd catalysts (Table 1). However, side reactions are abundant with Pd/C (Table 1, entry 5). GC-MS identified two diastereomers of bis(1-phenylethyl)amine **4**, together with ethylbenzene (Scheme 1). These products can be formed by initial dehydrogenation of phenethylamine **1** to the imine **2**, followed by attack of a second phenethylamine on the imine. Rapid NH_3 elimination from the aminal results in α-CH_3-*N*(1-phenylethylidene)benzylamine **3**, and this imine is readily hydrogenated to bis(1-phenylethyl)amine **4**. Further hydrogenation then yields ethylbenzene as a hydrogenolysis product, together with racemic phenethylamine.†

Hydrogenolysis of secondary benzylic amines on Pd/C at low hydrogen pressures is well known;[10] it has been found that this reaction is promoted by acid. However, washing of Pd/C with base, or catalyst pretreatments such as pre-reduction did not improve the selectivity of the racemization reaction. No improvement was found either when the reaction was conducted in triethylamine as the solvent, as previously suggested.[7]

When instead of charcoal, alkaline earth supports are used for the Pd, the amine is much better preserved during the racemization (Table 1, entries 1–4). The likely mechanism for the racemization is dehydrogenation, followed by hydrogenation of the imine. Ethylbenzene is the main side product, with a selectivity of less than 20% at ~50% conversion on Pd/$BaSO_4$ and Pd/$CaCO_3$. This means that the final reaction mixture contains 90% or more of the original amine. Bis(1-phenylethyl)amine is only present in minute quantities, *e.g.* 0.5% for the Pd/$BaSO_4$ catalyzed reaction.

Table 1 Racemization of (*S*)-1-phenylethylamine over supported Pd[a]

—	Catalyst	Conversion (%)	Sel.$_{R\text{-amine}}$ (%)	Sel.$_{ETB}$ (%)	ee_{amine} (%)
1	5% Pd/$BaSO_4$	35[b]	91	8	25
—	5% Pd/$BaSO_4$	56	81	19	2
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	40[c]	38	11	60
—	5% Pd/C	98	2	41	6

[a] Standard racemization conditions. Typical racemization reactions were performed in stainless steel autoclaves of 10 ml at 70 °C under a hydrogen pressure of 0.1–2 bar, using 0.33 mmol of (*S*)-1-phenethylamine, 4 ml of toluene and 40mg of catalyst. The reactions were monitored by chiral GC and GC-MS. DKR was performed similarly, with 0.33 mmol racemic 1-phenylethylamine, 4 ml toluene, 100 mg immobilized *Candida antartica* lipase B (Novozym 435) as a resolution catalyst, 40 mg racemization catalyst and the acylating agent. 5% Pd on $BaSO_4$, $SrCO_3$ and $BaCO_3$ were prepared following reported procedures.[11] 5% Pd/C catalyst was from Johnson Matthey, 0.1 bar H_2, 24h. [b] 5h. [c] 1h.

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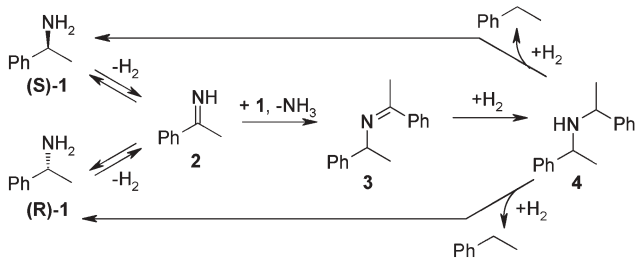

Scheme 1

Table 2 DKR of 1-phenylethylamine[a]

—	—	Conversion (%)	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 conditions‡, with 0.35 mmoles ethyl acetate, 0.1 bar H_2, 24 h.

Therefore, we propose that the main role of a basic support is to suppress the condensation of the amine **1** with the imine **2**. Physicochemical analysis of the supported Pd catalysts shows that typical 5 wt% Pd catalysts, *e.g.* Pd/$BaSO_4$, contain zerovalent Pd metal particles with diameters between 5 and 10 nm (TEM), and dispersions between 1 and 3% based on CO chemisorption.

With performant and selective racemization catalysts at hand, the dynamic kinetic resolution of racemic amines was attempted, by adding an immobilized lipase and an acyl donor to the reaction suspension (Table 2). In general, by-product selectivities in the DKR of phenethylamine are equal to or even lower than in the racemization, since the amine is acylated to the amide before it can be irreversibly lost by hydrogenolysis. Pd/C is again the least selective catalyst, producing large amounts of coupling products and ethylbenzene. With Pd on the alkaline earth supports, the amide yield is always far above the 50% limit, and the product *ee* exceeds 99% in all cases, proving that there are no parallel aselective routes to the amide. Pd/$BaSO_4$ offers a good compromise of sufficient activity and high selectivity for the desired (*R*)-amide; with the other catalysts, *e.g.* Pd/$CaCO_3$, slightly lower amide selectivities were obtained. Further work concentrated on Pd/$BaSO_4$. Extending the reaction time from 24 to 72 h slightly increases conversion, while preserving the same selectivity (Table 3). The H_2 pressure has a subtle influence on the DKR: H_2 directly participates in the equilibrium reaction that results in racemization (**1** ⇔ **2**), but too high pressures might result in selectivity loss through hydrogenolysis. A maximum yield of chiral amide is found at a H_2 pressure of 0.2 bar (Table 3). Additional improvements can be made by varying the acyl donor. EtOAc and ^{i}PrOAc both give fast conversion and high selectivity. An even better selectivity for (*R*)-amide (98%) is obtained with methyl decanoate, but the reaction is slower.

The activity of 5% Pd/$BaSO_4$ in the DKR of other amines was also tested (Table 4). DKR was successful with at least six substrates. With a Cl-substituted amine, hydrogenolysis of the C–Cl bond was observed. Especially for aromatic amines with electron-donating substituents, excellent amide selectivity can be combined with high product *ee* and high yield. Re-use of the enzyme/Pd catalyst was possible through three consecutive cycles, without loss of activity or selectivity.

In summary, Pd immobilized on supports such as $BaSO_4$, $CaCO_3$ or $BaCO_3$ is an efficient heterogeneous catalyst for the racemization of chiral benzylic amines. The racemization can be combined with enzymatic kinetic resolution in a one-pot process leading to enantiomerically pure amides from the racemic amines with good yields.

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Table 3 DKR of 1-phenylethylamine on 5% Pd/$BaSO_4$[a]

p_{H2}/bar	Acyl donor/mg	Conversion (%)	Sel.$_{R\text{-amide}}$ (%)	Sel.$_{ETB}$ (%)	$ee_{R\text{-amide}}$ (%)
0.1[b]	EtOAc, 30	95	90	10	>99
0.2[b]	EtOAc, 30	98	90	10	>99
2.0[b]	EtOAc, 30	99	85	15	>99
0.1[c]	EtOAc, 30	89	90	10	>99
0.1[c]	^{i}PrOAc, 30	91	94	6	>99
0.1[c]	Me decanoate, 60	72	98	2	>99

[a] standard conditions‡. [b] 72 h. [c] 24 h.

Table 4 DKR of benzylic amines using 5% Pd/$BaSO_4$[a]

Substrate	Time/h	Conversion (%)	Sel.$_{R\text{-amide}}$ (%)	$ee_{R\text{-amide}}$ (%)
1-Phenylethylamine[b]	24	91	94	>99
1-(4-MeO-phenyl)ethylamine[c]	48	90	98	>99
1-(2-Naphthyl)ethylamine[d]	48	89	87	99
1-(1-Naphthyl)ethylamine[d]	48	64	87	99
1-(4-Tolyl)ethylamine[e]	24	73	97	>99
1,2,3,4-Tetrahydro-1-naphthylamine[e]	72	84	90	>99

[a] standard conditions‡, 0.1 bar H_2. [b] 0.33 mmoles of ^{i}PrOAc. [c] 0.60mmoles of EtOAc. [d] 0.60 mmoles of ^{i}PrOAc. [e] 0.35mmoles EtOAc.

Notes and references

† Analysis of the reaction kinetics indeed confirms that the (*R*)-amine is the primary reaction product, while bis(1-phenylethyl)amine and especially ethylbenzene are only detected at a later stage of the reaction. This supports hydrogenolysis *via* **4** as the pathway for side reactions.

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