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Heterogeneous Raney Nickel and Cobalt Catalysts for Racemization and Dynamic Kinetic Resolution of Amines

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Abstract: Raney metals were studied as heterogeneous catalysts for racemization and dynamic kinetic resolution (DKR) of chiral amines, as an alternative to metals like palladium or ruthenium. Both Raney nickel and cobalt were able to selectively racemize various chiral amines with high selectivity. In the racemization of benzylic primary amines, the minor formation of side products, e.g., secondary amines, can be suppressed by varying the hydrogen pressure. In the racemization of aliphatic amines over Raney catalysts, the selectivity is very high, with the enantiomeric amine as the sole product. DKR of racemic aliphatic amines can be performed with immobilized *Candida antarctica* lipase B and Raney nickel in one pot; for 2-hexylamine, a yield of 95% of the acetylated amide was achieved, with 97% *ee*. Attention is devoted to the compatibility of the enzyme and the metal catalyst during the DKR. For benzylic primary amines, a two-pot process is proposed in which the liquid is alternatingly shuttled between two vessels containing the solid racemization catalyst and the biocatalyst. After 4 such cycles, the amide of (*R*)-1-phenylethylamine was obtained with 94% yield and more than 90% *ee*.

Keywords: chiral amides; chiral amines; dynamic kinetic resolution; kinetic resolution; Raney cobalt; Raney nickel

Introduction

Enantiomerically pure amines are an important product class in the pharmaceutical and agrochemical industry. They are used as resolving agents, as chemical building blocks for active compounds or as chiral auxiliaries.[1] Kinetic resolution, usually with enzymatic catalysts, is a widely used method for production of chiral amines, as it is usually more favorable regarding price, chemoselectivity and *ee* than alternative methods such as diastereomeric crystallization or asymmetric hydrogenation of imines, enamines or oximes.[1,2] Kinetic resolution uses relatively cheap racemic amines and enzymes,[3] but faces the limitation that the yield per run cannot exceed 50%.

In order to increase the yield, the kinetic resolution can be combined with an *in situ* continuous racemization of the unwanted enantiomer. The resulting process is termed *dynamic kinetic resolution* (DKR) and provides the desired product in theoretical yields up to 100%. In chosing a racemization catalyst, compatibility with the enzyme, usually a lipase, and the other reagents is a crucial issue. Most reports on successful DKR focus on secondary alcohols, for which homogeneous Ru complexes, supported metal catalysts or solid acids can be used as racemization catalysts.[4] For amines, on the other hand, racemization catalysts are scarce. Pd on C or on alkaline earth supports can racemize benzylic amines, but is not effective for aliphatic amines.[5,6] Only Park's group has succeeded in applying Pd for the racemization of aliphatic amines, by designing a highly specific nanoparticulate catalyst.[5c] Even then, reactions with aliphatic amines require strongly increased concentrations of Pd and enzyme, and operation at 100 °C. Bäckvall and co-workers have described the use of the Shvo Ru complex for the racemization of aliphatic amines,[7] but the complex is expensive and still requires long reaction times, e.g., 3 days. An alternative approach to metal-catalyzed racemization *via* imine formation is the racemization catalyzed by alkylsulfanyl radicals.[8] This method seems to work well for aliphatic amines but the question of the recovery and reuse of these organocatalysts is still open.

In the search for new heterogeneous racemization catalysts, the use of less expensive transition metals would be a great advantage. A 'dirt-cheap' catalyst like Ni on charcoal has in recent years proven to be a

Table 1. Racemization of (*S*)-1-phenylethylamine over Raney catalysts in various reaction conditions.[a]

Catalyst [mg]	p_{H_2} [MPa]	X [%]	$S_{R\text{-amine}}$ [%]	*ee* [%]	$S_{sec\text{-amine}}$ [%]	S_{hyd} [%]
Ideal	-	50	100	0	-	-
Raney Ni, 40	0	62	62	0	38	-
Raney Ni, 70	0.01	62	61	0	25	11
Raney Ni, 40	**0.01**	**53**	**90**	**0**	**10**	**-**
Raney Co, 80	0.01	14	100	71	-	-
Raney Co, 45[b]	0.02	21	100	59	-	-
Raney Co, 80[b]	**0.02**	**46**	**98**	**7**	**2**	**-**

[a] *Reaction conditions:* 0.33 mmoles (*S*)-1-phenylethylamine, 4 mL toluene, 70 °C, 24 h. X, conversion of the (*S*)-amine; $S_{R\text{-amine}}$, selectivity for the (*R*)-amine; $S_{sec\text{-amine}}$, selectivity for the secondary amine; S_{hyd} = selectivity for hydrogenation of the aromatic ring.
[b] 72 h.

worthwhile alternative to Pd catalysts in various coupling reactions;[9] in some enantioselective hydrogenations, Ni, modified with tartrate, is as well an alternative to the use of noble metals.[10] Similarly, one may therefore explore Ni or Co metals as catalysts in racemization or dynamic kinetic resolution. In the patent literature, the use of Ni and Co as metal oxides or Raney catalysts has been described for racemization of chiral amines; but as the process is conducted at high temperature and with a mixture of hydrogen, ammonia and the corresponding ketone, it rather resembles the industrial reductive amination route for the synthesis of amines than a selective low-temperature process that could become compatible with enzymatic resolution.[11] Raney Co has been used in the racemization of 2-aminobutanol[12] and in the racemization of (*S*)-3-quinuclidinol as a key step in the synthesis of (*R*)-3-*tert*-butoxycarbonyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid from (*R*)-L-penicillamine.[13] However, it is at present unclear whether Raney catalysts are generally useful as racemization catalysts. The aim of the present paper is therefore to explore the substrate scope of Raney catalysts in amine racemization, and to investigate the coupling with an enzymatic resolution in a DKR process.

Results and Discussion

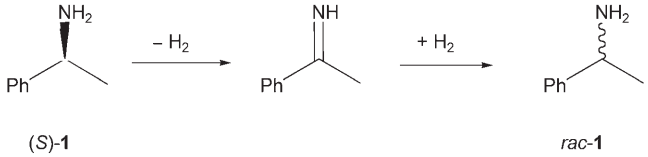
Racemization

Initial Screening of Catalysts and Conditions

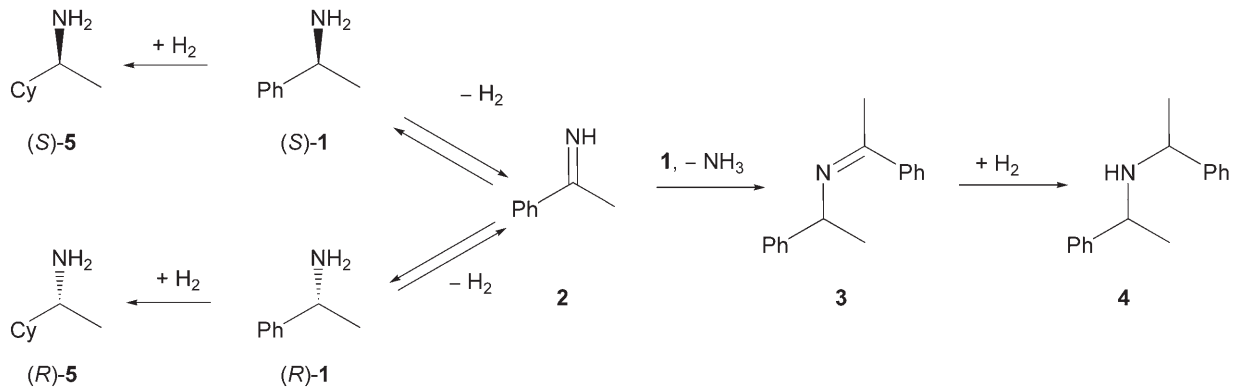
Starting from a pure enantiomer with 100 % *ee*, racemization should ideally yield 50 % conversion of the initial enantiomer with 100 % selectivity for the enantiomer, leading to an *ee* of 0 %. Moreover, the racemization catalyst should operate in relatively mild conditions in order to be compatible with an enzymatic resolution. (*S*)-1-Phenylethylamine, chosen as the initial substrate, was converted with commercial Raney Ni and Co catalysts in various reaction conditions. After short optimization of the conditions, the performance of both catalysts became close to the ideal behavior (Table 1). Raney Ni is the more active catalyst: after 24 h, 50 % conversion is reached using a lower catalyst loading than with Co.

Effects of Hydrogen Pressure

The racemization reaction likely occurs *via* the dehydrogenation-hydrogenation route depicted in Scheme 1. Even if the racemization process does not consume H_2, the hydrogen pressure may affect the position of the equilibrium between amine and imine, and therefore the rates of the dehydrogenation, hydrogenation and possible side reactions. Consequently, the overall racemization process is expected to depend on the hydrogen pressure. Table 1 shows that hydrogen pressure affects the selectivity: besides the desired (*R*)-amine, by-products are the secondary amine bis(1-phenylethyl)amine (Scheme 2, **4**), as a mixture of diastereomers, and, in some cases, the hydrogenation product 1-cyclohexylethylamine (Scheme 2, **5**). In line with our previous observations using Pd racemization catalysts, formation of bis(1-phenylethyl)amine may proceed as depicted in Scheme 2.[6] Attack of the amine (**1**) on the imine (**2**) results in an aminal intermediate, from which NH_3 is readily eliminated to form imine (**3**). Reduction of **3** results in the secondary amine bis(1-phenylethylamine) (**4**). The latter compound seems to be stable in the presence of hydrogen and Ni or Co catalysts;



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



Scheme 2. Reaction mechanism for racemization of (*S*)-1-phenylethylamine over Raney metal catalysts.

hydrogenolysis to ethylbenzene and racemic phenylethylamine, which is a major reaction on Pd catalysts,[6] is not observed with the base metals Ni or Co. Ring hydrogenation with formation of 1-cyclohexylethylamine (**5**) was observed when a large amount of the catalyst was used (Table 1) combined with a sufficient availability of hydrogen.

In discussing the effect of hydrogen pressure on the reaction, it should be considered that commercial Raney Ni catalysts contain a considerable amount of hydrogen, either as chemisorbed or as interstitial H.[14] This is not the case for Raney Co catalysts, and explains that the effects of hydrogen pressure on the activity of the two catalyst types are different, as shown in Figure 1. In absence of hydrogen no reaction takes place for Co Raney. Increasing the hydrogen pressure results in activity increase and *ee* decrease. At pressures above 0.02 MPa, the selectivity decreases. Whereas after 24 h at 0.2 MPa H_2, the *ee* is almost zero, ring-hydrogenated compounds have been formed with a selectivity of 18%. Hence, 0.02 MPa H_2 seems to be the optimum for Raney Co. Contrarily, Raney Ni even performs racemization without added H_2, and its activity decreases upon hydrogen addition, suggesting that an excess of H_2 suppresses the dehydrogenation step. In the absence of external hydrogen, racemization on the Raney Ni catalyst is almost complete after 200 min, and only traces of secondary amine ($\leq$2%) were found together with the amines. At 0.01 MPa H_2 the racemization was slightly slower, but selectivity was still 100%. At higher hydrogen pressures ring hydrogenation became the dominant reaction, with a selectivity over 50% at 0.2 MPa of H_2. In further experiments with Raney Ni, the H_2 pressure was set at 0.01 MPa.

Substrate Scope and Catalyst Stability

The catalytic activity of the two Raney catalysts was tested for 14 other substrates comprising benzylic and aliphatic amines. The nature of the amine, and in particular its aliphatic or benzylic character, plays a very important role. For the benzylic amines (Table 2, entries 1–9) the Raney catalysts present satisfactory activity, even if side product formation may decrease

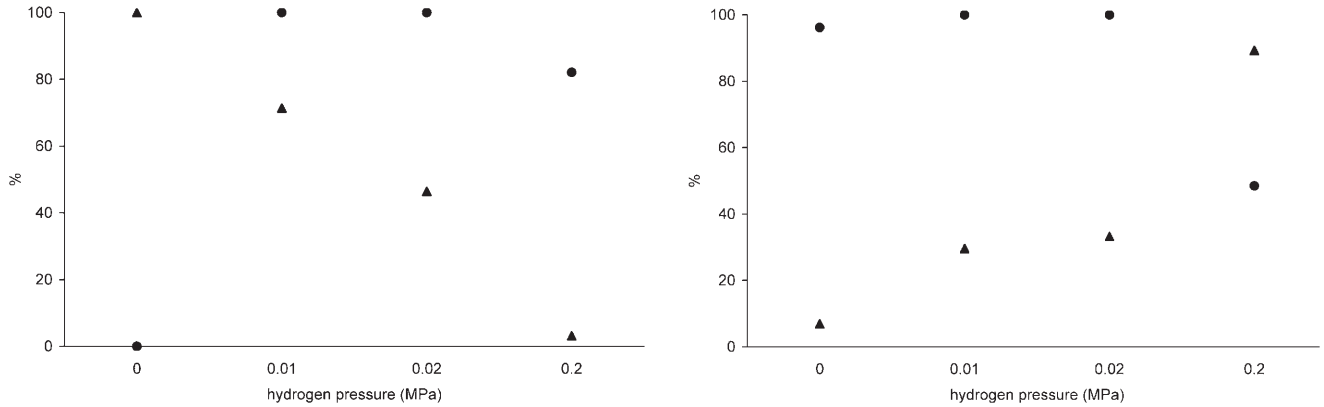


Figure 1. Hydrogen pressure influence on the racemization of (*S*)-1-phenylethylamine over: (*left*) Raney Co, 24 h in standard racemization conditions; (*right*) Raney Ni, 200 min in standard racemization conditions; ● selectivity toward (*R*)-enantiomer; ▲ enantiomeric excess.

Table 2. Racemization activity of Raney catalysts for optically active amines.[a]

Entry	R^1	R^2	R^3	Catalyst	t [h]	X [%]	$S_{R\text{-amine}}$ [%]	ee [%]
1	Ph	CH_3	H	Ni	24	53	90	0
				Co	72	46	98	9
2	4-MeO-C_6H_4	CH_3	H	Ni	48	33	77	44
				Co	72	49	100	2
3	4-Me-C_6H_4	CH_3	H	Ni	24	50	84	8
				Co	72	28	90	48
4	4-F-C_6H_4	CH_3	H	Ni	24	13	0	100
				Co	72	21	64	71
5	Ph	CH_3	CH_3	Ni	48	19	100	61
				Co	72	11	80	83
6	1-naphthyl	CH_3	H	Ni	48	9	100	82
				Co	72	22	86	61
7	2-naphthyl	CH_3	H	Ni	48	36	91	33
				Co	72	43	86	22
8	-(o-C_6H_4)-$(CH_2)_3$-		H	Ni	72	49	100	2
				Co	72	48	100	3
9	Ph	CH_2OH	H	Ni	24	16	100	68
				Co	72	-	-	100
10	c-C_6H_{11}	CH_3	H	Ni	24	42	100	16
				Co	72	47	100	6
11	n-C_4H_9	CH_3	H	Ni	24	46	100	8
				Co	72	31	100	38
12	n-C_5H_{11}	CH_3	H	Ni	24	47	100	7
				Co	72	50	100	0
13	n-C_6H_{13}	CH_3	H	Ni	24	46	100	9
				Co	72	17	100	67
14	Ph-CH_2CH_2	CH_3	H	Ni	48	50	100	0
				Co	72	22	100	57
15	2-methylpiperidine			Ni	24	20	100	59
				Co	72	-	-	100

[a] *Standard racemization conditions:* H_2 pressure 0.01 MPa for Raney Ni, 0.02 MPa for Raney Co. Symbols as in Table 1.

the selectivity of the process. The substitution pattern on the benzylic amines has marked effects as well. Raney Ni was very active in the racemization of (*S*)-1-phenylethylamine (entry 1) and (*S*)-*p*-tolylethylamine (entry 3), but the activity was lower toward (*S*)-*p*-methoxyphenylethylamine (entry 2). On the contrary, with the Co catalyst, the methoxy-substituted amine reacted faster than the methyl-substituted amine. A challenging substrate is (*S*)-*p*-fluorophenylethylamine, in which the carbon-fluorine bond is susceptible to hydrogenolysis (entry 4). For Raney Ni the latter reaction was the only one observed, but the cobalt catalyst showed a much higher selectivity for racemization compared to dehalogenation. Both catalysts presented limited activity towards a secondary benzylic amine (entry 5) and to (*S*)-1-naphthylethylamine (entry 6). By contrast, (*S*)-2-naphthylethylamine was well racemized on both catalysts, showing that reactant structure has a subtle effect on reactivity (entry 7). Excellent results are also obtained with 1-aminotetralin (entry 8). Raney Ni was active towards racemization of (*S*)-2-phenylglycinol (entry 9) while Raney Co was totally inactive. For benzylic amines the selectivities were sometimes lower because of the formation of side products. Secondary amines were the side products for Raney Ni; hydrogenolysis products were only identified in the case of Raney Co, in very small amounts of less than 5% yield (entries 5–7).

For both Raney catalysts, the racemization selectivity was much higher for aliphatic amine substrates (entries 10–15): no side products were identified at all. The substrate scope comprises various 2-alkylamines, optionally substituted with cycloalkyl or phenyl groups. Generally, Raney Ni was able to completely racemize these compounds after 24 h with 100% selectivity, while Raney Co needed longer reaction times. As in the case of the benzylic amines (entry 5), racemization of secondary amines is slower but still highly selective, as illustrated by the case of 2-methylpiperidine (entry 15).

It has been reported that Raney catalysts such as Raney Ni loose some of their activity in alkene hydrogenation because of agglomeration of the Ni parti-

cles in the porous structure.[15] Therefore, the re-use of the Raney Ni catalyst has been attempted in the racemization of (*S*)-1-phenylethylamine. After four reaction cycles of 24 h, an overall activity decrease of 38% was indeed observed, but the racemization selectivity remained constant. No leaching of the Ni was observed during the process.

Dynamic Kinetic Resolution

Choice of Enzyme and Acylating Agent

Apart from the racemization, the kinetic resolution (KR) is the other essential event in dynamic kinetic resolution (DKR). Success in KR depends on the choice of appropriate resolving enzymes and reagents. As a biocatalyst, *Candida antarctica* lipase B (CALB) immobilized in acrylic resin was selected. This immobilized enzyme has a broad substrate tolerance, comprising primary amines and secondary alcohols, and has a high thermal stability. Previously, it has been reported that this enzyme allows one to resolve 1-phenylethylamine with an *E* value higher than 2000.[6] Additionally, the acrylic matrix of the immobilized enzyme is sufficiently inert to avoid unwanted effects on the enzyme or side reactions.[16] A second crucial element is the choice of the acylating agent, as it should fit well in the enzyme's active site and give a high *E* value. On the other hand, spontaneous reaction of the acylating agent with formation of racemic amide is to be avoided. Besides simple esters, e.g., isopropyl acetate, ethyl methoxyacetate is an excellent reagent for enantioselective acylation of aliphatic amines in the presence of CALB.[17] Acylating agents bearing C=C double bonds must be avoided, as hydrogenation catalysts are used for the racemization.

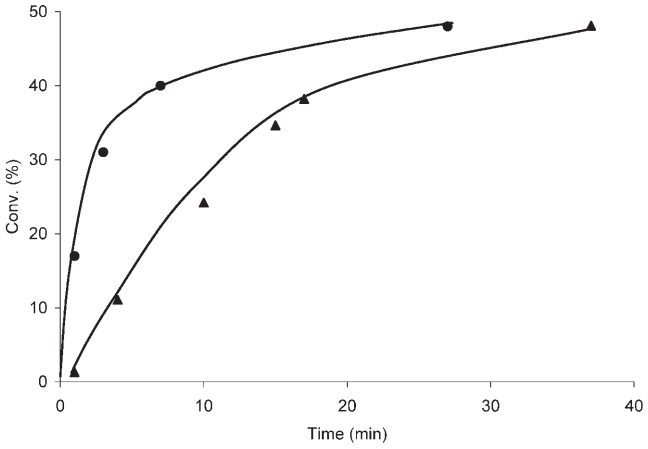
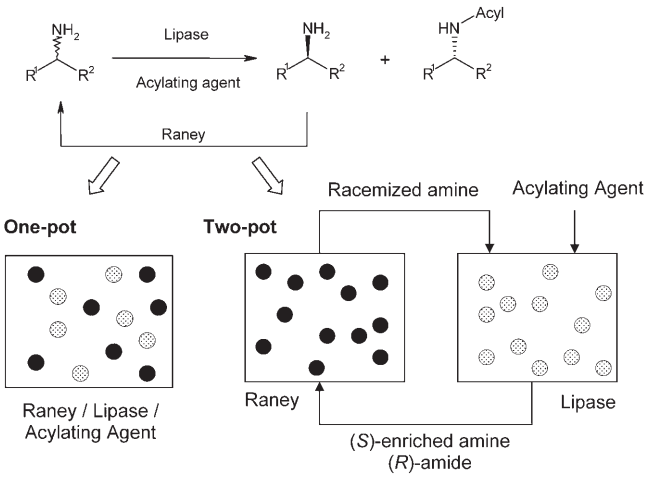


Figure 2. Kinetic resolution of 2-heptylamine (●) and 1-phenylethylamine (▲) with 100 mg immobilized enzyme and 0.35 mmol ethyl methoxyacetate at 70 °C.



Scheme 3. Combined kinetic resolution and racemization of amines in one-pot or two-pot configuration.

In our experiments, kinetic resolutions using CALB and ethyl methoxyacetate indeed resulted in very strong enantiodifferentiation. From the experiments shown in Figure 2, an *E* value of ~1200 could be calculated for resolution of 1-phenylethylamine, based on the formula proposed by Rakels et al.[18] In agreement with literature,[3] the value is somewhat lower for 2-heptylamine, with *E* ~600.

In the present work, racemization and kinetic resolution were either combined in one pot in a true DKR; or a two-pot procedure was applied in which the solid biocatalyst and the solid chemocatalyst were separated and the liquid reaction mixture was alternatingly allowed to contact one or the other catalyst (Scheme 3).

One-Pot Dynamic Kinetic Resolution of Aliphatic Amines

In the one-pot system, the enzyme and the acyl donor were added to the reaction suspension containing the racemization catalyst. Results of DKR with CALB and the Raney catalysts are presented in Table 3. The conversion strongly depends on the nature of the catalyst and the nature of the substrate. Raney Co showed little activity in DKR of 1-phenylethylamine (entry 1) and was even completely inactive in DKR of aliphatic amines (entry 7). Raney Ni was more active in the DKR of chiral amines, with yields well over 50%, even if the reaction times were considerably longer than for the racemization of the corresponding amines (Table 2). Moderate results were obtained in DKR of benzylic amines: after 120 h, 63% of the 1-phenylethylamine was converted by CALB and the Raney Ni catalyst (entry 2). For some of the benzylic amines, the *ee* of the amide product was somewhat lower than expected (entries 3 and 4).

Table 3. One-pot dynamic kinetic resolution of optically active amines using Raney metal catalysts and lipases.[a]

Entry	Substrate	Cat.	t [h]	T [°C]	X [%]	$S_{R\text{-amide}}$ [%]	$ee_{R\text{-amide}}$ [%]
1	1-phenylethylamine[b]	Co	72	70	63	100	100
2	1-phenylethylamine[c]	Ni	120	80	62	98	94
3	1-*p*-tolylethylamine[d]	Ni	72	70	72	90	80
4	1-aminotetralin[d]	Ni	72	70	65	94	87
5	2-hexylamine[d]	Ni	48	70	64	99	98
6	2-hexylamine[d]	Ni	96	70	98	97	97
7	2-heptylamine[e]	Co	96	80	50	100	100
8	2-heptylamine[d]	Ni	96	70	74	99	98
9	2-heptylamine[d]	Ni	48	80	78	97	94
10	2-heptylamine[d]	Ni	96	80	87	96	94
11	2-octylamine[d]	Ni	96	80	75	92	82
12	1-cyclohexylethylamine[d]	Ni	96	80	70	98	96
13	1-methyl-3-phenylpropylamine[d]	Ni	96	80	79	100	98

[a] Standard DKR conditions. Symbols as in Table 1.
[b] 80 mg Raney Co, 0.35 mmoles isopropyl acetate and 0.02 MPa H_2.
[c] 40 mg Raney Ni, 0.35 mmoles methyl decanoate and 0.01 MPa H_2.
[d] 40 mg Raney Ni, 0.35 mmoles ethyl methoxyacetate and 0.01 MPa H_2.
[e] 80 mg Raney Co, 0.35 mmoles ethyl methoxyacetate and 0.02 MPa H_2.

In the case of aliphatic amines (entries 5–13), the high chemoselectivity observed in the racemization using Raney Ni was preserved in the DKR experiments, even if the reaction times were again longer. Results were excellent for the 2-alkylamines (entries 6, 10 and 13). The yields in this series decreased with the length of the alkyl chain, 2-hexylamine giving the best result, *viz*. 95% yield combined with 97% *ee* (entry 6). Increasing the reaction time or the temperature raised the conversion without affecting the selectivity (entries 5, 6 and 8–10). A good yield of 79% (*R*)-amide at 98% *ee* was obtained for 1-methyl-3-phenylpropylamine (entry 13).

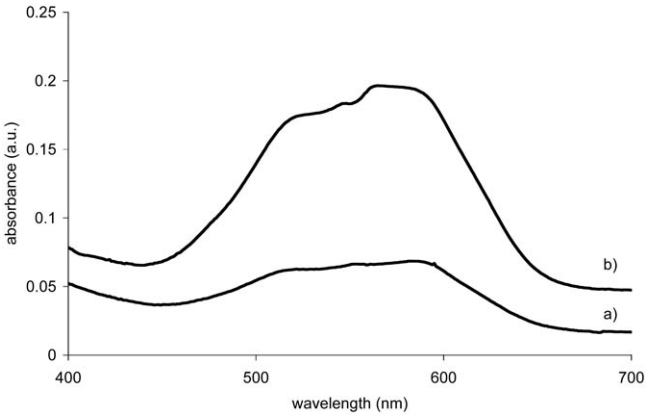


Figure 3. UV/Vis spectra of supernatants of: **a)** DKR of 1-phenylethylamine in one-pot procedure with Raney Co and *i*-PrOAc as acylating agent, 24 h; **b)** racemization of (*S*)-1-phenylethylamine with Raney Co and 1 equivalent of AcOH, 24 h.

Compatibility of Enzyme and Raney Catalysts in One-Pot DKR

For the Co Raney catalyst, oxidative corrosion was pinpointed as the reason for the catalyst deactivation in the DKR. The oxidation was evidenced by the appearance of a pink hue in the solution, as well as by a colour change of the catalyst from dark brown to pink. UV/Vis spectra of the solution recovered from DKR of 1-phenylethylamine with Raney Co (Figure 3) confirmed the presence of a mixture of octahedral and tetrahedral divalent Co species, with absorption maxima at 520 nm and 580 nm.[19] Based on the extinction coefficients for such species, it could be estimated that ~5% of the total Co is dissolved. In the presence of one equivalent of acetic acid, the leaching is even much more pronounced, with dissolution of ~13% of the total Co. Note that background hydrolysis of the acylating agent, caused by, e.g., the enzyme's hydration water, could maximally produce one equivalent of acid.

In contrast, leaching to the solution was not observed for the Raney Ni catalyst. This enhanced stability may be due to the high hydrogen content of the framework which helps to keep the Ni in a zerovalent state. Moreover, Raney Ni catalysts are frequently doped with acids such as tartaric acid, proving the relative stability of this metal catalyst towards acids.[10] Even then, the conversion rates in the one-pot DKR are considerably lower than could be expected based on the rates of the separate racemization or kinetic resolutions, especially for the benzylic amines. In order to assess whether a decreased racemization rate is at the origin of the decreased DKR rate, the effect of various compounds on the racemization activity of

Table 4. Influence of various molecules on the racemization of (*S*)-1-phenylethylamine using a Raney Ni catalyst.[a]

	Additive	Mole additive/mole amine	X [%]	$S_{R\text{-amine}}$ [%]	*ee* [%]
1	-	-	53	90	0
2	*N*-(1-phenylethyl)acetamide	0.37	60	68	0
3	methyl alcohol	1.4	45	93	15
4	enzyme[b]	-	29	100	43
5	methyl decanoate	1.4	62	67	3
6	isopropyl acetate	1.4	19	80	70
7	octanoic acid	0.08	13	100	74
8	octanoic acid	1.4	2	100	96
9	acetic acid	0.2	7	100	87
10	acetic acid	1.4	3	100	95

[a] *Standard racemization conditions:* 40 mg Raney Ni, 24 h. Symbols as in Table 1.
[b] 100 mg immobilized CALB (Novozyme 435).

Raney Ni was tested (Table 4). The compounds used are either added in a typical DKR experiment, or they are formed as products or by-products. The amide product or an alcohol like methanol hardly have an effect on the racemization (entries 2 and 3). The enzyme itself, and an ester like isopropyl acetate slightly decrease the activity of the Ni catalyst (entries 4, 5 and 6). However, a strong activity decrease is observed with acetic and octanoic acid, even at a molar ratio of 0.08–0.2 with respect to the amine (entries 7 and 9). This shows that even minor hydrolysis of the acyl donor could strongly slow down the racemization. However, Ni is not susceptible to dissolution, not even when an excess of the acids is added (entries 8 and 10).

The most appropriate way to identify the rate-determining step in a DKR is to follow the *ee* of the residual amine. Indeed, if this *ee* is high, the racemization is too slow; if, on the contrary, the *ee* stays low, the racemization is sufficiently fast, and the decreased DKR rate is to be ascribed to slow resolution. Relevant data are gathered in Figure 4 and Figure 5, for a benzylic and a linear aliphatic amine during KR or DKR with CALB and Raney Ni. Clearly, the amine's *ee* remains low during the DKR of 1-phenylethylamine (Figure 4). This proves that low enzyme activity in this case is the bottleneck. Rates are somewhat better matched in the DKR of 2-heptylamine (Figure 5), in which a high yield of enantiopure amide is eventually reached (Table 3, entry 10). At first sight, it might seem surprising that reduced enzyme activity is yield-limiting for the benzylic amine, but not for the linear aliphatic amine. However, one should consider that linear aliphatic amines react much faster with the enzyme than the benzylic ones, as proven by Figure 2. Hence, if the enzyme loses part of its activity when it is mixed with the Raney cata-

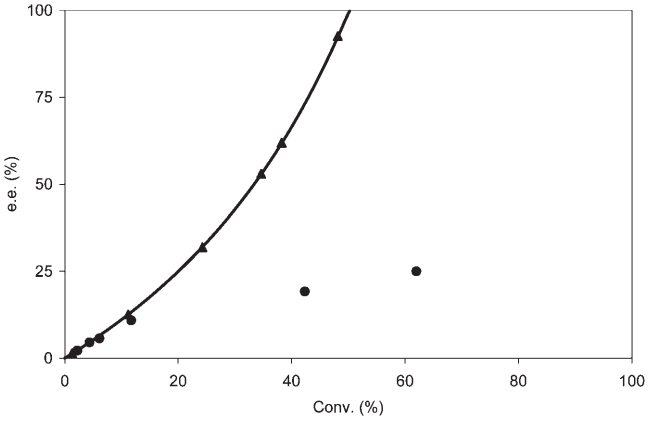


Figure 4. The *ee* of the remaining amine in DKR and in KR of 1-phenylethylamine *vs.* conversion: ● *ee* in DKR; ▲ *ee* in KR. The full line represents the theoretical course of the *ee vs.* conversion for a KR with $E=1200$. DKR was performed at 70 °C in toluene with Raney Ni, 100 mg immobilized enzyme and 0.35 mmol ethyl methoxyacetate.

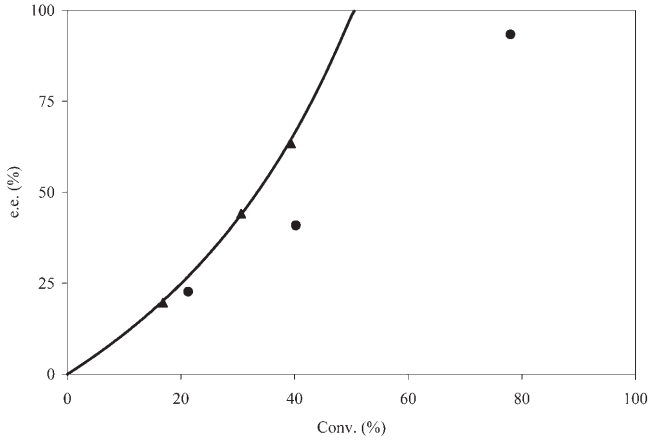


Figure 5. The *ee* of the remaining amine in DKR and in KR of 2-heptylamine vs. conversion: ● *ee* in DKR; ▲ *ee* in KR. The full line represents the theoretical course of the *ee vs.* conversion for a KR with $E=600$. DKR was performed at 70 °C in toluene with Raney Ni, 100 mg immobilized enzyme and 0.35 mmol ethyl methoxyacetate.

Table 5. Two-pot dynamic kinetic resolution of 1-phenylethylamine over Raney/lipase catalysts.[a]

Entry	Catalyst	Runs	X [%]	$S_{R\text{-amide}}$ [%]	$ee_{R\text{-amide}}$ [%]
1	Raney Co	2	70	100	99
2	Raney Ni	4	100	94	91

[a] *Standard DKR conditions:* (i) 80 mg Raney Co, 0.6 mmoles *i*-PrOAc, 0.02 MPa H_2; (ii) 40 mg Raney Ni, 0.5 mmoles ethyl methoxyacetate, 0.01 MPa H_2. Symbols as in Table 1.

lyst, this will be particularly felt in the reaction of the benzylic amine, while there still remains sufficient activity for the DKR of the linear aliphatic amine.[20]

A final concern are the amide *ee*s in the one-pot DKR. While these *ee*s are generally very good, they are substantially lower than expected in a few cases (Table 3, entries 3, 4 and 11). There are several possible causes for such an *ee* deterioration. First, the amine and the acylating agent may react in a non-enantioselective way, either in an uncatalyzed reaction, or under the influence of the base-leached Raney catalysts. Control experiments have, however, shown that amides are not at all produced in the absence of the enzyme. Secondly, the amide product itself might be susceptible to racemization. Tests in the presence of the Raney catalysts have shown, however, that this effect can be neglected as well. Finally, it can be speculated that, if the enzyme loses part of its activity in the mixture with the Raney catalyst, it might also loose some of its enantiospecificity.

Two-Pot Resolution and Racemization of Benzylic Amines

In a two-pot system, deactivating effects of one catalyst on the other, e.g., poisoning of the enzyme by Ni ions can be largely avoided. The liquid reaction mixture is then shuttled between the two reaction vessels. In order to better control the undesired hydrolysis of the acylating agent, it is added in small portions before each resolution step, in quantities that are sufficient to acylate half of the residual amine. The method was tested in the DKR of 1-phenylethylamine, for which DKR in a one-pot system was not successful. As shown in Table 5, two runs with Raney Co lead to an amide yield of 70% with an *ee* of 99%, *vs.* a theoretical yield of 75%. With Raney Ni, the amide yield after 4 runs (52 h) was 94% with an *ee* of 91%, *vs.* a theoretical yield of 93.75%. The major advantage in comparison with the transformation of 1-phenylethylamine in the one-pot system is that yields are much higher after shorter reaction times (compare Table 5, entry 2 with Table 3, entries 1 and 2).

Conclusions

Raney metals are efficient heterogeneous catalysts for liquid-phase racemization of optically active amines. Noteworthily, Raney Ni is one of the few compounds known to racemize even aliphatic primary amines with high selectivity. Raney Ni generally presented a higher racemization activity and a better stability than Raney Co. Hydrogen pressure was shown to be the critical parameter in controlling the chemoselectivity of the racemization on both catalysts. For aliphatic amines, racemization and enzymatic resolution could be combined in one pot, resulting in an efficient DKR. For the benzylic amines, which react less fast with the enzyme, it could be demonstrated that the slow enzymatic conversion of the amine in the presence of the Ni catalyst is the main effect impeding efficient one-pot DKR. However, benzylic amines could be efficiently converted to the enantiopure amide by alternating reaction with the lipase and with the racemization catalyst.

Experimental Section

All reagents were obtained from commercial sources and were used as received. Raney Ni was from Strem Chemicals; Raney Co was a gift from Degussa. The catalysts were kept under solvent and were carefully washed with ethanol and toluene for total removal of the initial solvent water. *Candida antarctica* lipase B, immobilized in acrylic resin (Novozyme 435) was purchased from Aldrich.

Racemization reactions were performed in 10-mL stainless steel autoclaves at 70 °C under a hydrogen pressure of 0–0.2 MPa. In order to obtain a pressure below 0.1 MPa, a 5% H_2 dilution in N_2 was used as the reactive gas. A standard racemization reaction contained chiral amine (0.33 mmoles), toluene (4 mL) and Raney Ni (40 mg) or Raney Co (80 mg). Catalyst weights are expressed as dry solid powder mass.

Dynamic kinetic resolution was performed using either a one-pot or a two-pot reaction system. One-pot reactions were performed in conditions similar to those of the racemization, using the same amount of racemization catalyst, racemic amine (0.33 mmoles) and toluene (4 mL). Immobilized *Candida Antarctica* Lipase B (Novozym 435) (100 mg) was added as the resolution catalyst, together with 0.35 mmoles of the acylating agent. The reaction in the two-pot system was started with the racemic amine (0.33 mmoles), the resolving enzyme (100 mg) and the acylating agent (0.17 mmoles) in 4 mL toluene. Upon depletion of the (*R*)-enantiomer, the mixture was centrifuged, the Raney catalyst was added to the supernatant and the racemization was started. When the amine was close to racemic, the Raney catalyst was removed by centrifugation, and the supernatant was mixed again with the enzyme of the first racemization step, together with 0.17 mmoles fresh acylating agent. Throughout the experiment, the initial batches of biocatalyst and Raney catalyst were employed, without addition of fresh catalyst.

Between the successive uses, the catalysts were kept under a dry N_2 atmosphere.

At the end of the reaction according to the one-pot procedure, the autoclave was cooled to room temperature and a sample was taken from the supernatant. In the two-pot procedure samples were taken after each reaction step.

Yields and enantiomeric purities of reactants and products were determined with GC (HP 6890) on a CP-CHIRASIL-DEX CB chiral column (25 m) with FID detector using tetradecane as internal standard. In the analysis of the racemization reactions, the aliphatic amines were transformed to the corresponding amides by adding two drops of acetic anhydride and two drops of triethylamine to the GC vial (2 mL). The secondary amines and the ring-hydrogenated products were identified with a Agilent 6890-N GC-MS and an Agilent 5973 mass spectrometer on a 30 m HP-5 MS column.

UV-Vis spectrophotometry was performed using a Perkin–Elmer Lambda 12 spectrophotometer and quartz cuvettes. The sample was taken after the reaction was stopped and the catalyst was removed by filtration.

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References

[1] M. Breuer, K. Dietrich, T. Habicher, B. Hauer, M. Keβ eler, R. Stürmer, T. Zelinski, *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824.

[2] K. Faber, *Biotransformations in Organic Chemistry*, 3th edn., Springer, Heidelberg, Berlin, **1997**.

[3] F. van Rantwijk, R. A. Sheldon, *Tetrahedron* **2004**, *60*, 501–519.

[4] a) B. A. Persson, A. L. E. Larsson, M. Le Ray, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1999**, *121*, 1645–1650; b) O. Pamiès, J.-E. Bäckvall, *Chem. Rev.* **2003**, *10,* 3247–3261; c) N. J. Turner, *Curr. Opin. Chem. Biol.* **2004**, *8*, 114–119; d) J. H. Choi, Y. H. Kim, S. H. Nam, S. T. Shin, M. J. Kim, J. Park, *Angew. Chem. Int. Ed.* **2002**, *41*, 2373–2376; e) M.-J. Kim, Y. Ahn, J. Park, *Curr. Opin. Biotechnol.* **2002**, *13*, 578–587; f) S. Wuyts, D. E. De Vos, F. Verpoort, D. Depla, R. De Gryse, P. A. Jacobs, *J. Catal.* **2003**, *219*, 417–424; g) S. Wuyts, K. De Temmerman, D. E. De Vos, P. A. Jacobs, *Chem. Commun.* **2003**, 1928–1929; h) K. Yamaguchi, T. Koike, M. Kotani, M. Matsushita, S, Shinachi, N. Mizuno, *Chem. Eur. J.* **2005**, *11*, 6574–6582; i) D. Klomp, T. Maschmeyer, U. Hanefeld, J. A. Peters, *Chem. Eur. J.* **2004**, *10*, 2088–2093; j) D. Klomp, K. Djanashvili, N. C. Svennum, N. Chantapariyavat, C. S. Wong, F. Vilela, T. Maschmeyer, J. A. Peters, U. Hanefeld, *Org. Biomol. Chem.* **2005**, *3*, 483–489; k) L. Veum, L. T. Kanerva, P. J. Halling, T. Mashmeyer, U. Hanefeld, *Adv. Synth. Catal.* **2005**, *347*, 1015–1021; l) N. Kim, S. B. Ko, M. S. Kwon, M. J. Kim, J. Park, *Org. Lett.* **2005**,*7*, 4523–4526; m) A. Berkessel, M. L. Sebastian-Ibarz, T. N. Muller, *Angew. Chem. Int. Ed.* **2006**, *45*, 6567–6570.

[5] a) M. T. Reetz, K. Schimossek, *Chimia* **1996**, *50*, 668–669; b) Y. K. Choi, M. J. Kim, Y. Ahn, M.-J. Kim, *Org. Lett.* **2001**, *3*, 4099–4101; c) M.-J. Kim, W. H. Kim, K. Han, Y. K. Choi, J. Park, *Org. Lett.* **2007**, *9*, 1157–1159.

[6] a) A. Parvulescu, D. De Vos, P. Jacobs, *Chem. Commun.* **2005**, *42*, 5307–5309; b) A. N. Parvulescu, P. A. Jacobs, D. E. De Vos, *Chem. Eur. J.* **2007**, *13*, 2034–2043.

[7] a) O. Pamiès, A. H. Ell, J. S. M. Samec, N. Hermanns, J.-E. Bäckvall, *Tetrahedron Lett.* **2002**, *43*, 4699–4702; b) J. Paetzold, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2005**, *127*, 17620–17621.

[8] S. Gastaldi, S. Escoubet, N. Vanthuyne, G. Gil, M. P. Bertrand, *Org. Lett.* **2007**, *5*, 837–839.

[9] B. H. Lipshutz, *Adv. Synth. Catal.*, **2001**, *343*, 313–326.

[10] A. Tai, T. Sugimura, in: *Chiral Catalyst Immobilization and Recycling*, (Eds.: D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim, **2000**, pp 173–208.

[11] a) T. Inoue, Y. Hirayama, (Nagase and Co., Ltd. Japan), Japanese Patent 96,231741, **1998**; *Chem. Abs.* **1998**, *128*, 217182; b) H. Kutsuki, J. Hasegawa, K. Watanabe, (Karegafuchi Chemical Industry Co., Ltd. Japan), Japeanese Patent 87,16842, **1988**; *Chem. Abs.* **1988**, *110*, 23517; c) G. Vitt, (BASF AG, Germany), German Patent DE 79,2903589, **1980**; *Chem. Abs.* **1980**, *94*, 15376.

[12] Y. Zhang, G. Bai, Y. Li, X. Yan, L. Chen, *J. Mol. Catal. A: Chem.* **2006**, *255*, 269–274.

[13] a) M. Ikunaka, *Catal. Today* **2004**, *96*, 93–102; b) F. Nomoto, Y. Hirayana, M. Ikunaka, T. Inoue, K. Otsuka, *Tetrahedron: Asymmetry* **2003**, *14*, 1871–1877.

[14] I. Nicolau, R. B. Anderson, *J. Catal.* **1981**, *68*, 339–348.

[15] J. P. Mikkole, H. Voinio, T. Salmi, R. Sjoholm, T. Ollonqvist, J. Vayrynen, *Applied Cata. A: General* **2000**, *196*, 143–158.

[16] N. W. J. T. Heinsman, C. G. P. H. Schroën, A. van der Padt, M. C. R. Franssen, R. M. Boom, K. Van't Riet, *Tetrahedron: Asymmetry* **2003**, *14*, 2699–2704.

[17] a) I. Lavandera, S. Fernández, J. Magdalena, M. Ferrero, R. J. Kazlauskas, V. Gotor, *ChemBioChem*, **2005**, *6*, 1381–1390; b) U. Hanefeld, *Org. Biomol. Chem.* **2003**, *1*, 2405–2415.

[18] J. L. L. Rakels, A. J. J. Straathof, J. J. Heijnen, *Enzyme Microb. Technol.* **1997**, *21*, 559–571.

[19] A. B. P. Lever, *Studies in physical and theoretical chemistry: Inorganic electronic spectroscopy*, 2nd edn., Elsevier, Amstesrdam, **1984**, pp 478–505.

[20] M. Nechab, N. Azzi, N. Vanthuyne, M. Bertrand, S. Gastaldi, G. Gil, *J. Org. Chem.* **2007**, *72*, 6918–6923.

