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Microwave-promoted racemization and dynamic kinetic resolution of chiral amines over Pd on alkaline earth supports and lipases

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Abstract

Microwave irradiation was applied in the racemization and dynamic kinetic resolution of primary benzylic amines. Racemization reactions catalyzed by 5% $Pd/BaSO_4$ and 5% $Pd/CaCO_3$ were faster and more selective when performed under microwave conditions. The use of microwave irradiation stopped the formation of side products, such as secondary amines and ethylbenzene. This was correlated with the selective heating of the metal sites under microwave heating. The influence of the microwave irradiation also was checked in the kinetic resolution; no influence on the activity and enantioselectivity of the immobilized *Candida Antarctica* Lipase B (Novozym 435) was observed when both conventional and microwave heating were compared. The racemization catalysts were combined in one pot with the biocatalyst Novozym 435 to perform the dynamic kinetic resolution of benzylic amines under microwave irradiation. High yields (up to 88%) of enantiopure amides were obtained in less than 1 h when microwave irradiation was applied.

Keywords: Pd catalyst; Chiral amines; Dynamic kinetic resolution; Kinetic resolution; Microwave irradiation

1. Introduction

Enantiomerically pure amines are valuable optically active compounds that have great importance as chemical intermediates in the pharmaceutical and agrochemical industries. Besides such classic methods as diastereomeric crystallization and asymmetric hydrogenation of imines, enamines, and oximes [1,2], chiral amines can be separated by *kinetic resolution*. Although this is a highly enantioselective process that starts from relatively cheap racemic mixtures, kinetic resolution has a major drawback—the yield is limited to 50%. To increase the yield, the unwanted enantiomer should be transformed to the racemic mixture and then submitted to a new resolution. Combination of continuous racemization of the remaining enantiomer with kinetic resolution, called dynamic kinetic resolution (DKR), provides the desired enantiomer in yields theoretically close to 100%. Whereas lipases are used for resolution [3], racemization requires a chemocatalyst. To have a good DKR process, the two catalysts should be able to work together, and as a further condition, the reaction rates of the two processes should be of similar orders of magnitude [4]. There are few reports on successful catalysts for racemization of chiral amines [5,6] compared with the numerous studies on alcohol racemization [7]. Most of the racemization catalysts are metal-based, and the reactions occur through a redox mechanism. Recently, some of us proposed Pd on alkaline earth supports as racemization catalysts for benzylic amines [6]. Although the catalysts were highly active and selective for racemization of benzylic amines, the reaction times for dynamic kinetic resolution were still longer than 24 h in some cases, and small amounts of side products were formed (4–19 mol% of the total substrate converted).

To improve the performance of these Pd catalysts, we chose to test microwave irradiation as a heating source. Microwave irradiation has been reported to be a very attractive tool for chemical applications in both organic and materials synthesis [8]. The unconventional nature of the heating occurs at a molec-

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ular level by direct excitation of molecules, which induces a rapid and simultaneous heating of the whole reaction mixture. The thermal effects caused by microwave irradiation are a consequence of the inhomogeneity of the microwave field within the sample due to selective absorption of the radiation by polar compounds. These thermal effects can be used to efficiently improve processes or modify selectivities [8]. Although there are increasing reports on the application of microwave irradiation in various organic syntheses, its application in asymmetric synthesis is limited, particularly in heterogeneously catalyzed asymmetric synthesis [9–11]. Most of the reports on asymmetric transformations deal with the use of microwave irradiation in the enzymatic resolution of chiral alcohols [10,11,13]. Although microwave irradiation seems to improve the thermal stability of the enzymes [10–12], there are conflicting reports regarding the effect on enzyme activity and enantioselectivity [10,11,13]. To the best of our knowledge, no reports exist on the use of microwave irradiation for the enzymatic resolution or dynamic kinetic resolution of chiral amines. In this paper, we investigate the use of microwave irradiation in the DKR of benzylic amines with Pd on alkaline earth supports and lipases and compare the results with those obtained under normal heating conditions.

2. Experimental

All reagents were obtained from commercial sources and used as received. The 5% Pd/$BaSO_4$ was prepared as reported previously [6a]; the 5% Pd/$CaCO_3$ was a gift from Johnson Matthey. The catalysts were used further with no other pretreatment. *Candida antarctica* lipase B immobilized in acrylic resin (Novozym 435) was purchased from Aldrich.

The following reactions were conducted under conventional heating conditions:

- *Racemization reactions*. Reactions were performed in 10-ml stainless steel autoclaves that were heated at 70–120 °C by inserting them in a copper block, placed on top of a heating plate equipped with magnetic stirring and a thermocouple temperature controller. The hydrogen partial pressure was set at 0.005–0.01 MPa. To easily obtain H_2 partial pressures <0.1 MPa, a 5% H_2 dilution in N_2 was used as the reactive gas. For the standard racemization, 0.33 mmol of (*S*)-1-phenylethylamine, 4 ml of toluene, and 40 mg of catalyst were used.
- *Kinetic resolution*. Reactions were performed in 10-ml closed glass vials at 70–100 °C on a heated copper block. For the standard resolution, 0.33 mmol of (*R*, *S*)-1-phenylethylamine, 0.35 mmol of acylating agent, 4 ml of toluene, and 100 mg of biocatalyst were used.
- *Dynamic kinetic resolution*. Reactions were performed under similar conditions as for racemization, using 0.33 mmol of racemic 1-phenylethylamine, 4 ml of toluene, 100 mg of immobilized *Candida antarctica* lipase B (Novozym 435) as a 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 catalysts were separated by centrifugation, and a sample was obtained for further analysis.

Microwave reactions were performed in a commercially available single-mode microwave unit (CEM Discover) consisting of a continuous focused microwave power delivery system with operator-selectable power from 0–300 W and a microwave frequency source of 2.45 GHz. The reactions were performed in closed glass tubes. In the racemization and DKR conditions, reaction mixtures were flushed with hydrogen before vials were closed; the H_2 partial pressure inside each vial was 0.005 MPa. The reactions were magnetically stirred. Temperature control was ensured with a vertically focused infrared temperature sensor. Temperature, pressure, and power profiles were monitored using commercially available software provided by the microwave manufacturer. Reactions were conducted at 70–120 °C.

Yields and enantiomeric purities of the substrate and reaction products were determined with GC (HP 6890) on a CP-CHIRASIL-DEX CB chiral column (25 m) with a flame ionization detector using tetradecane as an internal standard. Reaction products also were identified by GC-MS, using an Agilent 6890-N unit with an Agilent 5973-MSD on a silica column HP-5MS (30 m).

3. Results and discussion

3.1. Racemization

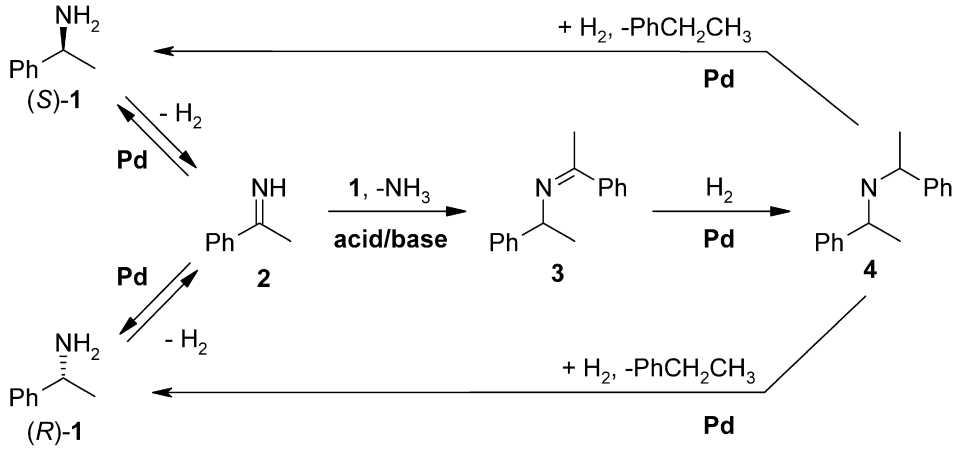
Dynamic kinetic resolution consists of two simultaneous processes: racemization and kinetic resolution. To evaluate the effect of microwaves on the overall process, we first investigated how each individual process is affected by the microwave irradiation. As heterogeneous catalysts, Pd on alkaline metal supports are active in the racemization of benzylic amines [6]. Table 1 presents the racemization of (*S*)-1-phenylethylamine (**1**) under both normal and microwave conditions over Pd on alkaline earth supports. Because it is known that reactions under microwaves work very well at unusually high temperatures, we performed the experiments between 70 and 120 °C, a broader temperature range than used in previous work with conventional heating. Table 1 reports amine conversion and the ensuing e.e. decrease, along with selectivity. Indeed, Scheme 1, for which kinetic evidence has been gathered previously, shows that the main racemization reaction follows a metal-catalyzed, H_2-dependent dehydrogenation–hydrogenation route, with formation of an intermediate prochiral imine (**2**). However, the selectivity of the reaction may be decreased by acid- and metal-catalyzed secondary reactions to the putative aminal and imine (**3**) intermediates, and eventually to the secondary amine bis-(1-phenyl)ethylamine (**4**), or the hydrogenolysis products racemic amine (**1**) and ethylbenzene (**5**). In particular, compounds (**4**) and (**5**) account for the selectivity deficiency displayed in Table 1.

Hydrogen pressure is a key parameter for this racemization reaction, and it strongly affects catalyst activity. Even if hydrogen does not appear in the net racemization equation, it influ-

Table 1
Normal vs. microwave heating in racemization of (*S*)-1-phenylethylamine over Pd/alkaline earth supports[a]

Entry	Catalyst	Heating	Time (min)	Press. H_2 (MPa)	*T* (°C)	Conversion (%)	Sel.$_{R\text{-amine}}$ (%)	e.e.$_{S\text{-amine}}$ (%)
1	5% $Pd/BaSO_4$	Normal	150	0.01	70	24	97	52
2		Normal	40	0.01	80	21	98	59
3		Microwave	15	0.005	80	21	100	58
4		Microwave	13	0.005	100	38	100	25
5	5% $Pd/CaCO_3$	Normal	90	0.01	70	30	96	42
6		Microwave	15	0.005	80	22	100	66
7		Microwave	15	0.005	100	37	100	25
8		Normal	15	0.01	100	36	99	28
9		Normal	15	0.005	100	11	99	78
10		Microwave	15	0.005	120	45	100	11

[a] Standard racemization conditions.



Scheme 1. Racemization mechanism of (*S*)-1-phenylethylamine over Pd/alkaline earth supports.

ences the equilibrium between the amine and imine (Scheme 1). In conventional conditions, the activity of Pd on alkaline earth for (*S*)-1-phenylethylamine racemization is highest in a hydrogen pressure range of 0.01–0.02 MPa [6]. At lower pressure, the racemization rate sharply decreases. The data in Table 1 show that under microwave irradiation, the racemization catalysts work very well even at a lower hydrogen pressure of 0.005 MPa. For both 5% $Pd/BaSO_4$ and 5% $Pd/CaCO_3$, better results were obtained with 0.005 MPa H_2 under microwave than with 0.01 MPa H_2 under normal conditions. Under microwave conditions at 80 °C and 0.005 MPa H_2 (entry 3), 5% $Pd/BaSO_4$ gave similar conversion and better selectivity after 15 min compared with the results obtained under normal heating conditions at 0.01 MPa H_2 after 40 min (entry 2). For 5% $Pd/CaCO_3$ as well, a lower hydrogen pressure of 0.005 MPa suffices for microwave conditions (entries 7 vs. 8), whereas this pressure gave low conversion under normal heating conditions (entry 9).

Switching to the microwave conditions not only was beneficial for the conversion, but also ensured 100% selectivity. At a reaction temperature of 120 °C, a 45% conversion with 100% selectivity was reached within 15 min, corresponding to virtually complete racemization (entry 10). The data of Table 1 suggest that microwave irradiation promotes the redox racemization process while suppressing formation of the secondary products. Such a promotion of redox processes on metallic catalysts also was observed previously when microwave radiation was used instead of classical heating [9b,13,14]. When microwave irradiation is used as an energy source for heterogeneous catalytic systems, the microwaves can interact directly with the metal sites on the catalysts' surface, creating hot spots. Meanwhile, the adsorbed organic layers do not heat up substantially, resulting in significant temperature gradients between the catalyst and the bulk liquid [8d,9c,16]. Thus, the desired metal-catalyzed reactions from (*S*)-(**1**) to (**2**), and back to (*R*, *S*)-(**1**), are promoted while the decisive step in the side-product formation, viz. the reaction to (**3**), is occurring on acid–base sites and is not accelerated (Scheme 1). This explains why the selectivities are systematically improved when microwaves are used. Together with the use of an optimized basic support, this results in the 100% selectivity during racemization. Similar selectivity promoting the effects of microwaves were reported by Roussy et al. for Pt/Al_2O_3 reforming catalysts; along besides thermal effects, they claimed that the microwaves may also modify the geometric and/or electronic properties of the metallic particles [15].

All previous reactions were performed in toluene, which is known to be almost transparent to the microwave energy. The degree of interaction between an organic molecule and the microwave field is measured by the loss factor, $\tan\delta$ [8]. The loss factor is dependent on the dielectric constant, and on the

Table 2
Solvent effect on racemization of (*S*)-1-phenylethylamine over 5% Pd/$CaCO_3$ in microwave and normal heating conditions[a]

Solvent	tan δ	Heating	Time (min)	Conversion (%)	Sel.$_{R\text{-amine}}$ (%)	e.e.$_{S\text{-amine}}$ (%)
Toluene	0.04	Microwave	15	37	100	25
Toluene		Normal	15	11	99	78
Tetrahydrofuran	0.047	Microwave	5	32	100	37
Tetrahydrofuran		Normal	5	5	99	91
Isopropyl acetate	na	Microwave	10	21	100	58
Isopropyl acetate		Normal	15	9	75	87
Dimethylformamide	0.161	Microwave	12	39	100	23
Dimethylformamide		Normal	12	38	78	35

[a] Standard racemization conditions, 0.005 MPa H_2, 4 ml solvent, 100 °C. na = not available.

Table 3
Microwave-promoted racemization of chiral amines over 5% Pd/$CaCO_3$[a]

Substrate	Heating	Conversion (%)	Sel.$_{R\text{-amine}}$ (%)	e.e.$_{S\text{-amine}}$ (%)
(*S*)-1-Phenylethylamine	Microwave	45	100	11
	Normal	34	99	31
(*S*)-1-(*p*-methoxyphenyl)-ethylamine	Microwave	35	100	30
	Normal	13	100	74
(*S*)-1-*p*-Tolylethylamine	Microwave	28	100	45
	Normal	8	100	83
(*S*)-2-Naphthylethylamine	Microwave	6	100	89
	Normal	1	100	98
(*S*)-1-Aminotetraline	Microwave	28	100	44
	Normal	20	98	61
(*S*)-*N*-Methyl-1-phenyl-ethylamine	Microwave	28	100	45
	Normal	15	100	70
(*S*)-1-Methyl-3-phenyl-propylamine	Microwave[b]	36	100	28
	Microwave[c]	3	100	94
	Normal[b]	4	100	91

[a] Reaction conditions: 0.33 mmol substrate, 40 mg 5% Pd/$CaCO_3$, 4 ml solvent, 0.005 MPa H_2, 15 min, 120 °C.
[b] 4 ml isopropanol.
[c] 4 ml toluene, 50 min.

ability of a molecule to be polarized by an electric field. To detect any relationship between the loss factor of the solvent and the racemization activity of Pd catalysts, we chose solvents with different polarities for testing. Our results (Table 2) suggest no evident relationship between a solvent's microwave-absorbing capacity of a racemization activity. The activity of 5% Pd/$CaCO_3$ was almost the same when toluene (tan δ = 0.04) or DMF (tan δ = 0.161) were used, even if there was a significant difference in their loss factors. The best results under microwave conditions were obtained in THF (tan δ = 0.047), which had a loss factor comparable to that of toluene.

In these different solvents, the beneficial effects of the microwaves on the selectivity are again apparent. Clear examples are the reactions performed in isopropyl acetate and DMF. For the microwave reaction, the selectivity to the corresponding (*R*)-enantiomer was 100%. When classical heating was used, selectivity decreased significantly, with 75% selectivity to the (*R*)-amine obtained in isopropyl acetate and 78% in DMF. In these cases, ethylbenzene was the main side product.

We also explored microwave promotion for the racemization of other benzylic amines. Table 3 provides comparative data for microwave and conventional heating. In most cases, the reactions were very fast when microwave irradiation was used. For (*S*)-1-(*p*-tolyl)ethylamine, the conversion under microwave irradiation was 28% after 15 min, whereas under classical conditions, it was only 8%. In addition, for bulkier amines, such as (*S*)-2-naphthylethylamine and (*S*)-1-aminotetraline, reactions performed under microwave were faster than those under normal heating conditions. Only for (*S*)-2-naphthylethylamine was the racemization reaction under microwave rather slow compared with the reactions of the other substrates, with only 6% conversion obtained after 15 min. The selectivity remained 100% for all reactions performed under microwaves. (*S*)-1-Methyl-3-phenylpropylamine is a particular substrate, a pseudo-aliphatic amine. When using toluene as the solvent, the conversion was low (3%) after 50 min under microwave, but changing to isopropanol increased the conversion to 36% after just 15 min. In isopropanol and with classical heating, the conversion was only 4% after the same period. Unfortunately, however, this result cannot be used in a DKR process, because lower-alcohol solvents often deactivate lipases. Pd on alkaline earth supports was not able to racemize any other chiral aliphatic amines, even when the reactions were performed under microwave conditions.

3.2. Kinetic resolution

The other component of a *dynamic kinetic resolution* is the enzymatic resolution. Microwave-mediated kinetic resolutions of alcohols using lipases have been reported previously [10,11]. For both alcohols and amines, *Candida antarctica* lipase B immobilized on an acrylic resin (CALB; commercially known as Novozym 435) is a potential catalyst. This immobilized enzyme has a broad substrate tolerance comprising primary amines and secondary alcohols. It is generally (*R*)-selective and has a high thermal stability, up to at least 90 °C. Besides the enzyme used, a proper choice of acylating agent is also critical to obtain a good kinetic resolution. It was previously observed that isopropyl acetate and ethyl methoxyacetate are excellent reagents for the enantioselective acylation of chiral amines in the presence of CALB [6,17]. Microwave irradiation has not yet been applied for the kinetic resolution of amines. Based on the re-

sults obtained in the kinetic resolution of alcohols over CALB, no clear conclusion can be established regarding the effect of the microwaves on enzyme activity [10,11]; therefore, we studied the activity of Novozym 435 in amine resolution using our monomodal microwave reactor (Table 4). For the kinetic resolution of 1-phenylethylamine, the results obtained under microwave conditions were very similar to those of reactions performed under normal conditions, both with isopropyl acetate and ethyl methoxyacetate. No differences in activity or enantioselectivity were seen between the two different heating systems. The enzymatic kinetic resolution was fastest when ethyl methoxyacetate was used as the acylating agent; toluene seemed to be the best solvent for application of Novozym 435. When isopropyl acetate was used both as the acylating agent and the solvent, the activity was doubled, but the enantioselectivity for the (*R*)-amide decreased.

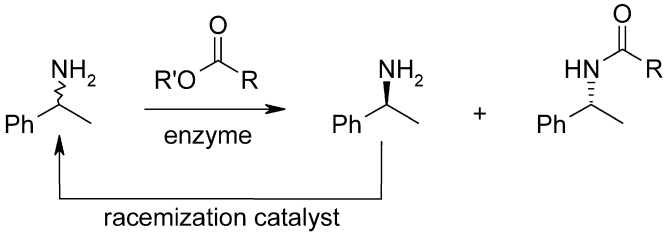
Table 4
Kinetic resolution of 1-phenylethylamine with Novozym 435[a]

Acylating agent (mmol)	Solvent	Heating	Conversion (%)	e.e.$_{R\text{-amide}}$ (%)
Isopropyl acetate, 0.35[b]	Toluene	Microwave	14	100
Isopropyl acetate, 0.35[b]	Toluene	Normal	14	100
Isopropyl acetate, 0.35[c]	Toluene	Microwave	11	100
Isopropyl acetate, 0.35[c]	Toluene	Normal	10	100
Isopropyl acetate, 0.35[d]	Isopropyl acetate	Microwave	24	96
Isopropyl acetate, 0.35[d]	Isopropyl acetate	Normal	23	97
Ethyl methoxyacetate, 0.35[c]	Toluene	Microwave	40	99
Ethyl methoxyacetate, 0.35[c]	Toluene	Normal	41	99
Ethyl methoxyacetate, 0.35[d]	THF	Microwave	13	100
Ethyl methoxyacetate, 0.35[d]	THF	Normal	12	99

[a] Reaction conditions: 0.33 mmol 1-phenylethylamine, 100 mg Novozym 435, 4 ml solvent, 100 °C.
[b] 20 min, 80 °C.
[c] 15 min.
[d] 10 min.

3.3. Dynamic kinetic resolution

After evaluating the effect of microwaves on racemization and kinetic resolution, we performed microwave-promoted dynamic kinetic resolution. The reactions were performed in one pot, by adding the immobilized enzyme and the acylating agent to the racemization mixture (Scheme 2). To achieve a good DKR, the rate of racemization should be at least of a similar order of magnitude as the kinetic resolution. This means that not only both catalysts should be operational in each other's presence, but also their relative amounts should be properly balanced. Insufficient racemization catalyst results in slow overall conversion and decreased product enantiopurity, because the enzyme encounters an excess of the (*S*)-enantiomer. In principle, excessive racemization catalyst does not harm the reaction, but an excess of the chemocatalyst is known to decrease the enzyme's activity [18]. Table 5 compares microwave and conventional conditions, keeping the amounts of racemization and resolution catalysts identical. Based on the results obtained in the kinetic resolution experiments, ethyl methoxyacetate is the preferred acylating agent. The strongly beneficial effect of microwaves on the DKR can be rationalized by assuming that the racemization is selectively promoted while the resolution is unaffected. This means that higher yields are reached after shorter reaction times. Concurrently, because the residual amine is racemized more efficiently, a sufficient concentration of the



Scheme 2. DKR of 1-phenylethylamine.

Table 5
Microwave vs. classical heating in the DKR of chiral benzylic amines over Pd/ alkaline earth supports[a]

Substrate	Catalyst	Heating	Conversion (%)	Sel.$_{R\text{-amide}}$ (%)	e.e.$_{R\text{-amide}}$ (%)
1-Phenylethylamine[b]	5% Pd/$BaSO_4$	Microwave	89	99	97
		Normal	75	99	99
	5% Pd/$CaCO_3$	Microwave	88	99	97
		Normal	73	81	99
1-*p*-Tolylethylamine[c]	5% Pd/$CaCO_3$	Microwave	97	91	98
		Normal	60	99	97
2-Naphthylethylamine[d]	5% Pd/$CaCO_3$	Microwave	84	92	95
		Normal	70	98	95
1-Aminotetraline[e]	5% Pd/$CaCO_3$	Microwave	64	95	95
		Normal	54	94	95

[a] Standard DKR reaction conditions: 100 °C, 100 mg Novozym 435, 0.35 mmol ethyl methoxyacetate, 40 mg racemization catalyst, 0.005 MPa H_2.
[b] 50 min.
[c] 75 min.
[d] 85 min.
[e] 75 min and 0.70 mmol ethyl methoxyacetate.

(*R*)-amine is available to the enzyme at any time, resulting in good enantiodiscrimination even at high conversion levels. The (*R*)-*N*-(1-phenylethyl)-2-methoxyacetamide was obtained at a 88% yield after just 50 min at 100 °C over 5% Pd/$BaSO_4$, with a good e.e. of 97% (Table 5). The slightly lower e.e.'s in some reactions may be caused by the uncatalyzed reaction of the amine with the acylating agent. For the DKR of 1-(*p*-tolyl)ethylamine, a slightly longer reaction time of 75 min was necessary. Using classical heating, the conversion of this substrate was just 60% after 75 min, whereas it attained 97% under microwave conditions in this same period. The same trends are apparent in the DKRs of 2-naphthylethylamine and 1-aminotetraline; for example, for 2-naphthylethylamine, 84% conversion with a 77% yield of the desired (*R*)-amide was obtained after 85 min under microwave conditions.

The stability of the catalytic system under microwave radiation was proven by recovering the catalysts and reusing them for two DKR cycles. No loss of activity or selectivity was observed.

4. Conclusion

Microwave irradiation proved to be an efficient tool for the racemization and DKR of chiral benzylic amines over Pd on alkaline earth metals and lipases. The nature of the heating seems to have the greatest impact on the racemization step. Under microwave irradiation, the racemization rate increased, as did the selectivity. It is thought that microwave heating selectively affects the temperature of the metal clusters, whereas protons responsible for side reactions are not influenced. The enzymatic kinetic resolution of chiral amines seems not to be influenced by the source of heating; identical results were obtained under microwave or classical heating conditions when CALB was used. The DKR of benzylic amines under microwave conditions gave the desired (*R*)-amides in high yields (often >80%) and with e.e.'s between 95% and 98% in 90 min or less, whereas longer times were needed to achieve similar conversion levels under conventional heating.

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