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An approach to chemoenzymatic DKR of amines in Soxhlet apparatus

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Dedicated to Prof. Maria José Calhorda on the occasion of her 65th birthday.

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ABSTRACT

The coexistence of thermolabile enzyme and metal catalyst for racemization of amines in chemoenzymatic dynamic kinetic resolution, requiring high temperature of operation, is enabled by carrying out the reaction in modified Soxhlet extraction system. Initial insights into the scope and limitations of the developed reaction system are discussed.

1. Introduction

Chiral amines are valuable building blocks for synthesis of fine chemicals including pharmaceuticals, fragrances and pesticides [1]. Consequently, several methods have been developed for their preparation, based on e.g., alkylation [2] and hydrogenation [3] of prochiral imines, enamines and aldimines, as well as reductive amination of prochiral ketones [3c,4]. Efficient enzymatic methods for kinetic resolution (KR) of various racemic amines utilizing lipases and proteases exist [5], while being hampered by the maximum theoretical yield of 50%, characteristic for all KRs. By converting such processes into dynamic kinetic resolutions (DKR) where the slower reacting amine enantiomer is racemized in situ by a chemocatalyst, often based on a transition metal [6], 100% yields of pure enantiomers can be obtained, at least in theory (Scheme 1).

While the field of chemoenzymatic DKR of secondary alcohols has advanced remarkably in recent years [6b,c,7], the analogous DKR of amines has remained challenging for various reasons. In general, racemization of amines is more difficult than the racemization of *sec*-alcohols, typically requiring much harsher conditions. Overall, the oxidation of an alcohol enantiomer to ketone and the subsequent reaction back to racemic alcohol is much more facile than the corresponding transformation from amine to imine [6b]. Furthermore, poisoning of metal-based racemization catalysts may take place in the presence of potentially ligating amines. Additional problems are encountered by the typically high temperatures required for racemization of amines being often detrimental for enzyme activity [8].

The first chemoenzymatic DKR of an amine utilizing Pd/C as the racemization catalyst in combination with CAL-B was described by Reetz [9]. The influence of support material has been studied with Pd on modified silica providing the best results [10]. The reactions were carried out in autoclave under slight excess of H_2 pressure in order to facilitate racemization and suppress the formation of side products. A similar approach has been described for DKR of selenium-containing amines over Pd supported on $BaSO_4$ [11]. Pd nanoparticles precipitated on $Al(OH)_3$ have likewise been employed [12], whereas attempts to use Raney Ni and Co have been less successful [13]. Bäckvall and coworkers investigated the homogeneous Shvo's catalyst [14] (Scheme 1) and its *para*-fluoro and *para*-methoxy substituted analogs for racemization of amines [15], with the last mentioned providing the best performance. The same *para*-methoxy substituted Shvo's catalyst has also been used by other investigators [16]. Other examples of homogeneous catalysts include half-sandwich iridium complexes investigated for DKR [17] and iridacycle based systems used for racemization only [18]. Photo-induced radical racemization in the DKR of amines has also been demonstrated [5b].

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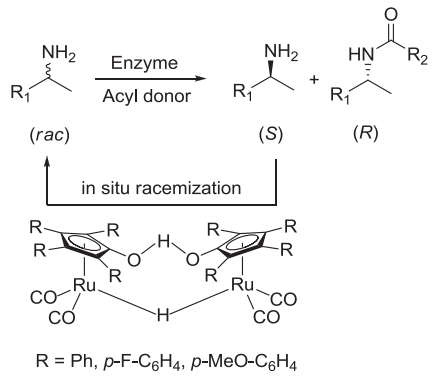


Scheme 1. Chemoenzymatic DKR of amines in the presence of Shvo's (R = Ph) catalyst and its close analogs.

The earlier described strategies have mainly been devised in order to circumvent the limitations for co-existence of the thermolabile enzyme and the amine racemization catalyst, requiring high temperatures for its operation. The enzyme and the catalyst can be separated in space, as exemplified by the MEDKR system where the DKR is carried out in an apparatus containing a "hot" racemization vessel and a "cold" enzyme vessel connected by tubing [19]. Circulation of the reaction mixture through the vessels was achieved by HPLC pump and leakage of enzyme into the "hot" racemization vessel was prevented by an ultra-filtration unit. In this note, we describe our initial approach towards an alternative reaction and reactor setup for chemoenzymatic DKR of amines based on a simple, modified Soxhlet extraction system. In this setup, the racemization catalyst operates in solution or suspension in the reaction flask under heating at reflux at high temperature, whereas the enzyme is placed in the extractor socket under continuous cooling. Prospects and limitations of the approach are discussed.

2. Results and discussion

2.1. Separation of the reaction vessels

A schematic illustration of the DKR Soxhlet reactor system is shown in Fig. 1. The reaction flask (**1**) is filled with solvent, racemization catalyst, and the corresponding amine and acyl donor. The enzyme, packed into porous polyethylene envelopes, is placed in the extractor chamber (**2**). Ideally, the solvent and the acyl donor may be selected in such a way that their boiling points are close to the boiling point of the racemic amine to be resolved, allowing for circulation and condensation of all compounds via the reflux condenser and the extraction socket. Potential examples of such combinations are diglyme (bp 165 °C and *iso*-propylmethoxyacetate (bp 160 °C) for amines with boiling points below 180–190 °C, triglyme (bp 210 °C) and ethyl caprylate (bp 208 °C) for amines with boiling points below 230 °C, and tetraglyme (bp 275 °C) and ethyl laurate (bp 269 °C) for amines with boiling points below 300 °C. A wide range of low-priced "glymes" and fatty acid esters for fine tuning of the system are commercially available. Upon heating of the reaction flask to reflux, all volatile compounds (solvent, acyl donor and the amine) will evaporate and pass through a side arm (**3**) of the extractor, cooling down to suitable temperature while condensing in the reflux condenser (**4**), and will then collect in the chamber (**2**) of the extractor where the enzymatic resolution reaction takes place. Then, the chamber is filled and the reaction mixture returns to the racemization flask (**1**) through a siphon side-arm (**5**).

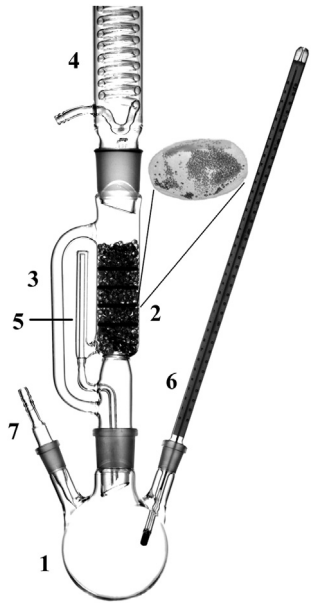


Fig. 1. Schematic illustration of the Soxhlet reactor setup.

Removal of an alcohol (ethanol or *i*-propanol) formed during the enzymatic acylation reaction by evaporation shifts the equilibrium towards the desired product [16]. Mixing of the extraction chamber content takes place mainly by liquid flow back to the racemization flask. In order to decrease the inner volume of the extraction chamber **2** of the Soxhlet extractor, and the duration of the extraction cycle, the chamber can be filled with glass beads. This also, subsequently, decreases the total volume of solvent required for the reaction.

Since most of the relevant target amines to be resolved have boiling points above 150 °C, the refluxing is ideally performed under reduced pressure. In principle, the extent of reduced pressure can be selected in such a way that the boiling point of the reaction mixture is sufficiently high for the metal catalyzed racemization of amines to proceed, i.e., close to 100 °C. During the condensation, the volatile components will cool down to approximately 50–60 °C temperature range which, in contrast to the reflux temperature in the reaction flask, is viable for the resolving CAL-B enzyme. In the case of thermolabile enzymes, the condensation temperature can be lowered by applying external cooling to the extractor vessel. After completion of the DKR, the solvent and excess of acyl donor can be removed by vacuum distillation and reused for a subsequent reaction with the same amine.

Further, for monitoring of the temperature in the racemization flask, an inner thermometer (**6**) can be applied. The temperature in the extraction chamber **2** can be determined by placing a thermometer into the glass beads. In such case, the reflux condenser **4** should have an appropriate construction allowing the insertion of thermometer into the center of the condenser. Uniform boiling can be further facilitated by capillar (**7**). Temperature of the oil bath or heating mantel used for heating of the flask **1** does not influence the boiling temperature but will define the rate of evaporation. In order to ensure that the local temperature in the enzyme envelope will not exceed the upper limit for enzyme stability and function during the reactions, disposable thermo-sensors can be incorporated to the enzyme package, for example sealed capillars filled with crystalline solid with predetermined melting point, such as tosylchloride (mp 69 °C) or benzophenone (mp 50 °C). After completion of the reaction, the thermosensors can easily be removed for inspection.

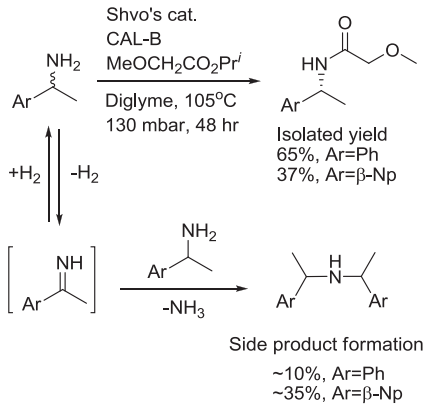
2.2. Proof-of-concept

For investigating the initial feasibility of the Soxhlet system, chemoenzymatic DKR of 1-(phenyl)ethylamine, was studied in the presence of CAL-B and the Shvo's catalyst (Scheme 2). First, regular KRs using 20 mmol of *rac*-1-(phenyl)ethylamine (bp 187 °C) in the Soxhlet reactor were performed providing optimized loadings for the acyl donor, enzyme and the solvent. By use of 200 mg of enzyme, 36 mmol of acyl donor and 70 ml of diglyme under reflux at 100 °C and reduced pressure (130 mbar) for 18 h, close to 50% conversion in the KR was observed after cooling down of the reaction mixture and analysis by chiral GC. Next, for DKR under similar conditions, the reaction loading was adjusted to 10 mmol and 1 mol% of Shvo's catalyst was added. In DKR, The reduced pressure applied and the air-sensitivity of the catalyst makes monitoring of the reaction by sampling difficult. For this reason, the test reactions were run for 24 h and only the final samples after cooling were analyzed showing in most cases conversions exceeding 90%. From these reactions, the (*R*)-product was isolated either by crystallization or column chromatography in 65–70% yield and 99% ee.

For preliminary investigations towards extension of the approach, also KR and DKR of 1-(*para*-fluorophenyl)ethylamine (bp ~175 °C), 1-(*para*-chlorophenyl)ethylamine (bp ~230 °C) and 1-(naphthyl)ethylamine (bp ~280 °C) were rapidly screened. For DKR of the low-boiling 1-(*para*-fluorophenyl)ethylamine, reaction conditions similar to those used for the unsubstituted parent compound 1-(phenyl)ethylamine could be utilized. According to chiral GC analysis, complete conversion of the starting material into reaction products was achieved. While the amount of the desired product did not exceed 65% by GC analysis, its enantiopurity was high (97%). For preliminary screening of the medium-boiling 1-(*para*-chlorophenyl)ethylamine, triglyme and ethyl caprylate were used. For this compound, lower pressure (15 mbar) was applied in order to adjust the boiling point. First, regular KR was performed indicating full conversion after 48 h [20]. Upon application of the DKR protocol to this system, full conversion of the starting material provided only a minor amount (20% by NMR) of the target product [21]. In the literature, dehalogenation of arylhalides with ruthenium hydride has been reported [22], although traces of this side reaction were not observed here.

Finally, both the KR and DKR of the high-boiling 1-(naphthyl)ethylamine using tetraglyme as the solvent and ethyl laurate as the acyl donor were screened. In this case, the KR proceeded fairly slowly (10% conversion in 9 h) due to lower activity of the bulk acyl donor. DKR, in turn, was performed by refluxing of the reaction mixture at 120 °C/0.5 mbar for 48 h with increased catalyst loading (2 mol%), providing moderate isolated yield of the target (*R*)-amide at the expense of excessive formation of side products.

In cases of the high-boiling amines 1-(*para*-chlorophenyl)ethylamine and 1-(naphthyl)ethylamine, enantiomeric excesses of the products were not determined in this work. Fatty acid derivatives of (aryl)ethylamides are not volatile, and, therefore, not applicable for chiral GC analysis. Hydrolysis of the products to the corresponding more volatile amides, in turn, proved problematic due to the low reactivities of the starting amides. Nevertheless, in earlier work, similar amines have been shown to undergo enzymatic acylation to yield products in excellent enantiopurities [14–16].

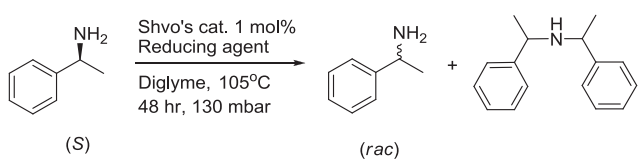


Scheme 2. DKR of 1-(phenyl)ethylamine and 1-(naphthyl)ethylamine in the Soxhlet reactor system.

2.3. Suppression of side product formation

DKR of amines is often complicated by formation of side products [6a,10b,15b]. Racemization of secondary amines commonly proceeds via an imine intermediate, which upon reaction with a second amine molecule irreversibly results in the formation of dimers (Scheme 2). In the present case, reduced pressure facilitates the oxidative dehydrogenation of amine to imine and suppresses the reverse reaction. The subsequent increase in the concentration of the imine intermediate then facilitates side product formation. Comparison of the DKRs of 1-(phenyl)ethylamine at 130 mbar and 1-(naphthyl)ethylamine below 1 mbar demonstrates the strong dependence of side product formation on the applied pressure in the Soxhlet reaction vessel. In the case of 1-(phenyl)ethylamine, 10% of side product was formed as determined by GC analysis. In the case of 1-(naphthyl)ethylamine, the amount of side product formed increased significantly and reached the level of 30–40%, as determined by NMR. In principle, different hydrogen donors can be utilized for reduction of the imine intermediate generated and, consequently, for suppression of the side product formation. For example, 2,4-dimethyl-3-pentanol as a hydrogen donor has been reported to suppress side product formation in one-pot DKR of amines [16]. This compound easily forms ketones while releasing hydrogen upon Ru-catalyzed transfer hydrogenation. The branched structure of 2,4-dimethyl-3-pentanol, in turn, prevents its enzymatic acylation. Due to its relatively low boiling point (140 °C), however, this alcohol is not compatible with the Soxhlet reactor setup when higher boiling components are used. We thus sought out to screen other reducing agents for suppression of dimerization under the presently described Soxhlet conditions. The model racemization reaction for reducing agent screening under reduced pressure is shown in Scheme 3 with the results collected in Table 1.

As evident from entry 1, racemization under reduced pressure in the absence of reducing agents results in significant dimerization. When the racemization reaction was performed at atmospheric pressure (entry 2), only minor amounts of the side product were detected. This observation is consistent with Le Chatelier's principle with inverse dependence of side product formation on the pressure applied. The use of hydroquinone, a widely utilized reducing agent (entry 3), did not suppress side product formation to any desired extent. A possible explanation may be related to the relatively high acidity of the OH group in hydroquinone ($pKa^1 = 10$), resulting in decomposition of the ruthenium hydride catalyst intermediate and the subsequent liberation of hydrogen gas. Promising results were



Scheme 3. Model reaction studied for suppression of side product formation.

Table 1
Screening of reducing agents for suppression of side product formation.

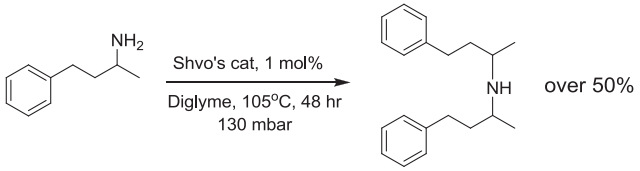
Entry	Reducing agent	Formation of side product, %
1	–	9
2	–[a]	1
3	Hydroquinone[b]	15
4	2-Octanol[b]	1
5	2,2,4-Trimethyl-1,3-pentanediol[b]	3
6	2,2,4-Trimethyl-1,3-pentanediol[c]	3
7	3-hydroxy-2,2,4-trimethylpentyl dodecanoate[b]	3
8	Bubbling of H_2	1

[a] $P = 1$ bar.
[b] 0.5 equiv.
[c] 1 equiv.

obtained by use of 2-octanol (entry 4). This compound has a boiling point of 180 °C and can only be utilized with low boiling amines in the Soxhlet system. In the case of higher boiling substrates, octanol will be carried together with the other vapors to the enzyme chamber resulting in enzymatic acylation and a loss of reducing properties. The economically viable and commercially readily available 2,2,4-trimethyl-1,3-pentanediol, likewise, demonstrated acceptable efficiency (entry 5). Increase in the loading of this reducing agent did not improve the result (entry 6). The high boiling point of this compound (232 °C) enables its use and compatibility with a broad range of amines. A model reaction on enzymatic acylation of this compound showed acylation mainly at the primary alcohol group with only minor amounts of secondary alcohol group acylation observed. The isolated acyl product from the enzymatic test reaction was evaluated for side product suppression (entry 7), showing similar behavior and efficiency compared to the non-acylated parent diol. Since the oxidation to ketone only involves the secondary alcohol moiety, the primary alcohol function does not influence the results of side product suppression. The introduction of gaseous hydrogen into the reaction mixture via capillar (entry 8) also efficiently suppresses side product formation being, however, complicated due to the high diffusion rate through the rubber tubing.

In accordance with earlier reports [10b,c], heterogeneous Pd/C demonstrates excellent racemization activity towards 1-(phenyl) ethylamine under atmospheric pressure without any detectable formation of side products. Unfortunately, when Pd/C was here employed instead of the Shvo's catalyst in the Soxhlet reactor setup, dimerization became the dominant reaction under reduced pressure. The interaction which binds hydrogen to palladium metal is weak compared to the covalent hydride bond in the Shvo's catalyst. Consequently, loss of hydrogen under reduced pressure followed by dimerization is likely to become a major reaction pathway in the case of heterogeneous catalysts.

Finally, it could be assumed that the imine intermediate formed during the racemization reaction will be further stabilized by conjugation of the C=NH double bond with the aromatic ring. To investigate this, also 4-phenyl-2-aminobutane, an amine without aromatic ring in the alpha-position to the nitrogen atom, was tested. To our disappointment, significant side product formation was observed in this case as well, possibly facilitated by the decrease in steric hindrance (Scheme 4).



Scheme 4. Dimerization of 4-phenyl-2-aminobutane.

3. Experimental section

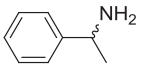
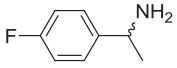
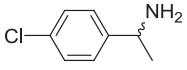
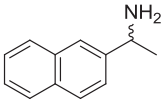
3.1. Reactor setup

General experimental conditions and results on the DKR reactions are collected in Table 2. First, 110 mg (1 mol%) of the Shvo's catalyst, 70 ml of the corresponding glyme, racemic 1-(aryl)ethylamine and the corresponding acyl donor were placed in a three-necked 100 ml round-bottom flask, equipped with a thermometer, a magnetic stirrer bar, a capillar and a Soxhlet head (50 ml) with a reflux condenser. The enzyme (Novozyme 435) was packed in 4 porous polyethylene bags, 50 mg in each. In the case of the slower reacting 1-(naphthyl)ethylamine, 6 bags containing 300 mg of enzyme in total were utilized. The bags containing the enzyme were placed into an extraction chamber of the Soxhlet extractor together with 5 mm glass beads. In this way the "dead volume" of the Soxhlet extractor was reduced to approximately 20 ml. Disposable thermo-sensors were placed between the enzyme bags. If desired, with proper construction of the reflux condenser, a thermometer could also be inserted into the glass beads. The outlet of the reflux condenser was connected to an inlet of a membrane pump equipped with vacuum control unit. The argon inlet was connected to the capillar and to the gas inlet of the pump. We recommend the incorporation of a 1–2 l buffer flask between the apparatus and the vacuum pump for controlling the vacuum oscillation. The use of Teflon thermostable grease for the hot joints is likewise recommended. The side arm of the extractor should be thermally insulated. Loops of rubber tubing with cooling water circulation can be applied around the extraction chamber for additional cooling of the enzyme.

3.2. Operation [pressure and temperatures given for 1-(phenyl) ethylamine]

The reaction was performed at 130 mbar pressure and temperature of 105 °C. The reaction flask was heated on an oil bath. Temperature of the oil bath influences the evaporation rate but not the boiling temperature. Maintaining the bath temperature at 140 °C allowed for 3–5 min duration of the extraction cycle. After 24 h, the heating was stopped and the apparatus was cooled down under argon atmosphere. Completion of the reaction was verified by chiral GC or NMR. The extraction chamber was washed thoroughly with toluene. The combined liquid phases were concentrated under reduced pressure and the residue was purified by chromatography (hexane-ethylacetate) in the case of 1-(phenyl) ethylamine or recrystallized from hexane in the case of 1-(naphtyl) ethylamine to yield 1.25 g (65%, 99% ee) of (*R*)-2-methoxy-*N*-(1-phenylethyl)acetamide, or 0.65 g (37%) of (*R*)-*N*-(1-(naphthalen-2-yl)ethyl)dodecanamide. The amount of the side product formed was quantified by chiral GC or ^{1}H NMR. Physical and spectral properties of (*R*)-2-methoxy-*N*-(1-phenylethyl)acetamide [mp 58–61 °C, $[\alpha]_D^{22} = +78.4$ ($c = 5\%$, $CHCl_3$)] are in accordance with those previously reported for this compound [23]. For (*R*)-*N*-[1-(naphthalen-2-yl)ethyl]dodecanamide, only the negative sign of rotation without numerical value has been reported for the opposite enantiomer in the literature [24]. Analytical data obtained here for this compound: mp 77–80 °C, $[\alpha]_D^{22} = +89.2$ ($c = 5\%$, $CHCl_3$); ^{1}H NMR (600.13 MHz, $CDCl_3$): δ_H 7.81–7.78 (3H, m, Ar*H*), 7.73 (1H, s, Ar*H*), 7.48–7.41 (3H, m, Ar*H*), 5.86 (1H, br d, $J_{HH} = 8.0$ Hz, N*H*), 5.32–5.27 (1H, m, C*H*–NH), 2.17 (2H, t, $J_{HH} = 7.0$ Hz, CO–CH_2), 1.65–1.59 (2H, m, CO–CH_2–CH_2), 1.56 (3H, d, $J_{HH} = 7$ Hz, CH(NH)–CH_3), 1.32–1.20 (16H, m, aliphatic chain), 0.88 (3H, t, $J_{HH} = 7.0$ Hz, $(CH_2)_{10}$–CH_3). ^{13}C{^{1}H} NMR (150.9 MHz, $CDCl_3$): δ_C 172.28, 140.72, 133.34, 132.71, 128.46, 127.88, 127.61, 126.22, 125.87, 124.82, 125.50,

Table 2
Reaction conditions for DKR of the 1-(aryl)ethylamines.[a]

Substrate/loading	Acyl donor/loading	Solvent	Temperature[b]/pressure	Results
 10 mmol [c]	$MeOCH_2COO$-*i*-Pr 18 mmol	Diglyme	105 °C/130 mbar	Full conversion; Isol. yield 65%; ee 99%
 10 mmol	$MeOCH_2COO$-*i*-Pr 15 mmol	Diglyme	105 °C/130 mbar	Full conversion; GC yield 65%; ee 97%
 10 mmol	$CH_3(CH_2)_6COOEt$ 15 mmol	Triglyme	110 °C/15 mbar	Full conversion; NMR yield 20%
 5 mmol [d]	$CH_3(CH_2)_{10}COOEt$ 10 mmol	Tetraglyme	120 °C/0.5 mbar	Slow reaction; Isol. yield 37%

[a]Unless otherwise stated, 1 mol% of the Shvo's catalyst, 4 × 50 mg of Novozym 435, 48 h reaction time.
[b]Temperature in the racemization vessel.
[c]24 h.
[d]2 mol% of catalyst and 6 × 50 mg of Novozyme 435.

48.57, 36.94, 31.92, 29.62, 29.52, 29.38, 29.34, 29.31, 25.81, 22.70, 21.63, 14.14.

3.3. Side product suppression experiments

Shvo's catalyst (22 mg, 2 mol%), amine (2 mmol), diglyme (40 ml) and the appropriate reducing agent (Table 1) were placed into a 100 ml three-necked round-bottom flask equipped with a thermometer, a capillar and a reflux condenser. Argon input was connected to a capillary and a membrane pump intake was connected to the exit of a reflux condenser. In case of using hydrogen as the reducing agent, a heavy walled rubber balloon with hydrogen was connected to a capillar. The reaction mixture was refluxed at 105 °C/130 mbar for 48 h, cooled down under an argon atmosphere and analyzed by chiral GC and ^{1}H NMR.

4. Summary and conclusions

To summarize, a flexible system for chemoenzymatic DKR of amines based on space separated racemization and enzyme vessels in a Soxhlet-type reactor setup has been developed and its feasibility demonstrated in a proof-of-concept study. Mass transfer of the reaction mixture is performed by repeating cycles of evaporation, condensation and siphon flow. This approach allows the usage of membrane pump instead of HPLC pump for liquid circulation. Different solvents and acyl donors with a broad range of boiling points are widely available from commercial sources and should allow the further fine tuning of the system. Currently, the main limiting factor with the developed system is the vacuum enhanced loss of hydrogen which facilitates side product formation, complicates the DKR process and decreases the yield of the desired product to the level of conventional kinetic resolution. Preliminary results demonstrate that such side product formation can be suppressed by additional hydrogen donors in the system, requiring, however, further improvement and optimization. Other modifications of the system can, likewise, be envisioned for future investigation. For example, when using the Shvo's catalyst for racemization, temperatures above 80 °C are required for activation of the dimeric catalyst precursor to form the catalytically active monomer(s) [25]. In principle, a "catalyst saving mode" could be applied in the beginning of the reaction by adjusting the pressure inside the system to allow for refluxing below the activation temperature of the racemization catalyst. Under such conditions only conventional kinetic resolution should take place. After this initial period, the pressure can be increased, simultaneously increasing the boiling point and inducing activation of the racemization catalyst and starting the DKR reaction.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2013.11.005.

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