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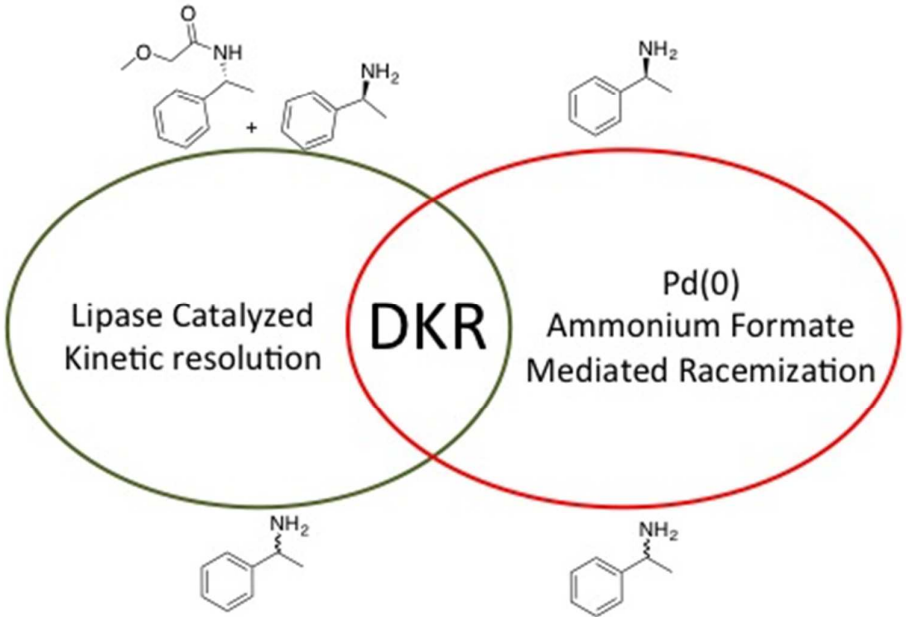
Graphical Abstract



Ammonium Formate as Green Hydrogen Source for Clean Semi-Continuous Enzymatic Dynamic Kinetic Resolution of (+/-)-α-Methylbenzylamine

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Keywords: Dynamic kinetic resolution • racemic amines • continuous flow . ammonium formate.

Abstract: Abstract: The chemoenzymatic dynamic kinetic resolution of (+/-)-α-Methylbenzylamine under continuous flow conditions in the presence of $Pd/BaSO_4$ as racemization catalyst and ammonium formate as reductant is described. Under the conditions developed good conversions and excellent enantiomeric excess are reported

Introduction

Recently, continuous processing and biocatalysis have been elected as key green engineering research areas for sustainable manufacturing[1a] and it is clear that joint efforts between these areas can lead to great improvements on continuous manufacturing in agreement with green chemistry principles [1b,c].

Optically pure amines are ubiquitously present in nature and active pharmaceutical ingredients (APIs). However, their synthesis still represents an ongoing synthetic challenge that can be inferred by the great amount of work and methodologies dealing with this issue in the literature.

Over the years, several methods have been developed, including the multi-step protocol addition of carbanions to chiral sulphinyl, sulphonyl or phosphoryl imines;[2] the hydrogenation of acyl enamines with chiral phosphorus ligands;[3] transition metal and organocatalyzed asymmetric imine reduction,[4] asymmetric hydroamination of olefins[5] and kinetic resolutions. All of these methodologies suffer from limited scope, greenness and no definitive approach exists.

Among them, enzymatic kinetic resolution has proven to be useful for the preparation of enantioenriched primary chiral amines due to its low operational and catalyst cost being generally more suitable concerning green chemistry principles. In this process, a racemate is resolved through enantioselective enzymatic acylation, providing enantioenriched amide and an amine with the opposite configuration.[6] If only one enantiomer is desired, a metal catalyzed racemization reaction can be coupled with the kinetic resolution in a one-pot procedure, a process known as dynamic kinetic resolution (DKR) [7].

The dynamic kinetic resolution of amines is a developing field. When compared to the DKR of chiral secondary alcohols the resolution of amines presents additional

challenges rooted in the high nucleophilicity of primary amines. This inherent nucleophilicity leads to a competition between enzymatic and chemical acylation in the kinetic resolution step, as well as trapping of the imine intermediate and its deamination, which is responsible for the low selectivity for the desired racemic amine in the racemization process.

Reetz and co-workers[8] reported the first example of chemoenzymatic DKR of amines, by using palladium on carbon to promote racemization of the amine and Novozyme 435 (commercial immobilized *Candida antarctica* lipase B - CALB) to achieve enantioselective acylation. However, moderate conversion was observed only after 8 days. Since then, many other approaches towards the biocatalyzed DKR of amines have been developed[6a,b], most of them based on free CALB or its immobilized form as biocatalyst for the kinetic resolution step. On the other hand, racemization is still a challenge and several methods have been developed based on Pd, Ni, Ru and Ir catalysts.[7c]

In the case of palladium, catalysts supported on heterogeneous basic supports have proven to be very useful for DKR of amines.[9] However, Pd promoted racemizations are usually accomplished under harsh conditions, such as high temperatures, in which lipase activity can be compromised. Besides, amine racemization is prone to formation of by-products derived from reaction of imine with unreacted amine. In figure 1 is depicted the catalytic cycle that leads to the racemization process as well as the collateral reactions that lead to the observed by-products. In order to circumvent such drawbacks the use of a reductive atmosphere, such as the presence of hydrogen gas, is usually required.[9a,b]

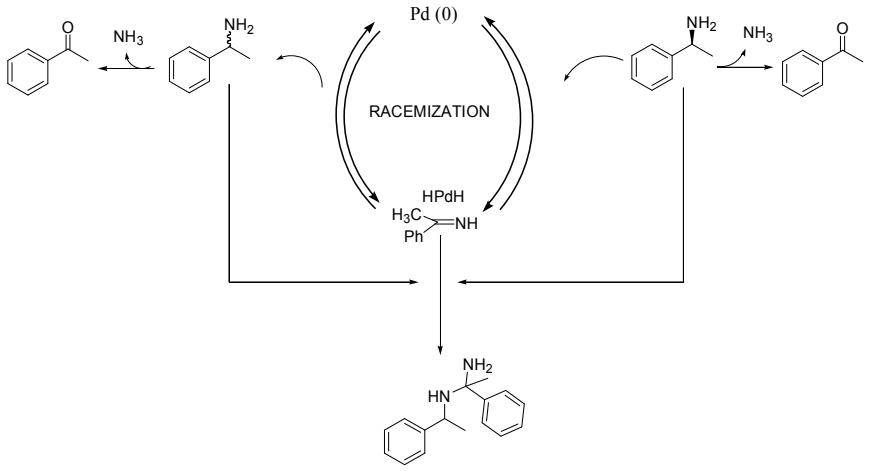


Figure 1. : The racemization cycle and the by-products observed in the Dynamic Kinetic resolution of **1**.

In such context, the use of continuous flow technology can offer some solutions to the above mentioned scenario, as it allows one to conduct the racemization and lipase-catalyzed kinetic resolution in different compartments leading to the maximization of both transformations, independently. However, this approach has not been fully exploited since only few examples of DKR of amines under continuous flow conditions have been reported.[10]

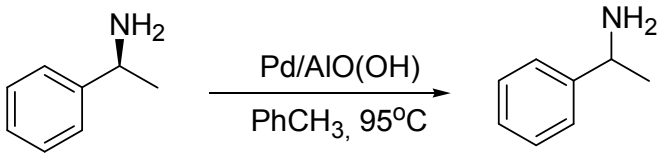
In the present work we describe the use of ammonium formate as an alternative and greener hydrogen source for Pd-promoted racemization and DKR of (+/-)-α-Methylbenzylamine. To the best of our knowledge, use of ammonium formate in chemoenzymatic dynamic kinetic resolutions has not been reported yet. Additionally, we report our efforts towards the development of a continuous flow dynamic kinetic resolution of (+/-)-α-Methylbenzylamine.

Results and discussion

As reported in the previous paragraphs, racemization represents the most challenging step in the context of DKR of amines. Before moving towards a continuous flow procedure we decided to begin studying the racemization process by screening catalysts and reaction conditions for racemization of (*S*)-(-)-α-Methylbenzylamine (**1**). Our starting point was the work of Kim and co-workers,[11] who reported the preparation of a Pd nanocatalyst supported on AlO(OH) and its use as an efficient catalyst for racemization and DKR of amines, even in the absence of an external source of hydrogen.

With this information in hands we decided to begin with commercially available Pd nanoparticles entrapped in AlO(OH) matrix (Table 1).

Table 1. Racemization of (*S*)-(-)-α-Methylbenzylamine catalyzed by Pd(AlO(OH))



(-) -1 (+/-) 1

Entry	Amount of catalyst (mol %)	t (h)	Sel. (%)[a]	*e.e.* (%)
1	1	5	88	>99
2	5	1	73	93
3	5	3	19	2

a: See experimental section for details

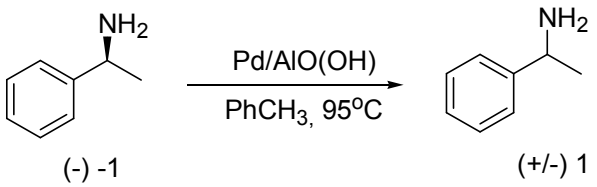
As depicted in Table 1, commercial Pd nanocatalyst entrapped in aluminum hydroxide matrix was not able to racemize (*S*)-(-)- α-Methylbenzylamine with acceptable selectivity when no source of hydrogen was used. However, complete racemization was achieved after 3h with catalyst loading of 5 mol% (Entry 3, Table 1).

Under these conditions large amounts of by-products were observed, mainly secondary amine and acetophenone. It is worth mentioning that successful racemization of amines reported by Kim and co-workers 11 was achieved with non-commercial Pd nanocatalyst entrapped in aluminum hydroxide matrix, whose efficiency is affected by the methods of preparation and is related to the size and surface area of nanoparticles.

As pointed out by others, the observed by-products may be due to the building up of concentration of the imine intermediate in the reaction media, which is trapped by the unreacted amine[9a,b;11a]. Molecular hydrogen has been used in Pd promoted racemizations in order to improve efficiency and selectivity.[9a,b;11a] In fact, some racemization of chiral secondary alcohols and most Pd promoted racemization and DKR of amines are carried out under reductive conditions such as a hydrogen atmosphere. However, these protocols also lead to deamination by-products.

In order to circumvent these drawbacks we attempted to use ammonium formate as an alternative hydrogen source (Table 2), since it is cheap, readily available, safe and operationally easier to use in the laboratory compared to a hydrogen atmosphere.

Table 2. Racemization of (*S*)-(-)-α-Methylbenzylamine catalyzed by Pd(AlO(OH) with ammonium formate.



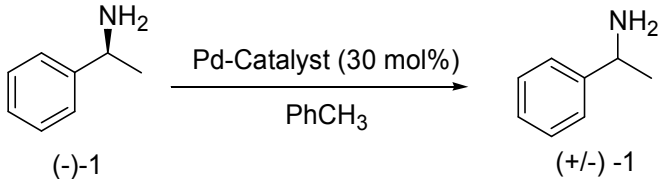
Entry	*Catalyst (mol %)*	Ammonium Formate (eq.)	t(h)	Sel (%)	*ee* (%)
1	1	0.5	5	76	55
2	1	1.0	5	78	42
3	1	1.0	5	90	61
4	1	1.5	5	92	42
5	1	3.0	5	94	87
6	1	5.0	5	88	95
7	5	1.0	1	75	32
8	5	1.0	3	34	1

As depicted in Table 2, addition of ammonium formate improved racemization rate and selectivity. Addition of 0.5 and 1.0 equivalent of ammonium formate (entries 1 and 2, Table 2) led to lower enantiomeric excess with higher selectivity when compared to the results in its absence (Table 1, Entries 1 and 2). When catalyst loading of 5 mol% was used, an *ee* of 32% was observed after only 1h (Table 2, Entry 7) and complete racemization was observed after 3h (Table 2, entry 8), though large amounts of by-products arose.

On the other hand, increasing the amount ofammonium formate to 3 or 5 eq. did not improve efficiency or selectivity (entries 5 and 6, Table 2). This result is in agreement with previous works of Parvulescu and co-workers [9b]. These authors reported that when they used hydrogen as the reducing agent, high *ee* in Pd catalyzed racemizations are observed, probably by suppressing imine formation.

The nature of the support is known to strongly affect both the activity and selectivity of heterogeneous Pd catalysts in racemization reactions.[9b,c] Thus, in the search for a more selective reaction, we decided to study other heterogeneous Pd catalysts, such as $Pd/BaSO_4$, which has been reported to be useful for amine racemization reactions.[9b] These data are present in table 3.

Table 3. Racemization of (*S*)-(-)-α-Methylbenzylamine catalyzed by different palladium sources with ammonium formate.

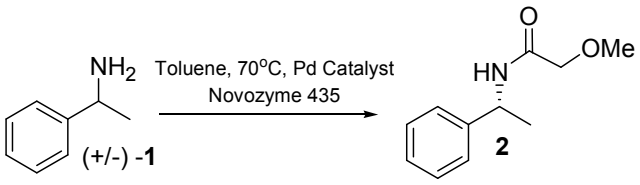


Entry	Catalyst	T (°C)	Ammonium Formate (eq.)	t (h)	Sel (%)	*ee* (%)
1		95	0	12	88	>99
2		95	1.5	3	76	2
3		70	1.5	2.5	96	3
4	$Pd/BaSO_4$	70	1.0	2.5	90	0
5		70	1.5	2.5	89	24
6		70	1.5	5	83	6
7	$Pd/CaCO_3$	70	1.5	2.5	76	2
8	Pd/C	70	1.5	2.5	17	1

The effect of adding ammonium formate was found to be greater for racemization catalyzed by Pd on $BaSO_4$ than for Pd nanocatalyst entrapped in AlO(OH). When the former was used without any source of hydrogen no racemization occurred even after 12h (entry 1, Table 3), even with catalyst loading as high as 30 mol%. On the other hand, almost complete racemization was achieved after only 3h in the presence of ammonium formate (entry 2, Table 3), thus indicating a fundamental role of this reductant in the racemization process. Decreasing temperature improved selectivity (entry 3, Table 3), leading to an *ee* of 3% after 2.5 h with loss of only 4% of amine. Decreasing catalyst loading resulted in longer reaction time and lower selectivity (entry 5 and 6, Table 3). Complete racemization was also achieved when $Pd/CaCO_3$ and Pd/C were used as catalyst, but selectivity was only moderate for the former (Table 3, Entry 7) and very poor for the latter (Table 3, Entry 8).

The next step comprehended in chemoenzymatic dynamic resolution involving combining the lipase kinetic resolution mediated by Novozyme 435 and the ammonium formate-assisted racemization process reported above. In spite of the good results obtained for the racemization reaction, dynamic kinetic resolution gave conversions lower than expected even for kinetic resolution after 12h (see experimental section), as depicted in Table 4 (entries 1 to 3). The results obtained when reactions were performed in a closed vessel system, led us to suppose that the ammonium formate needed for the racemization process could be inhibiting lipase, perhaps through the NH_3 or CO_2 released in the course of the reaction.

Table 4. Dynamic kinetic resolution of (+/-)-α-Methylbenzylamine catalyzed by Novozyme 435, $Pd/BaSO_4$ and ammonium formate as green hydrogen source.



Entry	$Pd/BaSO_4$ (mol%)	NOV 435 (mg/mmol)	Reaction Time (h)	**2** (%)	*ee* (%)
1	10	94	12	37	92
2	30	94	12	31	90
3	30	188	12	43	92
4	30	94	12	94	99

By changing the reaction system to a closed vessel linked with a gas bubbler we could successfully perform DKR with 30 mol% of $Pd/BaSO_4$, 1.5 eq. of ammonium formate and methyl methoxyacetate as acyl donor with conversions of 94% and *ee* of 99% after 12h (Table 4, Entry 4). The remaining amine was detected in about 3% and other 3% was identified as byproduct (see experimental section for details). Interestingly, low conversion (65%) was obtained when the DKR was performed with 10 mol% of $Pd/BaSO_4$, even with reaction time as long as 21h and using a gas bubbler (see experimental section for details).

With the optimized DKR conditions, we moved to the design of a continuous-flow system based on a kinetic resolution using packed bed reactors containing immobilized lipases, as already published by our group.[12] Performing the kinetic resolution step under continuous flow conditions in a different compartment from the racemization step would allow it to be run at room temperature and in shorter reaction

time, thus avoiding enzyme activity decrease due to high temperature required for the racemization step.

In order to deal with the low solubility of ammonium formate and the heterogeneous palladium catalyst in the reaction conditions developed for the racemization process, we decided to use a loop-like reactor. This set-up, depicted in figure 2, presents some important features that can help to deal with the difficulties mentioned above. In this set-up, the suspended solids are kept outside the flow reactor with the use of an appropriate filter, allowing the catalysts to remain separated during the entire process, under independent conditions applied in each step (kinetic resolution and racemization). Conversion and enantiomeric excess were each monitored until 10 hours of reaction in the loop system and the results are presented in Table 5.

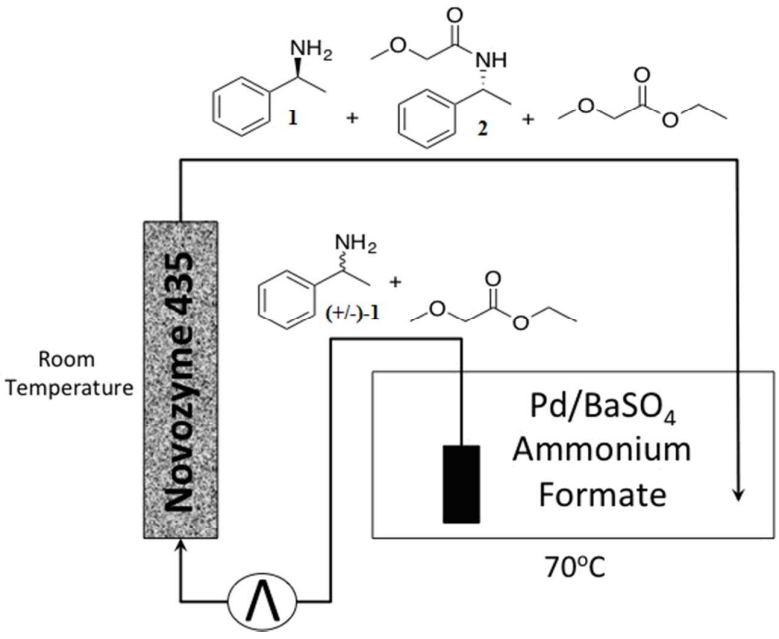


Figure 2. Schematic of the loop continuous flow reactor for the DKR of **1**

Table 5. Dynamic kinetic resolution of (+/-)-α-Methylbenzylamine catalyzed by Novozyme 435, $Pd/BaSO_4$ and ammonium formate as green hydrogen source, under semi-continuous flow conditions.

Entry	Reaction Time (h)	**2** (%)	*ee* (%)
1	2.5	53	99
2	4.5	64	97
3	7	68	96
4	8	76	96
5	10	77	95

Dynamic kinetic resolution of (+/-)-α-Methylbenzylamine (**1**) could be performed with commercially available palladium catalyst under continuous flow conditions, leading to good conversion and high *e.e.* after 10h (entry 5, Table 10). It is important to note that from 4.5 hours of reaction to 10 hours (Table 5, Entries 2 to 5) a small increase in conversion is observed without affecting enantiomeric excess of the product. Although the continuous flow process herein reported still requires further improvement, it is important to stress that to the best of our knowledge this is the first report of dynamic kinetic resolution of amines under continuous flow conditions.

Conclusion

In conclusion, a new method for dynamic resolution of (+/-)-α-Methylbenzylamine has been developed by the using commercially available $Pd/BaSO_4$ as racemization catalyst and ammonium formate as an alternative and greener reducing agent, leading to the desired product in excellent conversion and optical purity. The developed

conditions were then applied in a loop-like continuous flow system where moderate conversion and excellent enantiomeric excess were obtained. The results presented here can help to expand the scope of dynamic resolution of (+/-)-α-Methylbenzylamine by compartmentalization of chemical and biocatalyzed steps under continuous flow, overcoming the drawbacks found in DKRs performed in batch mode, such as incompatibility of conditions required for the racemization and enzymatic steps.

Experimental Section

1.1. General:

Toluene was purchased from Vetec and distilled over 3 Å molecular sieves before use. (+/-)-α-Methylbenzylamine was purchased from Sigma-Aldrich and distilled and stored under argon atmosphere. (*S*)-(-)-α–Methylbenzylamine was purchased from Fluka, Methyl 2-methoxyacetate was purchased from Sigma-Aldrich and both were used as received. Immobilized *Candida antarctica* lipase B (Novozyme 435) was purchased from Novozymes and used as received. All Pd catalysts and ammonium formate were purchased from Sigma-Aldrich and used as received.

Reactions under continuous flow were performed using an Asia system which consists of a syringe pump, a solid phase glass column reactor (d = 1.0000 cm^2) with adjustable ends and pipes equipped with filter. All equipment was purchased from Syrris.

Chiral GC analysis was performed on a Shimadzu GC-2010 chromatograph equipped with a FID, an AOC-20i autosampler and a chiral CP-Chirasil-Dex CB (25 m X 0.25 mm ID) or a chiral β-Dex325 (30 m X 0.24 mm ID) column using hydrogen as carrier gas. Injector and detector temperatures were set at 220 °C. GC-FID temperature program for 1-Methylbenzylamine (**1**) using β-Dex325 column: 90°C | 30 min → 180°C, 40°C/min |10 min. GC-FID temperature program for α-Methylbenzylamine (**1**) using CP-Chirasil-Dex CB column: 90°C | 30 min → 180°C, 40°C/min |10 min. GC-FID temperature program for 2-methoxy-*N*-(1-phenylethyl)acetamide (**2**) using CP-Chirasil-Dex CB column: 105°C | 9 min → 180°C, 140 °C/min | 10 min. GC-MS analysis were performed on a Shimadzu GC-MS-QP2010 Plus chromatograph mass spectrometer equipped with an AOC-20i autosampler and a 5-(Phenyl)Methylpolysiloxane Quadrex (29.6 m X 0.25 mm ID) column using Helium as carrier gas.. Injector temperature was set at 250 °C. GC-MS temperature program: 60°C | 2 min → 280°C, 20 °C/min | 15min.

Conversion in the DKR experiments was determined according to the following formula: [(α-Methylbenzylamine peak area at specified reaction time/internal standard peak area)/(α-Methylbenzylamine peak area before reaction/internal standard peak area)]X100.

Selectivity in the racemization experiment was determined according to the following formula:

$$\%S = [(\mathbf{Amba}t_n \,/\, \mathbf{Ais}t_n) \,/\, (\mathbf{Ambat_0} \,/\, \mathbf{Aist_0})] \times 100$$

Ambat_n is the peak area of α-Methylbenzylamine of a sample collected at the reaction time t_n.

Aist1 is the peak area of internal standard a sample collected at the reaction time t_n.
Ambat$_0$ is the peak area of α-Methylbenzylamine of a sample collected before the beginning of the reaction.
Aist$_0$ is the peak area of internal standard in a of a sample collected before the beginning of the reaction.1.2. Synthesis of (+/-)-2-methoxy-*N*-(1-phenylethyl)acetamide (**2**):

A solution of racemic (+/-)-α-Methylbenzylamine (0.24 mmol) and methyl 2-methoxyacetate 0.96 mmol) in toluene (3 mL) was stirred at 70°C for 24h. The reaction media was washed with a 10% aqueous solution of HCl and dried over Na_2SO_4. An aliquot of 300 μL was collected, diluted in 700 μL of toluene and directly analyzed by GC-MS spectrometer and used for optimization of chiral GC-FID temperature program

1.3 General procedure for racemization reactions

Racemization reactions were performed in toluene (3 mL) with (*S*)- (–)–α-Methylbenzylamine (39 uL, 0.32 mmol), palladium catalyst (see tables 1 and 2), Na_2CO_3 (12 mg), molecular sieves (375 mg), ammonium formate (see table) and biphenyl (30 mg) as internal standard. Reactions were carried out in 4 mL vials heated at 70°C or 95°C in silicon carbide plates. Aliquots of 300 μL were collected, diluted in toluene to 1.0 mL and analyzed after derivatization with 5 μL of trifluoracetic

anhydride and 5 μL of triethylamine. Enantiomeric excesses were determined by GC equipped with a chiral column.

1.4 Kinetic resolution of *(+/-)*-α-Methylbenzylamine

Kinetic resolution reactions were performed in toluene (3 mL) with *rac*- α-Methylbenzylamine (39 μL, 0.32 mmol), methyl 2-methoxyacetate (68 μL, 0.64 mmol), molecular sieves (375 mg), Na_2CO_3 (12 mg), immobilized *Candida antarctica* lipase B (NOV 435, 30 mg, 94 mg/ mmol of substrate) and ammonium formate (see table). Reactions were carried out in closed 4 mL vials heated at 70 °C in silicon carbide plates. Aliquots of 300 μL were collected, diluted in toluene to 1.0 mL and analyzed by GC directly for *ee* of product (ee_p). The *ee* of substrate (ee_s) was determined by GC after derivatization with 5 μL of trifluoracetic anhydride and 5 μL of triethylamine. Conversion was calculated as $C = ee_s/(ee_s + ee_p)$.

1.5 Dynamic kinetic resolution of *rac*- α–Methylbenzylamine.

Dynamic kinetic resolutions were performed in toluene (3mL) wtih (+/-)-α-Methylbenzylamine (39 uL, 0.3 mmol), 5% Pd supported on $BaSO_4$ (se table 4), molecular sieves (375 mg), Na_2CO_3 (12 mg), ammonium formate (30 mg, 1.5 eq), NOV435 (30 or 60 mg; 94 or 188 mg/ mmol of substrate), methyl methoxyacetate (68 μL, 0.6 mmol) and biphenyl (30 mg) as internal standard. Reactions were carried out in closed 4 mL vials (equipped or not with a gas bubbler) heated at 70 °C in silicon carbide plates. Aliquots of 300 μL were collected and diluted in toluene to 1.0 mL for analysis. Enantiomeric excesses were determined by GC equipped with a chiral column. A GC-MS was used to identify by-products and to determine the relative

amount of (+/-)-α-Methylbenzylamine, 2-methoxy-*N*-(1-phenylethyl)acetamide and reaction byproducts.

1.6 Dynamic resolution under continuous flow conditions.

A solution of *rac*- α–Methylbenzylamine (390 μL, 3.2 mmol) and methyl 2-methoxyacetate (640 μL, 6.4 mmol) in toluene (15 mL) was poured into an Erlenmeyer containing Pd/$BaSO_4$ (900 mg, 0.48 mmol of Pd), Na_2CO_3 (60 mg) and molecular sieves (1.875 g) at room temperature and connected to a bed packet reactor filled with NOV435 (700 mg; volume = 1.9635 cm^3) through a pipe equipped with a filter. The solution was pumped through the bed packet reactor at a rate of 250 $\mu L.min^{-1}$ (corresponding to residence time of 7.9 min.) at room temperature. After 70 minutes ammonium formate (150 mg, 1.6 mmol) was added to the Erlenmeyer, which was heated to 70°C while the bed packet reactor filled with NOV435 remained at room temperature. The solution was allowed to flow through the closed system composed of the bed packet reactor and Erlenmeyer for 10h. Aliquots of 300 μL were collected and diluted in toluene to 1.0 mL for analysis. Enantiomeric excesses were determined by GC equipped with a chiral column. A GC-MS was used to identify by-products and to determine the relative amount of (+/-)-α-Methylbenzylamine, 2-methoxy-*N*-(1-phenylethyl)acetamide and reaction byproducts.

Keywords: Dynamic kinetic resolution • racemic amines • continuous flow . ammonium formate

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