JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

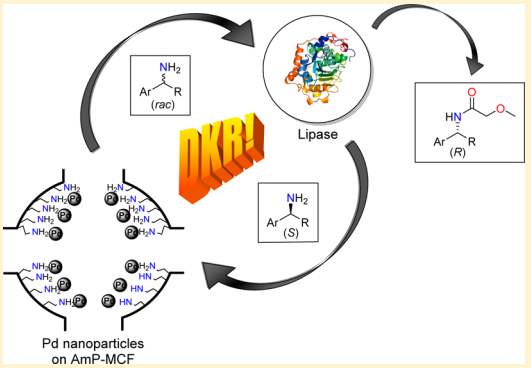
Chemoenzymatic Dynamic Kinetic Resolution of Primary Amines Using a Recyclable Palladium Nanoparticle Catalyst Together with Lipases

Karl P. J. Gustafson, Richard Lihammar, Oscar Verho, Karin Engström, and Jan-E. Bäckvall*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

Supporting Information

ABSTRACT: A catalyst consisting of palladium nanoparticles supported on amino-functionalized siliceous mesocellular foam (Pd-AmP-MCF) was used in chemoenzymatic dynamic kinetic resolution (DKR) to convert primary amines to amides in high yields and excellent ee's. The efficiency of the nanocatalyst at temperatures below 70 °C enables reaction conditions that are more suitable for enzymes. In the present study, this is exemplified by subjecting 1-phenylethylamine (**1a**) and analogous benzylic amines to DKR reactions using two commercially available lipases, Novozyme-435 (*Candida antartica* Lipase B) and Amano Lipase PS-C1 (lipase from *Burkholderia cepacia*) as biocatalysts. The latter enzyme has not previously been used in the DKR of amines because of its low stability at temperatures over 60 °C. The viability of the heterogeneous Pd-AmP-MCF was further demonstrated in a recycling study, which shows that the catalyst can be reused up to five times.



INTRODUCTION

During the past three decades, a significant part of synthetic organic chemistry has been dedicated toward the development of new and efficient methods for the preparation of enantiomerically enriched compounds. Many of these methods utilize chiral catalysts in the enantiodetermining step, thereby increasing the reaction efficiency and minimizing the amount of reagents required.[1] A common way to prepare enantiomerically enriched molecules is to utilize the chiral environment of an enzyme in a kinetic resolution.[2] In this process, the enzyme catalyzes the chemical transformation of one enantiomer faster than that of its mirror image, resulting in a separation of the two enantiomers. The drawback of this process is that the yield of the enantiomerically enriched product can never exceed 50%. An excellent way to circumvent this limitation is to carry out the kinetic resolution in parallel with an in situ racemization, thus creating a dynamic kinetic resolution (DKR), theoretically increasing the yield up to 100% of a single product enantiomer.[3] The enzymes employed are usually immobilized onto a solid support to increase stability, whereas the racemization is often catalyzed by homogeneous transition metal complexes. An attractive way to make the process more environmentally friendly and to enhance the recyclability is to attach the racemization catalysts to a heterogeneous support. Recently, heterogeneous metal nanoparticles have attracted considerable attention as they have been found to be highly efficient and selective catalysts for a wide range of organic transformations.[4] It has been demonstrated that the selectivity and reactivity exhibited by the nanoparticles are dependent on the size and shape of the particles as well as the type of support to which the particles are attached.[4c,d] Many different supports have been used for catalytic applications such as metal oxides,[5] metal organic frameworks (MOFs),[6] carbon-based polymers,[7] and silicas.[8] Within the last group mentioned, siliceous mesocelluar foam (MCF) has shown to be an excellent material for supporting metal nanoparticles, enzymes, and various heterogeneous complexes.[9] The MCF has a three-dimensional morphology with large pores and a high surface area. In addition, the material possesses a high surface concentration of silanol groups that enables grafting with a variety of functional groups in a straightforward fashion.[9]

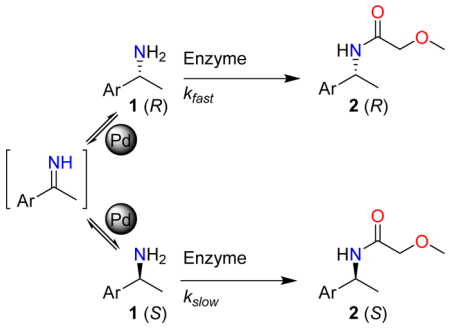
Recently, we have reported on an amino-functionalized MCF as a support for Pd nanoparticles and demonstrated several applications of this nanocatalyst.[10] For instance, the Pd nanocatalyst was found to efficiently racemize primary amines at low temperatures,[10a] which generally has been an issue with previously reported transition metal-based protocols. In the latter protocols elevated temperatures are required for racemization to occur at a useful rate.[11] The necessity of increased temperatures in the DKR has so far limited the use of enzymes to essentially thermostable lipases such as *Candida antarctica* Lipase A and B (CALA and CALB, respectively), where the latter is by far the most utilized owing to its high selectivity and activity.[12] Moreover, it has been shown that the formation of byproducts increases at elevated temperatures, mainly as a consequence of undesired side reactions with the sensitive imine intermediate that is formed during the course of

Received: March 3, 2014
Published: April 11, 2014

   dx.doi.org/10.1021/jo500508p | J. Org. Chem. 2014, 79, 3747−3751

the racemization (cf. Scheme 1). The imine intermediate can easily undergo hydrolysis to the corresponding ketone or self-condense with another molecule of amine to form a secondary amine. The secondary amine can then further react under reductive conditions, yielding the starting material and ethylbenzene.[11]

Scheme 1. Illustration of an (*R*)-Selective Dynamic Kinetic Resolution of Primary Benzyl Amines Using Palladium Nanoparticles as Racemization Catalyst and a Methoxyacetate Ester as Acyl Donor



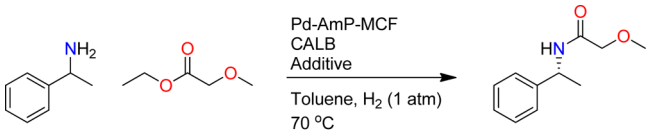
To date, only a few enzyme-compatible metal complexes exist that are capable of racemizing amines.[12a,13] Among these complexes, a homogeneous dimeric ruthenium hydride complex is still to date the most versatile catalyst for the DKR of amines.[12a,13a] However, the protocol required elevated temperatures (90 °C and higher), diluted reaction conditions, and suffered from long reaction times (3 days).[12a,13a] Kim and Park developed a nanostructured palladium catalyst supported on Al(O)OH that was optimized to perform the racemization at lower temperatures than the ruthenium catalyst; however, dilute reactions conditions and long reaction times were still required.[13b,c] By applying our recently developed Pd-AmP-MCF as racemization catalyst in a chemoenzymatic DKR, we envision addressing these drawbacks and allowing the use of less thermostable enzymes.

RESULTS AND DISCUSSION

To find the optimal reaction conditions, 1-phenylethylamine (**1a**) was selected as the model substrate and subjected to a DKR at 70 °C using CALB as resolving agent, 2 equiv of ethyl methoxyacetate (**3**) as acyl donor,[14] 2.5 mol % of Pd-AmP-MCF as racemization catalyst, and 1 equiv of Na_2CO_3 in dry toluene under H_2 atmosphere (1 atm). The DKR was found to proceed smoothly and resulted in 63% conversion after 24 h (Table 1, entry 1). By concentrating the reaction from 0.15 to 0.4 M, the efficiency of the DKR was significantly increased (entry 2), reaching completion after 16 h. To our delight, we were able to isolate amide **2a** in quantitative yield with no sign of byproduct formation. The most significant improvement was observed upon addition of molecular sieves (4 Å) to the reaction as this reduced the reaction time to 6 h (entry 3). Moreover, it proved to be possible to reduce the loading of the Pd nanocatalyst to 1.25 mol % and still maintain high yields and excellent enantioselectivity of the desired amide **2a** (entry 4). To the best of our knowledge, this is the lowest catalyst loading (Pd and CALB) ever used for these short reaction times in the DKR of primary amines.

Inspired by the efficient DKR at 70 °C, we set out to optimize the protocol to also provide a functioning DKR reaction at 50 °C. To maintain an efficient racemization even at this temperature, 5 mol % of Pd-MCF was used. Both molecular sieves and Na_2CO_3 could be used as additives to give full conversions and excellent ee's; however, the latter showed slightly higher ee (Table 2, entries 1 and 2). A control experiment on **1a**, where CALB was omitted, showed that molecular sieves caused a slow background amidation which could explain the lower ee obtained when the reaction time is prolonged.[15] When the amount of Pd nanocatalyst was reduced from 5 to 2.5 mol %, the reaction still gave **2a** in 99% ee but required a longer reaction time (36 h) to reach completion (entry 3). The possibility to run the reactions at lower temperatures also enables a broader range of enzymes to be used in the DKR, which potentially could widen the substrate scope. This novel feature was demonstrated by employing Amano Lipase PS-C1 (lipase from *Burkholdera cepacia*

Table 1. Optimization of the DKR of 1a at 70 °C[a]

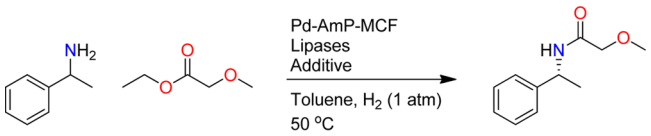


1a 3 2a

entry	Pd-loading (mol %)	additive	time (h)	toluene (mL)	conv[b] (%)	ee[c] (%)
1	2.5	Na_2CO_3 (1 equiv)	24	4	63	99
2	2.5	Na_2CO_3 (1 equiv)	16	1.5	99	99
3	2.5	mol sieves 4 Å	6	1.5	99	99
4	1.25	mol sieves 4 Å	6	1.5	99	99

[a]All reactions were carried out in dry toluene (1.5 mL) under 1 atm of hydrogen gas using **1a** (0.6 mmol), **3** (1.2 mmol), Novozyme-435 (CALB, 15 mg), molecular sieves (300 mg) or Na_2CO_3 (60 mg), and pentadecane as internal standard. [b]Determined using chiral GC and pentadecane as internal standard. [c]Determined using by chiral GC (99 ± 0.02)

Table 2. Optimization of the Reaction at 50 °C and Evaluation of Two Different Lipases[a]



1a 3 2a

entry	Pd-loading (mol %)	additive	time (h)	lipase	conv[b] (%)	ee[c] (%)
1	5	mol sieves 4 Å	24	CALB	99	98
2	5	Na_2CO_3 (1 equiv)	24	CALB	99	99
3	2.5	Na_2CO_3 (1 equiv)	36	CALB	99	99
4[d]	5	Na_2CO_3 (1 equiv)	36	Lipase PS	82[e]	99

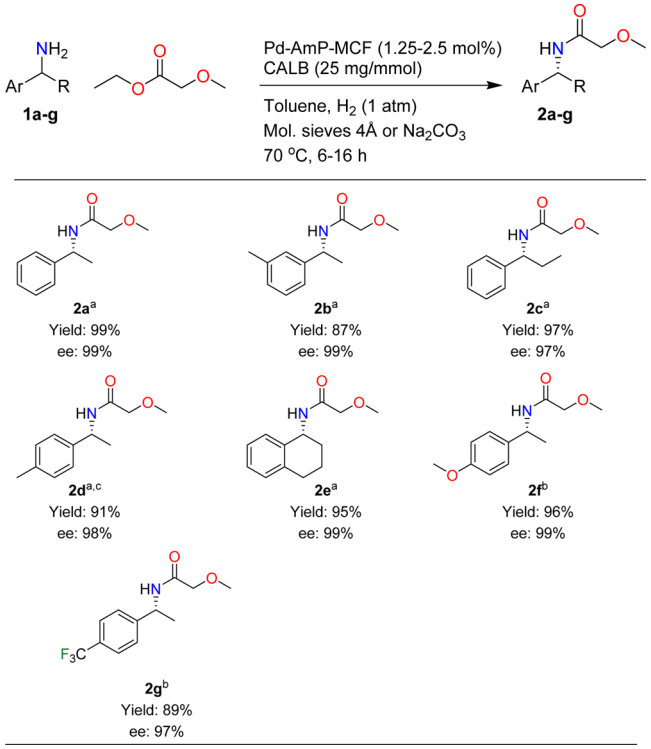
[a]All reactions were carried out in dry toluene (1.5 mL) under 1 atm of hydrogen gas using **1a** (0.6 mmol), **3** (1.2 mmol), Novozyme-435 (CALB, 15 mg), molecular sieves (300 mg) or Na_2CO_3 (60 mg), and pentadecane as internal standard. [b]Determined using chiral GC and pentadecane as internal standard. [c]Determined by chiral GC (98 ± 0.02; 99 ± 0.02). [d]The reaction was carried out in dry toluene (2 mL) under 1 atm hydrogen gas using **1a** (0.6 mmol), **3** (1.2 mmol), Amano Lipase PS-C1 (200 mg), and dry Na_2CO_3 (60 mg). [e]Isolated yield.

dx.doi.org/10.1021/jo500508p | J. Org. Chem. 2014, 79, 3747−3751

immobilized on ceramic beads) in a DKR with 5 mol % of Pd-AmP-MCF which afforded **2a** in a good isolated yield and excellent ee (entry 4).[16] This enzyme has previously been used in the kinetic resolution of **1a**, but to the best of our knowledge, this is the first example of a DKR of amines using this biocatalyst.[17]

After we established the optimized protocols for the DKR at 70 and 50 °C, a set of substrates were studied in the reaction at 70 °C (Table 3). Four benzylic amines substituted with

Table 3. Substrate Scope of the DKR at 70 °C Using Pd-AmP-MCF as Racemization Catalyst

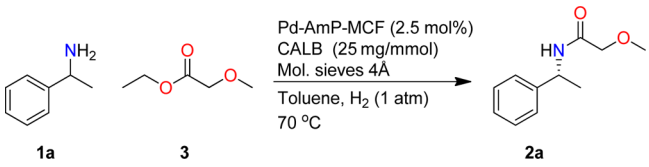


[a]Method A: Reaction was performed in dry toluene (1.5 mL) under 1 atm of hydrogen gas using Pd-AmP-MCF (10 mg, 1.25 mol %), amine **1** (0.6 mmol), ethyl methoxyacetate (1.2 mmol), Novozyme-435 (15 mg), and molecular sieves (300 mg). [b]Method B: Reaction was performed in dry toluene (1.5 mL) under 1 atm hydrogen gas using Pd-AmP-MCF (20 mg, 2.5 mol %), amine **1** (0.6 mmol), ethyl methoxyacetate (1.2 mmol), Novozyme-435 (15 mg), and dry Na_2CO_3 (60 mg). [c]2.0 mol % of racemization catalyst was used.

aliphatic substituents were chosen, and were all converted into their corresponding enantiomerically enriched amides in high yields as well as excellent ee's (**2a**–**d**). Bicyclic tetrahydronaphthyl compound **2e** was also isolated in close to quantitative yield and perfect ee. For the heteroatom-substituted benzyl amines **1f** and **1g** the molecular sieves needed to be exchanged for Na_2CO_3, and the catalyst loading was increased to 2.5 mol % in order to avoid unwanted background amidation. Substrate **1f** bearing an electron-donating substituent worked excellently, while **2g**, with an electron-withdrawing substituent, was obtained in slightly lower yield (89%) but still high ee. The amount of Pd nanocatalyst used in these DKR reactions with reasonably short reaction times is lower than previously reported for these compounds, and the reactions are made at a substrate concentrations of 0.4 M, which is significantly higher than those previously reported.[11]

Finally, the stability of the heterogeneous Pd nanocatalyst was assessed in a recycling study where the DKR of **1a** was carried out under the optimized conditions with 2.5 mol % of Pd nanocatalyst over five cycles. The DKR was allowed to continue for 15 h after which the Pd-AmP-MCF was separated, washed, and used in a new DKR reaction. In this recycling, the catalytic system showed excellent conversion and ee until the fifth run where the conversion dropped to 90% and the ee was 98% (see Table 4).[18]

Table 4. Recycling of the Catalyst in the DKR[a]



cycle	conv[b] (%)	ee[b] (%)
1	99	99
2	99	99
3	98	99
4	99	99
5	90	98

[a]All reactions were carried out in dry toluene (1.5 mL) under 1 atm of hydrogen gas at 70 °C using **1a** (0.6 mmol), **3** (1.2 mmol), Novozyme-435 (15 mg), molecular sieves 4 Å (300 mg), and pentadecane as internal standard. [b]Determined using chiral GC and pentadecane as internal standard. For error in ee, see Table 2.

In summary, we have developed a protocol for the DKR of primary benzylic amines using a recyclable catalyst consisting of palladium nanoparticles immobilized on siliceous amino-functionalized mesocellular foam. It was found that the DKR proceeds well at both 70 and 50 °C and that a range of benzylic amines can be used as substrates. The DKR reactions with these relatively short reaction times were carried out with much lower catalytic loading than previously reported. To our delight, we could also demonstrate the first successful application of lipase PS in the DKR of amines. Future efforts will aim at incorporating other lipases and proteases in the present protocol. Work will be dedicated to further improving the performance of the racemization part of the DKR reaction by developing related nanostructured catalysts.

EXPERIMENTAL PROCEDURES

General Methods. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. GC analysis was made either on a system equipped with a CP-Chirasil-DEX CB column (25 m × 0.32 mm × 0.25 μm) with H_2 as a carrier gas or IVADEX-I column (25 m × 0.25 mm × 0.25 μm) with N_2 as carrier gas. Both GCs had a gas flow of 1.8 mL/min and were equipped with FID detectors. The high-resolution mass spectra (HRMS) were recorded on an ESI-TOF mass spectrometer. 1-Phenylethylamine **1a** was distilled and stored on molecular sieves before use. The remaining chemicals were purchased from commercial sources and used without further purification. Dry toluene was obtained from a VAC-solvent purifier. Flash chromatography was performed on an automated flash machine equipped with a UV detector using 12 g silica columns (particle size 40–63 μm irregular, mesh size 230–400, pore size 60 Å) with a solvent flow of 30 mL/min. Reactions were monitored by thin-layer chromatography (TLC) using aluminum-backed plates (1.5 Å, 5 cm) precoated (0.25 mm) with silica gel and UV light for visualization. The Pd-AmP-MCF was synthesized according to previously described methods.[10b] CALB

dx.doi.org/10.1021/jo500508p | J. Org. Chem. 2014, 79, 3747–3751

(Novozyme-435) and Lipase PS (Amano Lipase PS-C1) are available from commercial sources.

General Procedure for the Dynamic Kinetic Resolution. Method A: Pd-AmP-MCF (1.25−5 mol %, 10−40 mg), drying agent [method A: molecular sieves 4 Å (300 mg); method B: dry Na_2CO_3 (60 mg)] and Novozyme-435 (15 mg) were added to a vial equipped with a magnetic stirring bar and sealed with Teflon cap. The vial was evacuated three times and refilled with hydrogen gas. Dry toluene (1.5 mL) was added to the vial, and then the system was evacuated followed by refilling with hydrogen gas. The mixture was heated to the indicated temperature followed by addition of ethyl methoxyacetate (141 μL, 1.2 mmol) and amine substrate (0.6 mmol) while being stirred at 750 rpm. After reaching completion, the reaction was diluted with ethyl acetate and washed with saturated sodium bicarbonate and brine. The organic phase was dried using Na_2SO_4, filtered, and concentrated in vacuo. Purification was carried out using column chromatography.

Procedure for Dynamic Kinetic Resolution with Lipase PS. Pd-AmP-MCF (5 mol %, 40 mg), dry Na_2CO_3 (60 mg), and Amano lipase PS-C1 (200 mg) were added to a vial and sealed. The vial was evacuated three times and refilled with hydrogen gas. Dry toluene (2.0 mL) was added to the vial, and the system was evacuated followed by refilling with hydrogen gas. The mixture was heated to 50 °C followed by addition of ethyl methoxyacetate (141 μL, 1.2 mmol) and amine **1a** (0.6 mmol) while being stirred at 750 rpm. Additional ethyl methoxyacetate (70 μL, 0.6 mmol) was added after 12 and 24 h. After 36 h, the reaction was diluted with ethyl acetate and washed with saturated sodium bicarbonate and brine. The organic phase was dried using Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 100:0 → 0:100) to give 95 mg (82%) of a white solid in 99% ee.

Procedure for Recycling of the Pd-MCF Catalyst. Pd-AmP-MCF (2.5 mol %, 20 mg), molecular sieves 4 Å (300 mg) and Novozyme-435 (15 mg) were added to a vial and sealed; the vial was evacuated three times and refilled with hydrogen gas. Dry toluene (1.5 mL) and internal standard pentadecane were added to the vial, which was then evacuated followed by refilling of hydrogen gas. The mixture was heated to 70 °C followed by addition of ethyl methoxyacetate (141 μL, 1.2 mmol) and amine **1a** (0.6 mmol). After 15 h, the reaction was analyzed using chiral GC, and the catalyst was separated using a pipet and washed in a separate tube using 4.5 mL of toluene and centrifuged (4100 rpm for 8 min). Excess toluene was removed, and the procedure was repeated three times. The catalyst was dried under vacuum overnight before use, and the procedure was repeated.

*(R)-2-Methoxy-N-(1-phenylethyl)acetamide (**2a**).* The reaction was performed according to method A using 1.25 mol % of Pd-AmP-MCF. The product was isolated after column chromatography (SiO_2, pentane/EtOAc 100:0 → 0:100) and afforded 115 mg (99%) as a white solid in 99% ee. Experimental data were in accordance with those previously reported.[13b] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38−7.23 (m, 5H), 6.75 (br s, 1H), 5.23−5.14 (m, 1H), 3.95−3.84 (m, 2H), 3.40 (s, 3H), 1.52 (d, 3H, J = 7.1 Hz). Chiral GC separation: CP-Chirasil-DEX CB column 125−3 °C/min to 160 °C, t_{R1} = 11.9 min (S), t_{R2} = 12.3 (R) min.

*(R)-2-Methoxy-N-(1-m-tolylethyl)acetamide (**2b**).* The reaction was performed according to method A using 1.25 mol % of Pd-AmP-MCF. The product was isolated after column chromatography (SiO_2, pentane/EtOAc 100:0 → 0:100) and afforded 108 mg (87%) as a white solid in 99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.26−7.21 (m, 2H), 7.15−7.06 (m, 2H), 6.73 (br s, 1H), 5.20−5.10 (m, 1H), 3.95−3.84 (m, 2H), 3.40 (s, 3H), 2.35 (s, 3H), 1.50 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.6, 143.1, 138.5, 128.7, 128.3, 127.1, 123.2, 72.1, 59.2, 48.2, 22.1, 21.6. Chiral GC separation: IVADEX-I column 145−2 °C/min to 200 °C, t_{R1} = 13.7 min (S), t_{R2} = 14.1 (R) min. HRMS (ESI): calcd for [M + Na] $C_{12}H_{17}NO_2Na$ 230.1151, found 230.1143; $[\alpha]^{25}_D$ = +99.5 (c 0.2, $CHCl_3$), 99% ee.

*(R)-2-Methoxy-N-(1-phenylpropyl)acetamide (**2c**).* The reaction was performed according to method A using 1.25 mol % of Pd-AmP-MCF. The product was isolated after column chromatography (SiO_2, pentane/EtOAc 100:0 → 0:100) to give 120 mg (97%) as a white solid in 97% ee. Experimental data were in accordance with those previously reported.[13b] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37−7.24 (m, 5H), 6.75 (br s, 1H), 4.96−4.89 (m, 1H), 3.96−3.83 (m, 2H), 3.41 (s, 3H), 1.90−1.81 (m, 2H), 0.90 (t, 3H, J = 7.4 Hz). Chiral GC separation: IVADEX-I column 140−1 °C/min to 200 °C, t_{R1} = 12.8 min (S), t_{R2} = 13.0 (R) min.

*(R)-2-Methoxy-N-(1-p-tolylethyl)acetamide (**2d**).* The reaction was performed according to method A using 1.25 mol % of Pd-AmP-MCF. The product was isolated after column chromatography (SiO_2, pentane/EtOAc 100:0 → 0:100) to give 113 mg (91%) as a white solid in 98% ee. Experimental data were in accordance with those previously reported.[13b] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.24−7.13 (m, 4H), 6.71 (br s, 1H), 5.20−5.10 (m, 1H), 3.95−3.83 (m, 2H), 3.39 (s, 3H), 2.33 (s, 3H), 1.50 (d, 3H, J = 7.2 Hz). Chiral GC separation: CP-Chirasil-DEX CB column 125−3 °C/min to 160 °C, t_{R1} = 14.5 min (S), t_{R2} = 14.8 (R) min.

*(R)-2-Methoxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (**2e**).* The reaction was performed according to method A using 1.25 mol % of Pd-AmP-MCF. The product was isolated after column chromatography (SiO_2, pentane/EtOAc 100:0 → 0:100) to give 125 mg (95%) as a white solid in 99% ee. Experimental data were in accordance with those previously reported.[13b] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.28−7.25, (m, 1H), 7.20−7.16 (m, 2H), 7.13−7.09 (m, 1H), 6.75 (br s, 1H), 5.28−5.20 (m, 1H), 3.95 (s, 2H), 3.39 (s, 3H), 2.89−2.72 (m, 2H), 2.14−2.02 (m, 1H), 1.90−1.78 (m, 3H). Chiral GC separation: CP-Chirasil-DEX CB column 125−20 °C/min to 150−0.5 °C/min to 163 °C, t_{R1} = 18.5 min (S), t_{R2} = 18.9 (R) min.

*(R)-2-Methoxy-N-(1-(4-methoxyphenyl)ethyl)acetamide (**2f**).* The reaction was performed according to method B using 2.5 mol % of Pd-AmP-MCF. The product was isolated after column chromatography (SiO_2, pentane/EtOAc 100:0 → 0:100) in 129 mg (96%) as a white solid in 99% ee. Experimental data were in accordance with those previously reported.[13b] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29−7.22 (m, 2H), 6.91−6.84 (m, 2H), 6.69 (br s, 1H), 5.19−5.09 (m, 1H), 3.94−3.83 (m, 2H), 3.79 (s, 3H), 3.39 (s, 3H) 1.50 (d, 3H, J = 6.8 Hz). Chiral GC separation: IVADEX-I column 140−1 °C/min to 200 °C, t_{R1} = 21.8 min (S), t_{R2} = 22.3 (R) min.

*(R)-2-Methoxy-N-(1-(4-(trifluoromethyl)phenyl)ethyl)acetamide (**2g**).* The reaction was performed according to method B using 2.5 mol % of Pd-AmP-MCF. The product was isolated after column chromatography (SiO_2, pentane/EtOAc 100:0 → 0:100) in 140 mg (89%) as a white solid in 97% ee. Experimental data were in accordance with those previously reported.[13b] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.59 (d, 2H, J = 8.3 Hz), 7.43 (d, 2H, J = 8.3 Hz), 6.77 (br s, 1H), 5.24−5.17 (m, 1H), 3.95−3.85 (m, 2H), 3.42 (s, 3H), 1.53 (d, 3H, J = 7.0 Hz) Chiral GC separation: IVADEX-I column 145−2 °C/min to 200 °C, t_{R1} = 10.6 min (S), t_{R2} = 11.4 (R) min.

■ ASSOCIATED CONTENT

Supporting Information

Investigation of the background chemical amidation, ^{1}H NMR of **2a**−**f** and ^{13}C NMR of **2b**, as well as GC chromatograms of compound **2a**-**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jeb@organ.su.se.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Berzelii Center EXSELENT, the European Research Council (ERC AdG 247014), the Knut and Alice Wallenberg Foundation, and the Swedish Research Council is gratefully acknowledged. We thank Dr. Mozaffar Shakeri for carrying out preliminary experiments of this study.

REFERENCES

(1) Ding, K.; Uozumi, Y. *Handbook of Asymmetric Heterogeneous Catalysis*; Wiley-VCH: Weinheim, 2008.

(2) (a) Polaina, J.; McCabe, A. P. *Industrial Enzymes Structure, Function and Applications*; Springer: Berlin, 2007. (b) Houde, A.; Kademi, A.; LeBlanc, D. *Appl. Biochem. Biotechnol.* **2004**, *118*, 155. (c) Faber, K. *Biotransformations in Organic Chemistry*, 4th ed.; Springer: Berlin, 2000.

(3) For recent reviews, see: (a) Kamal, A.; Azhar, M. A.; Krishnaji, T.; Malik, M. S.; Azeeza, S. *Coord. Chem. Rev.* **2008**, *252*, 569. (b) Marcos, R.; Martín-Matute, B. M. *Isr. J. Chem.* **2012**, *52*, 639.

(4) (a) Astruc, D.; Lu, F.; Aranzes, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 7852. (b) Somorjai, G. A.; Park, J. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 9212. (c) An, K.; Somorjai, G. A. *ChemCatChem* **2012**, *4*, 1512. (d) Chng, L. L.; Erathodiyil, N.; Ying, J. Y. *Acc. Chem. Res.* **2013**, *46*, 1825.

(5) (a) Hulea, V.; Dumitriu, E. *Nanomaterials in Catalysis*, 1st ed.; Serp, P., Phillopot, K., Eds.; Wiley-VCH: Weinheim, 2013; p 375. (b) Barakat, T.; Rooke, J. C.; Tidahy, H. L.; Hosseini, M.; Cousin, R.; Lamonier, J.-F.; Giraudon, J.-M.; De Weireld, G.; Su, B.-L.; Siffert, S. *ChemSusChem* **2011**, *4*, 1420.

(6) Jiang, H.-L.; Xu, Q. *Chem. Commun.* **2011**, *47*, 3351.

(7) Su, D. S. *Nanomaterials in Catalysis*, 1st ed.; Serp, P., Phillipot, K., Eds.; Wiley-VCH: Weinheim, 2013; p 331.

(8) (a) Luque, R.; Balu, A. M.; Campelo, J. M.; Garcia, M. D.; Losada, E.; Pineda, A.; Romero, A. A.; Serrano-Ruiz, J. C. *Catalysis* **2012**, *24*, 253. (b) Taguchi, A.; Schüth, F. *Microporous Mesoporous Mater.* **2005**, *77*, 1.

(9) (a) Schmidt-Winkel, P.; Lukens, W. W., Jr.; Yang, P.; Margolese, D. I.; Lettow, J. S.; Ying, J. Y.; Stucky, G. D. *Chem. Mater.* **2000**, *12*, 686. (b) Taguchi, A.; Schüth, F. *Microporous Mesoporous Mater.* **2005**, *77*, 1. (c) Erathodiyil, N.; Ooi, S.; Seayad, A. M.; Han, Y.; Lee, S. S.; Ying, J. Y. *Chem.—Eur. J.* **2008**, *14*, 3118. (d) Shakeri, M.; Engström, K.; Sandström, A.; Bäckvall, J.-E. *ChemCatChem* **2010**, *2*, 534. (e) Ping, E. W.; Wallace, R.; Pierson, J.; Fuller, T. F.; Jones, C. W. *Microporous Mesoporous Mater.* **2010**, *132*, 174. (f) Ping, E. W.; Pierson, J.; Wallace, R.; Miller, J. T.; Fuller, T. F.; Jones, C. W. *Appl. Catal., A* **2011**, *396*, 85. (g) Na-Chiangmai, C.; Tiengchan, N.; Kittisakmontree, P.; Mekasuwandurong, O.; Powell, J.; Panpronot. *Catal. Lett.* **2011**, *141*, 1149.

(10) (a) Shakeri, M.; Tai, C.-W.; Göthelid, E.; Oscarsson, S.; Bäckvall, J.-E. *Chem.—Eur. J.* **2011**, *17*, 13269. (b) Johnston, E. V.; Verho, O.; Kärkäs, M. D.; Shakeri, M.; Tai, C.-W.; Palmgren, P.; Eriksson, K.; Oscarsson, S.; Bäckvall, J.-E. *Chem.—Eur. J.* **2012**, *18*, 12202. (c) Engström, K.; Johnston, E. V.; Verho, O.; Gustafson, K. P. J.; Shakeri, M.; Tai, C.-W.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2013**, *52*, 14006. (d) Verho, O.; Nagendiran, A.; Johnston, E. V.; Tai, C.-W.; Bäckvall, J.-E. *ChemCatChem.* **2013**, *5*, 612. (e) Verho, O.; Nagendiran, A.; Tai, C.-W.; Johnston, E. V.; Bäckvall, J.-E. *ChemCatChem.* **2014**, *6*, 205. (f) Deiana, L.; Jiang, Y.; Palo-Nieto, C.; Verho, O.; Johnston, E. V.; Córdova, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 3447.

(11) Kim, Y.; Park, J.; Kim, M.-J. *ChemCatChem* **2011**, *3*, 271.

(12) Example using CALB as biocatalyst: (a) Thalén, L. K.; Zhao, D.; Sortais, J.-B.; Paetzold, J.; Hoben, C.; Bäckvall, J.-E. *Chem.—Eur. J.* **2009**, *15*, 3403. Example using CALA as biocatalyst: (b) Engström, K.; Shakeri, M.; Bäckvall, J.-E. *Eur. J. Org. Chem.* **2011**, *10*, 1827. Example using *Candida rugosa* as biocatalyst: (c) Stirling, M.; Blacker, J.; Page, M. I. *Tetrahedron Lett.* **2007**, *48*, 1247.

(13) (a) Paetzold, J.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 17620. (b) Kim, M.-J.; Kim, W.-H.; Han, K.; Kyung Choi, Y.; Park, J. *Org. Lett.* **2007**, *9*, 1157. (c) Kim, Y.; Park, J.; Kim, M.-J. *Tetrahedron Lett.* **2010**, *51*, 5581. (d) Parvulescu, A. N.; Jacobs, D. E.; De Vos, D. E. *Chem.—Eur. J.* **2007**, *13*, 2034. (e) Parvulescu, A. N.; Jacobs, D. E.; De Vos, D. E. *Appl. Catal., A* **2009**, *255*, 206. (f) Han, K.; Kim, Y.; Park, J.; Kim, M.-J. *Tetrahedron Lett.* **2010**, *51*, 3536. (g) Geukens, I.; Plessers, E.; Jin Won, S.; De Vos, D. E. *Eur. J. Inorg. Chem.* **2013**, *14*, 2623. (h) Qianru, J.; Guoqing, J.; Yanmei, Z.; Can, L. *Catal. Sci. Technol.* **2014**, *4*, 464.

(14) Balkenhohl, F.; Ditrich, K.; Hauer, B.; Ladner, W. *J. Prakt. Chem.* **1997**, *339*, 381.

(15) See the Supporting Information.

(16) Running the same reaction at 70 °C for 36 h gave **2a** with only 92% ee.

(17) Varma, R.; Kasture, S. M.; Gaikwad, B. G.; Nene, S.; Kalkote, U. R. *Asian J. Biochem.* **2007**, *2*, 279−283.

(18) Elemental analysis of the reaction mixture for the first three cycles revealed that the leaching of palladium in the first two cycles was negligible (<0.2 ppm) and in the third cycle it was 1.8 ppm. The latter number is still very low and corresponds to only 0.15% of the total palladium amount used in the reaction.