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Stereoselective Transformations of α-Trifluoromethylated Ketoximes to Optically Active Amines by Enzyme–Nanometal Cocatalysis: Synthesis of (*S*)-Inhibitor of Phenylethanolamine N-Methyltransferase

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One-pot cascade synthesis of optically active α-trifluoromethylated amines directly from ketoximes was accomplished with the use of *Candida antarctica* lipase B and catalysts prepared by atomic layer deposition (ALD). Compared to the commercial palladium catalyst, the ALD-prepared catalysts showed much higher activity and afforded various α-trifluoromethylated amides in good yields and with high enantioselectivity. One of the enantiopure amides was further hydrolyzed into the corresponding amine, which was treated as a crucial starting material for total synthesis of (*S*)-inhibitor of phenylethanolamine N-methyltransferase without loss of chiral information.

Introduction

Trifluoromethyl-containing compounds have attracted growing attention in various fields because the introduction of the trifluoromethyl group having powerful electron-withdrawing ability often leads to special physical, chemical, and biological properties.[1] α-Trifluoromethylated amines, especially the optically active ones, are very important building blocks in the synthesis of fluorinated pharmaceuticals, particularly in the design of bioactive products.[2] For example, inhibitors of phenylethanolamine N-methyltransferase (PNMT) exhibit interesting biological activity owing to the privileged chiral synthons of α-trifluoromethylated amines, and the synthetic routes of PNMT inhibitors have been reported; however, their enantiomers were separated only by chiral HPLC.[3]

To the best of our knowledge, rare reports have referred to chemoenzymatic synthesis of chiral α-trifluoromethylated amines especially by dynamic kinetic resolution (DKR). As the racemization rate of α-trifluoromethylated amines is very slow owing to the formation of a hydrogen bond between CF_3 and NH_2, which leads to difficult achievement of equilibrium between amine and imine. Recently, we have developed an elegant chemoenzymatic resolution of α-trifluoromethylated amines through a one-pot sequential process of KR/DKR/KR with palladium and lipase as the catalysts.[4] Although moderate conversions were obtained, the reaction time was very long (10 days). In addition, the methods related to DKR required a start from racemic amines, which are difficult to be synthesized and purified. Kim and co-workers reported that optically active amines could be transformed from ketoximes,[5] however, these reports did not involve trifluoromethylated amines and there was no consideration of hydrogen pressure in the reaction, which is the most critical reaction factor. Herein, we envisioned that optically active α-trifluoromethylated amines could be synthesized directly from ketoximes.

This work was focused on the design of an efficient catalyst for both hydrogenation of ketoximes and racemization of the following amines with the α-trifluoromethyl group. Atomic layer deposition (ALD) was used to prepare highly dispersed metal nanoparticles (NPs) for this study. ALD is a layer-by-layer process[6] and has received increasing attention for the preparation of metal NPs, such as Pt and Pd.[7] Owing to their high cohesive energy, metal NPs tend to form through an island growth mechanism (Volmer–Weber mechanism) during the initial stages of ALD processes, and metal NPs can be highly dispersed on porous catalyst substrates. Thermostable *Candida antarctica* lipase B (CALB; trade name, Novozym 435) was chosen as the catalyst for resolution (Scheme 1).

Results and Discussion

Metal nanocatalysts synthesized by ALD

With ten cycles of Pd ALD on r-alumina, the Pd content is 0.95 wt% based on inductively coupled plasma analysis combined with mass spectrometry (ICP-MS). The coated particles were visualized with a JEOL 2010F 200 kV Schottky field emis-

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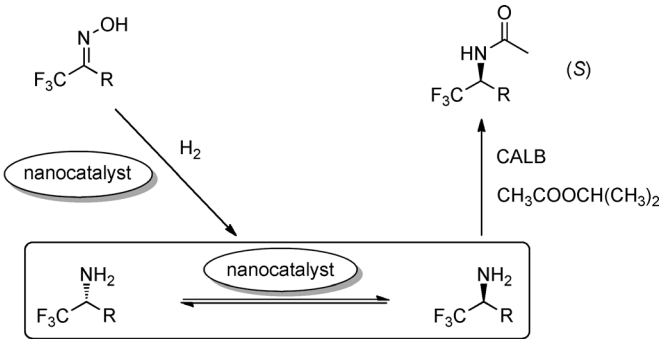


Scheme 1. Lipase–nanometal cocatalyzed transformations of α-trifluoromethylated ketoximes to optically active amides.

sion transmission electron microscope equipped with an Oxford detector unit for elemental analysis while imaging. In Figure 1 a one STEM image of cross-sectioned surface of r-alumina deposited with Pd NPs is shown . Pd NPs are clearly visible as white dots and are highly dispersed on the inside porous structure as well as on the outside surface of the particle substrate. The Pd NPs produced exhibit a narrow particle size distribution with an average particle size of approximately 3 nm diameter. Similar highly dispersed metal NPs were obtained by Ni ALD. After one cycle of Ni ALD, the content of Ni on r-alumina and silica gel is 1.59 wt% and 0.73 wt%, respectively. In Figure 1 b, one HRTEM image of Ni NPs dispersed on 20–30 nm silica particles is shown. The average Ni NP size is approximately 2.5 nm.

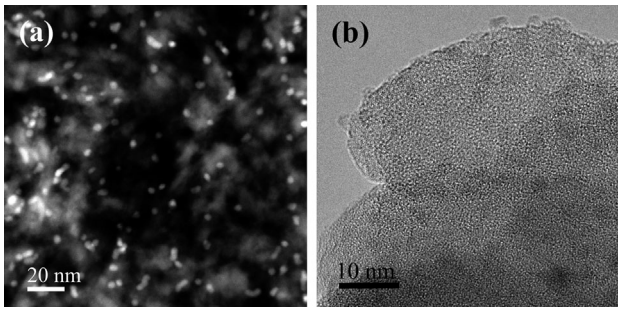
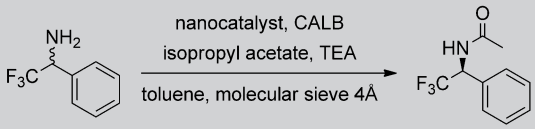


Figure 1. a) Cross-sectioned STEM image of Pd ALD-deposited Al_2O_3 particles and b) high-resolution TEM image of Ni ALD-deposited SiO_2 particles.

Dynamic kinetic resolution of α-trifluoromethylated amines

The dynamic kinetic resolution of α-trifluoromethylated amine (*rac*-**1 a**) was studied as a model substrate with the ALD NP catalysts and the commercially available Pd/Al_2O_3 that was studied in our previous report.[4] The conversion of α-trifluoromethylated amine **1 a** and the selectivity to the corresponding amide for different catalysts are listed in Table 1. The results indicate that almost all ALD catalysts have much higher activity than the conventional Pd/Al_2O_3 catalyst even at low temperature (entry 4) or during short reaction time (entry 2). The reason for the high reactivity of ALD catalysts could be ascribed to the highly dispersed metal NPs and uniform particle size. This set of experiments indicates that both palladium and nickel on Al_2O_3 as the basic support could be suitable for DKR of *rac*-**1 a**. However, nickel on acid support such as silica gel gave only low conversion (entry 6), which could be caused by the deactivation of the enzymatic resolution catalyst or hydrolysis of the acyl donor. The influence of the catalyst substrates was in accordance with what was discovered by Parvulescu and co-workers.[8]

Table 1. Dynamic kinetic resolution of α-trifluoromethylated amine **1 a**.



rac-**1a** (*S*)-**3a**

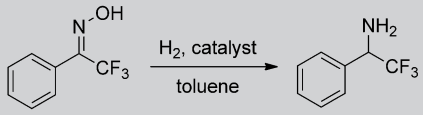
Entry[a]	Catalyst	*T* [°C]	*t* [d]	Conv. [%][b]	ee_{amide} [%][c]
1	commercial Pd/Al_2O_3	70	7	70	99
2	ALD Pd/Al_2O_3	70	5	88	99
3	ALD Pd/Al_2O_3	70	7	91	99
4	ALD Pd/Al_2O_3	60	7	84	99
5	ALD Ni/Al_2O_3	70	5	87	99
5	ALD Ni/Al_2O_3	70	7	92	99
6	ALD Ni/silica gel	70	5	75	99

[a] Reaction conditions: substrate *rac*-**1 a** (0.1 mmol), IPAC (0.5 mmol), TEA (0.2 mmol), CAL-B (50 mg), and nanocatalyst (0.002 mmol) in dry toluene (1 mL) in the presence of 4 Å molecular sieve (100 mg). [b] Determined by GC using AT·SE-30 column. [c] Determined by GC using chiral column.

Hydrogenation of α-trifluoromethylated ketoximes

A hydrogenation study on ketoxime **2 a** was then conducted in dry toluene with different catalysts. According to the data reported by Kim and co-workers,[5b] asymmetric reductive acyla-

Table 2. Hydrogenation of α-trifluoromethylated ketoxime **2 a**.



2a *rac*-**1a**

Entry[a]	Catalyst	H_2 [MPa]	*T* [°C]	*t* [h]	Conv. [%][b]
1	commercial Pd/Al_2O_3	2.00	100	48	96
2	ALD Pd/Al_2O_3	0.10	100	48	99
3	ALD Pd/Al_2O_3	0.10	70	48	99
4	ALD Pd/Al_2O_3	0.10	70	48	99
5	ALD Pd/Al_2O_3	0.10	70	36	98
6	ALD Pd/Al_2O_3	0.05	70	48	87
7	ALD Ni/Al_2O_3	0.10	70	36	98
8	ALD Ni/silica gel	0.10	70	36	95

[a] Reaction conditions: substrate ketoxime **2 a** (0.1 mmol) and nanocatalyst (0.001 mmol) in dry toluene (1 mL) under hydrogen pressure. [b] Determined by GC using AT·SE-30 column.

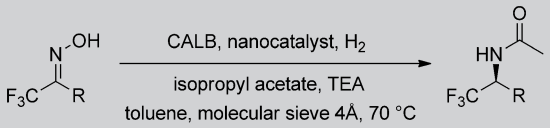
tion of aromatic ketoximes was performed at 1 atm of hydrogen or lower hydrogen pressure. However, at the referred hydrogen pressure (0.1 MPa),[5] no reduction of ketoxime **2a** was observed for the commercial Pd/Al_2O_3 even after 24 h. The inhibitive role for trifluoromethyl group could be attributed to the high negative inductive effect that decreased the electron density on C=N double bond of the ketoximes. Inspired by the conclusion made by Niedermann and co-workers,[9] the hydrogenation pressure was enhanced to 2.0 MPa and the reaction was observed (Table 2, entry 1). In contrast, using ALD catalysts, the hydrogenation reaction was completed within a very short time at 100 °C under 2.0 MPa. To achieve one-pot cascade chemoenzymatic reactions, which are hydrogenation of α-trifluoromethylated ketoximes followed by DKR of the intermediate amines, hydrogen pressure was lowered to 0.1 MPa and complete conversion was obtained (entry 2). The reaction time and temperature were further reduced to match the conditions required for DKR reactions, and the results were also satisfying. The results are consistent with those reported by Parvulescu and co-workers for racemization of chiral amines[8] and our group's previous work for DKR reactions.[4] However, if we further brought down the hydrogen pressure, the reaction was not complete with a significant amount of substrate **2a** left (entry 6). Similar results were obtained for the ALD-deposited nickel NPs on Al_2O_3 or silica gel.

One-pot chemoenzymatic synthesis of optically active α-trifluoromethylated amines

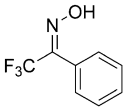
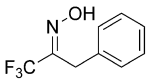
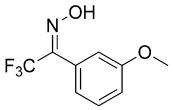
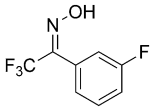
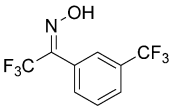
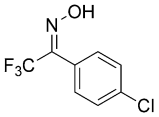
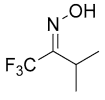
With the results from the separate investigations on the DKR and hydrogenation in hand, the combination in a one-pot cascade chemoenzymatic reaction is feasible. For commercial catalyst Pd/Al_2O_3, hydrogen pressure should be turned down manually for acylation after reductive process. To our satisfaction, with ALD prepared catalysts, hydrogen was consumed during reduction reaction to the appropriate pressure for the following acylation.

With respect to the substrate **2a**, different catalysts were used. The ALD catalysts under optimized conditions afforded the corresponding enantiopure amide (*S*)-**3a** in high yield and excellent *ee* (Table 3, entries 2 and 3). For economic benefit, ALD Ni/Al_2O_3 was chosen and the optimal reaction conditions were also applied to other substrates; the corresponding amides were obtained with good yield (70–95%) and high enantiomeric excess (90–99%, entries 5–7). However, at a hydrogen pressure of 0.1 MPa, lower catalytic activity was observed with relatively poor yield for the substrate **2b**. Therefore, higher pressure (0.15 MPa) and higher temperature (100 °C) were applied to the hydrogenation step (entry 4). With regards to the substrate **1f**, significant side reactions took place in hydrogenation of the ketoxime; therefore, lower pressure and temperature were used (entry 8). The results from Table 3 indicate that both aromatic and aliphatic α-trifluoromethylated ketoximes are good substrates toward the asymmetric reductive acylation by the combination of ALD catalysts and lipase. Notably, the

Table 3. Asymmetric transformations of α-trifluoromethylated ketoximes to chiral amides under optimized conditions.



2a-g (*S*)-**3a-g**

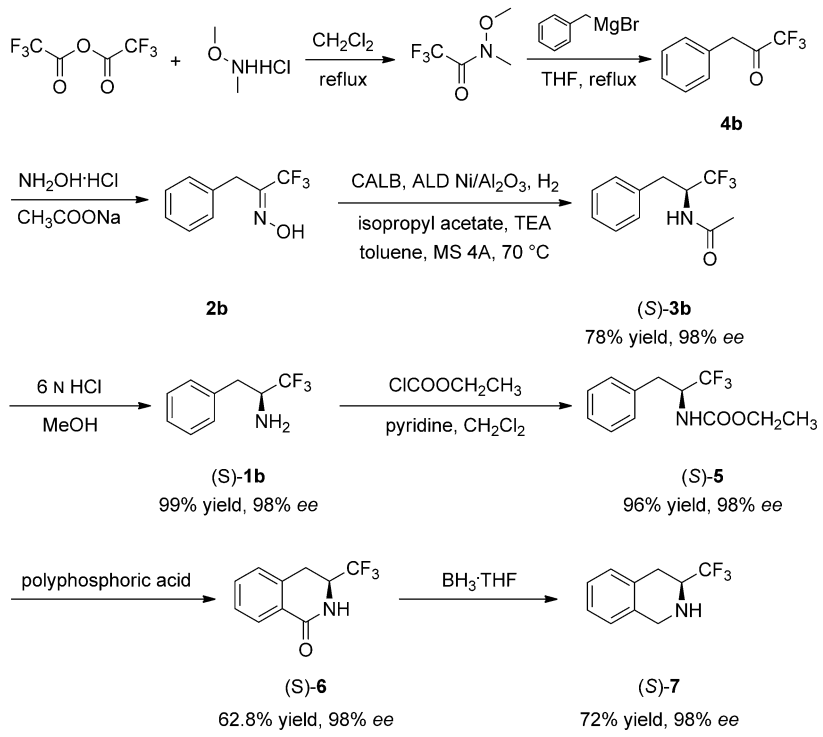
Entry[a]	Substrates		Catalyst	H_2 pressure [MPa] Reduction[b]	Acylation[c]	Yield [%][d]	ee_{amide} [%][e]
1		**2a**	commercial Pd/Al_2O_3	2.00[f]	0.01	62	99
2		**2a**	ALD Pd/Al_2O_3	0.10	0.01	93	99
3		**2a**	ALD Ni/Al_2O_3	0.10	0.01	92	99
4		**2b**	ALD Ni/Al_2O_3	0.15[g]	0.01	78	98
5		**2c**	ALD Ni/Al_2O_3	0.10	0.01	82	98
6		**2d**	ALD Ni/Al_2O_3	0.10	0.01	81	98
7		**2e**	ALD Ni/Al_2O_3	0.10	0.01	70	99
8		**2f**	ALD Ni/Al_2O_3	0.08[h]	0.01	85	99
9		**2g**	ALD Ni/Al_2O_3	0.10	0.01	95	90

[a] Reaction conditions: substrate ketoxime (0.1 mmol), IPAC (0.5 mmol), TEA (0.2 mmol), CAL-B (50 mg) and nanocatalyst (0.001 mmol for reduction, 0.002 mmol for acylation) in dry toluene (1 mL) in the presence of 4 Å molecular sieve (100 mg) at 70 °C. [b] For 36 hr. [c] For 6 days. [d] Determined by GC using AT·SE-30 column. [e] Determined by GC using chiral column. [f] Reduction for 48 hr. [g] Hydrogenation at 100 °C. [h] Hydrogenation at 60 °C.

nature of the substituent on the benzene ring affects the yield. Although a clear rationale is not available to the best of our knowledge, this could be attributable to electronic effect and steric hindrance.

Synthetic applications

The amide products can be readily hydrolyzed to the corresponding optically active α-trifluoromethylated amines, which are extremely useful as chiral building blocks. As a representative example, optically active amide **3b** was hydrolyzed under acidic condition (6 N HCl) to obtain (*S*)-amine **1b** quantitatively without loss of enantiopurity (Scheme 2). Amine **1b** was treated with ethyl chloroformate to form chiral carbamate **5**, which was cyclized with polyphosphoric acid to give lactam (*S*)-**6**. Reduction of the lactam with BH_3·THF produced 3-trifluoromethyl-tetrahydroisoquinoline (*S*)-**7** with 72% yield and 98% *ee*.[3] Notably, the ketoxime was starting from trifluoromethyl ketone, which was formed by the reaction of α-trifluoromethylated Weinreb amide with benzyl Grignard reagent. To our relief, the enantiomeric excess could be maintained at a high level (98% *ee*) during five synthetic steps and the target molecule could be easily separated and purified in the form of hydrochloride salt.



Scheme 2. Synthesis of (*S*)-inhibitor of PNMT starting from the α-trifluoromethylated ketoxime **2b**.

Conclusions

Asymmetrically conversion of prochiral α-trifluoromethylated ketoximes to chiral amides by enzyme–nanometal cocatalysts was demonstrated. Highly dispersed metal nanoparticles were prepared by atomic-layer deposition (ALD) method. Good yields and high enantiomeric excesses were obtained for the ALD-prepared catalysts combined with *Candida Antarctica* lipase B.

The amides could be readily hydrolyzed to optically active amines, which have been used as a crucial chiral synthon to accomplish total synthesis of (*S*)-3-trifluoromethyl-tetrahydroisoquinoline as an important (*S*)-inhibitor of phenylethanolamine N-methyltransferase . Interestingly, (*R*)-inhibitor of phenylethanolamine N-methyltransferase could be obtained in the same way by careful selection of lipase, and alkaline protease as an example is in progress to switch the enantioselectivity of amines.

Experimental Section

Metal nanocatalysts synthesized by ALD

The deposition of Pd and Ni nanoparticles by ALD was performed in a vibrating fluidized-bed reactor, which was similar to the one described in detail previously.[10] Pd ALD was performed at 200 °C by using alternating exposures to Pd^{II} hexafluoroacetylacetonate [Pd-$(hfac)_2$] and formalin (a 37% solution of formaldehyde in water containing 10–15% methanol), which were purchased from Sigma–Aldrich and were used as received. Prior to the Pd ALD, an alumina film with eight cycles of alumina ALD (≈1 nm) was deposited as a buffer or seed layer. The alumina ALD was performed using alternating reactions of trimethylaluminum (TMA, 97%, Sigma–Aldrich) and deionized water at 177 °C. Ni ALD was performed at 300 °C by using alternating exposures to nickelocene and H_2. Porous alumina particles, with a particle size of approximately 50 μm and a surface area of 103.5 $m^2 g^{-1}$, were used as the substrates for Pd and Ni ALD. Silica particles with a particle size of approximately 20–30 nm, and silica gel particles with a particle size of 30–75 μm, an average pore size of 15 nm, and a BET surface area of 240 $m^2 g^{-1}$ were also used as the substrates for Ni ALD. Ten cycles of Pd ALD and one cycle of Ni ALD were applied. The detailed procedures for the Pd[11] and Ni ALD[12] can be found elsewhere.

General procedure for chemoenzymatic transformations of α-trifluoromethylated ketoximes

A suspension containing substrate **2a** (0.1 mmol), isopropyl acetate (IPAC, 0.5 mmol), triethylamine (TEA, 0.2 mmol), CAL-B (50 mg), 1.59 wt% ALD Ni/Al_2O_3 (0.001 mmol) and 4 Å molecular sieve (100 mg) in dry toluene (1 mL) was stirred at 70 °C and 0.1 MPa hy-

drogen pressure in a 50 mL autoclave. After 36 h, another part of 1.59 wt% ALD Ni/Al_2O_3 (0.002 mmol) was added to the autoclave and the hydrogen pressure was declined to 0.01 MPa. Under the optimal conditions, the reaction mixture was stirred for 6 d, and then cooled to RT and filtered. The filtrate was concentrated and analyzed by GC to indicate that all of the substrate was consumed and the yield was 92%. The filtrate was then subjected to GC by using chiral column to confirm the enantiomeric excess of the product (*S*)-**3a** (99% *ee*).

Hydrolysis of the optically active amide 3b to the amine (*S*)-1b

The chiral amide **3b** (92.4 mg, 0.4 mmol), 6 N HCl (1.5 mL), and methanol (1.5 mL) were added to a round-bottomed flask with a reflux condenser, and then agitated together at 80 °C for 15 h. Once the reaction was complete, the mixture was concentrated to remove methanol, and then neutralized with 4 M NaOH, and thereafter extracted with dichloromethane. The organic layers were combined and the solvent was then removed to give (*S*)-amine **1b** (75 mg, 0.396 mmol, 99% yield, 98% *ee*). Thereafter, the optically pure amine **1b** was acted as the starting material for the total synthesis of 3-trifluoromethyl-tetrahydroisoquinoline (98% *ee*) as an important (*S*)-inhibitor of PNMT.

Keywords: amines · enzyme catalysis · fluorine · kinetic resolution · palladium

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