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Mesoporous Niobium Oxide Spheres as an Effective Catalyst for the Transamidation of Primary Amides with Amines

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Abstract: Mesoporous niobium oxide spheres (MNOS), conveniently prepared by a novel antisolvent precipitation approach, have been shown to be an effective catalyst for the transamidation of primary amides with amines. This novel transamidation can be efficiently carried out under solvent-free conditions and is applicable to a wide range of primary amides and amines to provide *N*-alkyl amides in good to excellent yields. The catalyst is highly stable and reusable. The application of this transamidation reaction has been demonstrated in the synthesis of antidepressant drug moclobemide and other drug-like compounds.

Keywords: amides; amines; catalysis; niobium oxide; transamidation

Introduction

The amide bond is one of the most ubiquitous functional groups found in natural products, polymers and pharmaceuticals.[1] Consequently, amide formation has been one of the most studied transformations in organic synthesis. Conventional amide formation involves the use of either carboxylic acid derivatives (acyl halides or anhydrides) or coupling reagents in stoichiometric quantities,[2] resulting in poor atom efficiency and formation of large amount of waste that poses potential environmental problems. These drawbacks have promoted the development of numerous alternative amide formation methods aimed to circumvent the existing problems.[3]

Transamidation of amides with amines under thermal conditions[4] is traditionally considered as an unfavorable method for amide synthesis due to the high reaction temperatures required to break the amide bond. The harsh reaction conditions often cause undesired reactions, especially with functionalized molecules. However, if efficient catalysts could be developed to lower the reaction temperature, transamidation can become an attractive method for amide synthesis as the reaction is simple in operation and atom-efficient, especially for primary amides which form ammonia as the only by-product. These advantages of transamidation have led to a revitalization of the field with several novel methods being recently developed,[5–10] exemplified by the use of organocatalysts [such as boron catalysts,[10c,d,g] $PhI(OAc)_2$,[10f] L-proline,[9] hydroxylamine hydrochloride[7a]] or metal catalysts [such as $Sc(OTf)_3$,[5a,6] $ZrCl_4$,[6] $Yb(OTf)_3$[10b] Cp_2ZrCl_2,[7b] $Cu(OAc)_2$[8] and CeO_2[6]]. Some of us have recently reported that mesoporous niobium oxide spheres (MNOS) are an effective, recyclable and highly stable solid acid catalyst for Friedel–Crafts alkylation and esterification reactions.[11] We envisioned that this solid acid catalyst could potentially catalyze the transamidation reaction which is known to be affected by solid acids such as CeO_2[6] and supported $HfCl_4$.[10e] In our continuing efforts in developing efficient and environmentally benign amide formation methods,[12] we report herein an efficient transamidation of primary amides catalyzed by mesoporous niobium oxide under solvent-free conditions.

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Results and Discussion

Niobium(V) oxide (Nb_2O_5) and its hydrated form ($Nb_2O_5 \cdot n\,H_2O$) are inexpensive and well known solid acids with the latter possessing a strong acidity comparable to that of 70% H_2SO_4.[13f] Consequently, Nb_2O_5 has been used to promote many important reactions, such as esterification, hydration of olefins and epoxides, condensation reactions, biodiesel production etc.[13] However, their application in transamidation has not been reported to date. In our recent work in developing novel materials for green and sustainable chemistry applications, we have established a convenient and cost-effective protocol for a scalable preparation of mesoporous niobium oxide spheres (MNOS) by using an antisolvent precipitation approach.[11] The sulfated mesoporous niobium oxide spheres have been shown to be efficient catalysts for a number of reactions including esterification, Friedel–Crafts alkylation and hydrolysis of esters.[11] To further explore the potential application of the catalyst, we have screened a number of other reactions and were delighted to find that the non-sulfated MNOS effectively catalyzes the transamidation of primary amides. This is particularly noteworthy as the catalyst can be prepared in a more convenient way without the sulfating step and the fact that transamidation is an important reaction of high relevance to pharmaceuticals and fine chemicals.

The mesoporous niobium oxide spheres were prepared from niobium(V) ethoxide according to our reported novel antisolvent precipitation approach using inexpensive diethylene glycol as a template reagent, acetone and water as the solvents.[11] These niobium oxide particles are uniform mesoporous spheres (Figure 1) with 400–500 nm diameters and a specific surface area of 312 $m^2 g^{-1}$ (BET method) which is much larger than that of commercial niobium oxide powder (54 $m^2 g^{-1}$).[10c]

In addition, an ammonia-temperature programmed desorption (NH_3-TPD) determination showed that the prepared Nb_2O_5 spheres (MNOS) had a total acidity (Lewis and Brønsted acids) of 3.23 mmol NH_3/g whereas the commercially available Nb_2O_5 powder essentially showed no ammonia absorption, revealing the great difference in their acidities. The NH_3 desorption profile of MNOS (Figure 2, solid line) showed a broad desorption temperature range (*ca.*

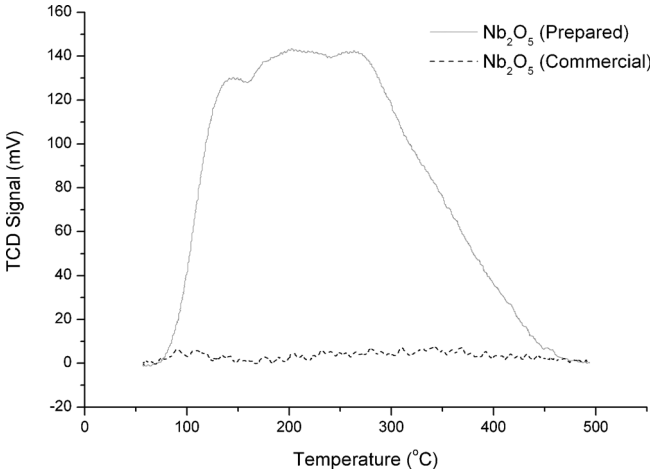

Figure 2. NH_3-TPD (with a thermal conductivity detector) profiles of prepared Nb_2O_5 spheres (MNOS) (solid line) and commercial Nb_2O_5 powder (dashed line).

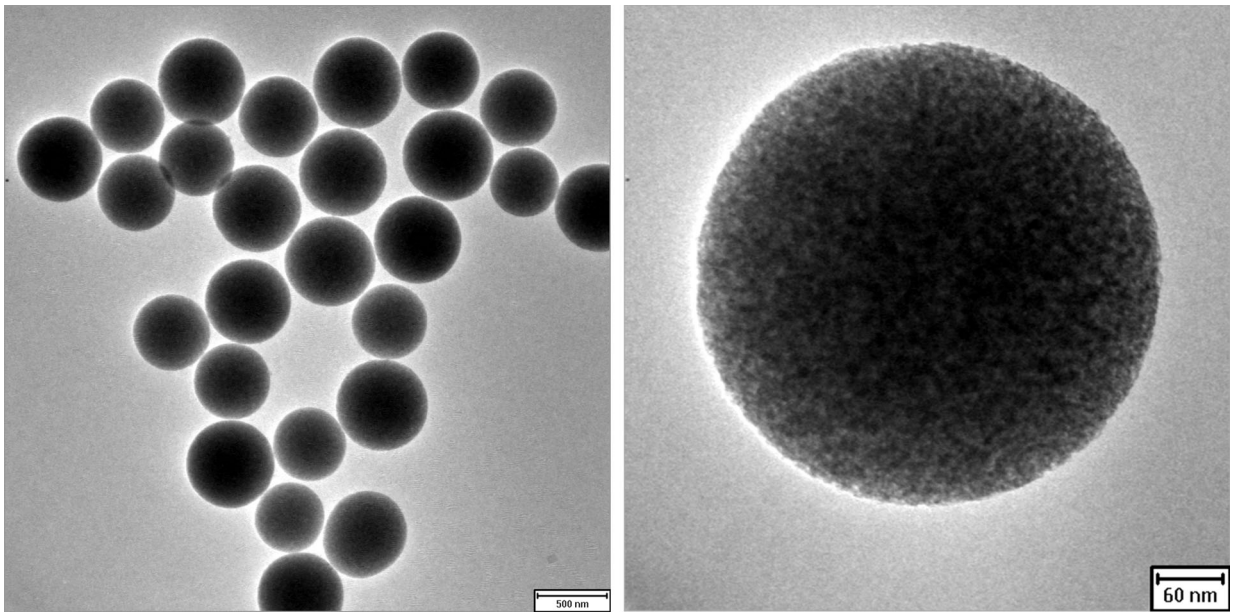

Figure 1. TEM images: (*left*) mesoporous niobium oxide spheres (MNOS) and (*right*) single MNOS particle.[11]

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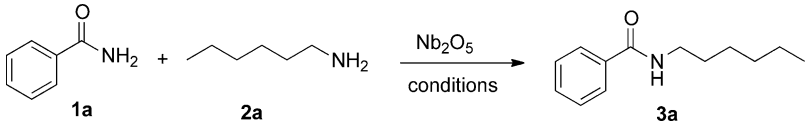
Table 1. Optimization of conditions for the MNOS-catalyzed transamidation of primary amides with amines.[a]



1a 2a 3a

Entry	Catalyst (mol%)	Solvent	Time [h]	Temperature [°C][b]	Yield [%][c]
1	Nb_2O_5 (5)	–	8	140	72
2	Nb_2O_5 (5)	–	24	140	93
3	Nb_2O_5 (1)	–	24	140	65
4	Nb_2O_5 (0.1)	–	24	140	15
5	Nb_2O_5 (5)	toluene	24	140	<5
6	Nb_2O_5 (5)	xylene	24	160	68
7	Nb_2O_5 (5)	mesitylene	24	160	86
8	Nb_2O_5 (5)[d]	–	24	140	10
9	no catalyst	–	24	140	<5

[a] The reactions were carried out with benzamide (1.0 mmol), *n*-hexylamine (2.0 mmol), Nb_2O_5 catalyst (loadings as indicated), under neat conditions (without solvent) or with a solvent (0.4 mL) at the indicated temperature.
[b] External temperature of oil bath.
[c] Yields were determined by quantitative GC analysis using dodecane as an internal standard.
[d] From a commercial source.

100–400 °C), indicating its high concentration of acid sites of moderate strength.[11]

The initial screening reaction of benzamide (**1a**) with *n*-hexylamine (**2a**) provided *N*-hexylbenzamide (**3a**) in 72% yield after 8 h at 140 °C (Table 1, entry 1). With this promising result, conditions for the reaction were optimized (Table 1). While prolonging the reaction time to 24 h improved the yield to 93% (entry 2), reducing the catalyst loading significantly decreased the yield (entries 3 and 4). The use of solvents including toluene, xylene and mesitylene was not beneficial even at higher reaction temperatures (entries 6 and 7). Nb_2O_5 from commercial sources afforded only 10% of the amide product (entry 8) whereas negligible product was formed in the absence of the catalyst (entry 9). These results clearly indicated the crucial role of MNOS in this transamidation reaction.

With the optimized conditions in hand, the substrate scope of this niobium oxide-catalyzed transamidation reaction was explored. This began with the reaction of a range of primary amides with *n*-hexylamine (Table 2). The results showed broad applicability of the reaction to primary amides including benzamides (**1a–1d**), aliphatic (**1e**, **1f**) and heteroaromatic amides (**1g–1i**), providing the corresponding amides in good to excellent yields. In general electron-deficient benzamides (**1a** and **1b**) are more reactive than electron-rich ones (**1c**, **1d**), which correlates well with the nucleophilic nature of the reaction.

The substrate scope was also examined by reacting benzamide (**1a**) with a variety of amines (Table 3). Benzylamines (**2b–2f**), aliphatic primary amines (**2g–2i**) and cyclic secondary amines (**2j–2k**) underwent transamidation smoothly to provide the corresponding amides. Particularly noteworthy is that unprotected amino alcohols (**2h** and **2k**) underwent transamidation without dehydration or transesterification, indicating good chemoselectivity of this MNOS-catalyzed transamidation.

The generality of this MNOS-catalyzed transamidation was further demonstrated in the combination of a variety of primary amides with amines (Table 4). Transamidation of nicotinamide (**1i**) with various amines (**2h**, **2i**, **2l** and **2m**) afforded its *N*-substituted analogues (**3t–3w**), providing a convenient access to this class of pharmaceutically important compounds.[14] The amidation of unsubstituted aliphatic amide (**1f**) proceeded well with various amines (**2c–2f**). However, the reactivity of α-substituted amide (**1j**) was significantly reduced, possibly caused by the steric hindrance which rendered its effective coordination to the catalyst surface. Urea (**1k**) also underwent transamidation with amine (**2n**) to form the substituted urea (**3ac**). The potential application of this MNOS-catalyszd transamidation was demonstrated in the synthesis of moclobemide [Aurorix®; 4-chloro-*N*-(2-morpholin-4-ylethyl)benzamide] which is an antidepressant in clinical use.[15] Thus, reaction of 4-chlorobenzamide (**1b**) with 4-(2-aminoethyl)morpholine (**2m**) under solvent-free conditions provided moclobemide (**3ad**) in 90% yield. This reaction was successfully scaled up to 6 mmol in a shorter reaction time of 12 h. After recovery of the catalyst and removal of excess amine by partition with water, the product (1.38 g 86%) was obtained by convenient crystallization, demonstrating the scalability and practicality of this MNOS-catalyzed transamidation reaction.

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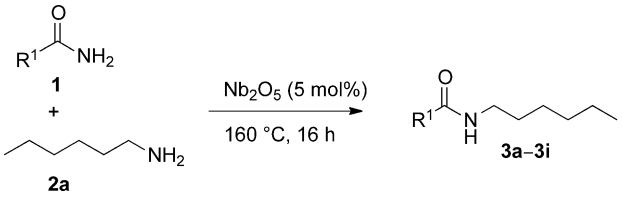
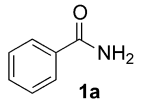
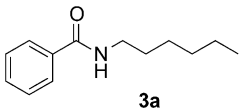
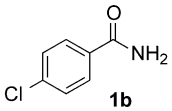
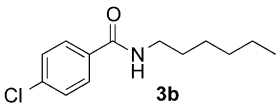
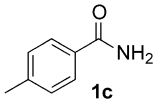
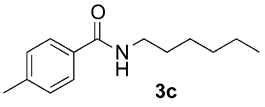
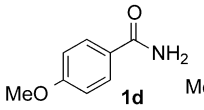
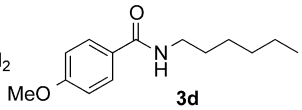
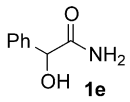
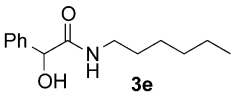
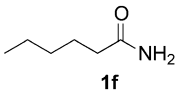
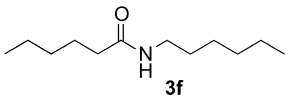
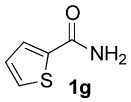
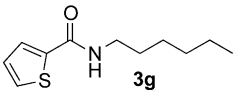
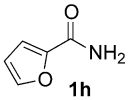
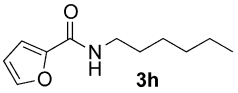
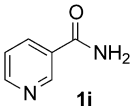
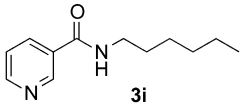
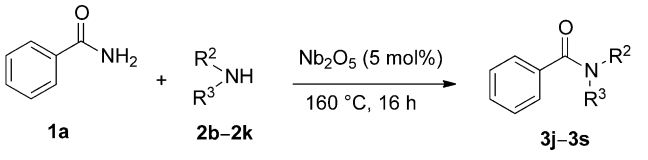
Table 2. MNOS-catalysed transamidation of primary amides with *n*-hexylamine.[a]

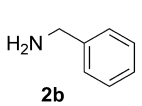
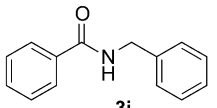
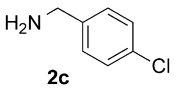
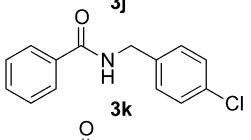
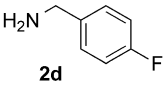
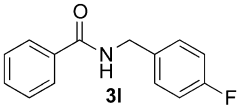
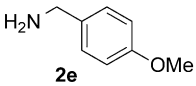
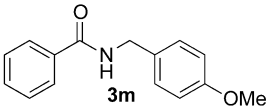
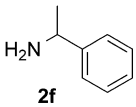
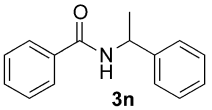
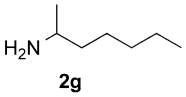
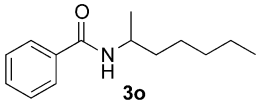
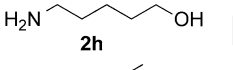
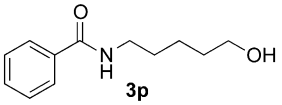
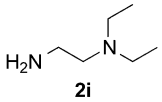
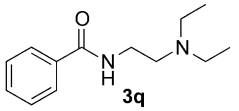
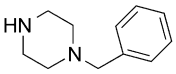
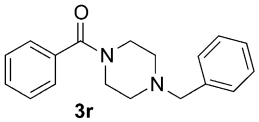
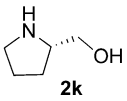
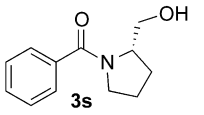


Entry	Primary amide	Product	Yield [%][b]
1	 1a	 3a	92
2	 1b	 3b	96
3	 1c	 3c	76
4	 1d	 3d	73
5	 1e	 3e	74
6	 1f	 3f	90
7	 1g	 3g	78
8	 1h	 3h	94
9	 1i	 3i	90

[a] The reactions were carried out with a primary amide (2.0 mmol), *n*-hexylamine (4.0 mmol), Nb_2O_5 catalyst (26 mg, 5 mol%) under neat conditions in a sealed tube at 160 °C.
[b] Isolated yield.

Table 3. Transamidation of benzamides with various amines.[a]



Entry	Primary amide	Product	Yield [%][b]
1	 2b	 3j	77
2	 2c	 3k	76
3	 2d	 3l	68
4	 2e	 3m	67
5	 2f	 3n	66
6	 2g	 3o	75
7	 2h	 3p	87
8	 2i	 3q	92
9	 2j	 3r	90
10	 2k	 3s	76

[a] The reaction was carried out with benzamide (2.0 mmol), an amine (4.0 mmol), Nb_2O_5 catalyst (26 mg, 5 mol%) under neat conditions in a sealed tube at 160 °C.
[b] Isolated yield.

Recyclability of the catalyst was also examined based on the optimal conditions for the transamidation of benzamide with *n*-hexylamine (Table 2, entry 1). The catalyst was recovered by simple centrifugation and drying at room temperature under reduced pressure (see the Experimental Section). After 5 cycles, the catalyst showed no appreciable change in activity (Figure 3), demonstrating the robustness of the catalyst and its reusability.

Based on the known fact that Nb_2O_5 contains both Lewis and Brønsted acid sites[11,13g] and both of which have been shown to catalyze transamidation,[5f,7a,10c,e,f] a possible mechanism is proposed as shown in Figure 4. Primary amide (**A**) could be activated by co-

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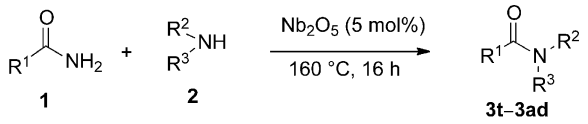
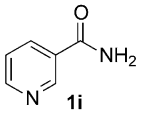
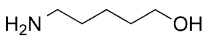
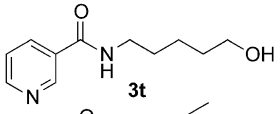
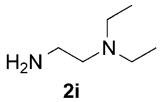
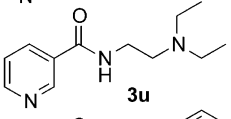
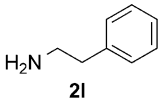
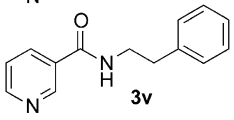
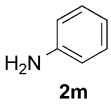
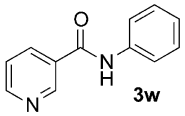
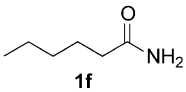
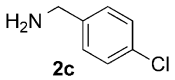
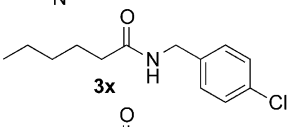
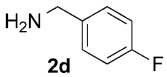
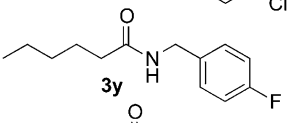
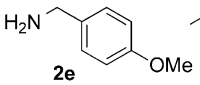
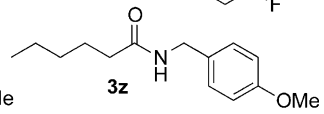
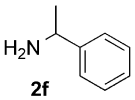
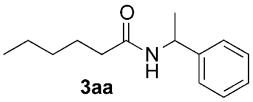
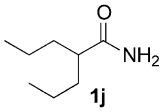
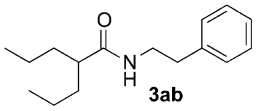
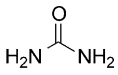
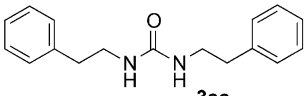
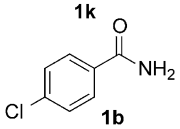
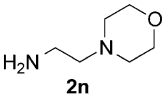
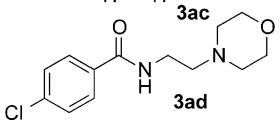
Table 4. Transamidation of various amides with various amines.[a]



1 + 2 → 3t–3ad

Entry	Primary amide	Amine	Product	Yield [%][b]
1	 1i	 2h	 3t	98
2	1i	 2i	 3u	95
3	1i	 2l	 3v	86
4	1i	 2m	 3w	84
5	 1f	 2c	 3x	96
6	1f	 2d	 3y	95
7	1f	 2e	 3z	74
8	1f	 2f	 3aa	91
9	 1j	2l	 3ab	15
10	 1k	2l[c]	 3ac	78
11	 1b	 2n	 3ad	90

[a] The reaction was carried out with a primary amide (2.0 mmol), an amine (4.0 mmol), Nb_2O_5 catalyst (26 mg, 5 mol%) under neat conditions in a sealed tube at 160 °C.
[b] Isolated yield.
[c] 8 mmol of amine **2l** were used.

ordination to the acid sites (denoted as A for both Lewis and Brønsted acid sites) of MNOS. This would facilitate the attack of amine (**B**) to the amide carbonyl group, leading to the formation of intermediate (**II**) which could undergo reversible proton exchange to form **III**. The amide product (**C**) and ammonia are then released from **III**, thus making the active sites for further turnovers. The driving force for this reaction is the release of gaseous ammonia from the reversible process, leading to the formation of the amide containing a less volatile amine.

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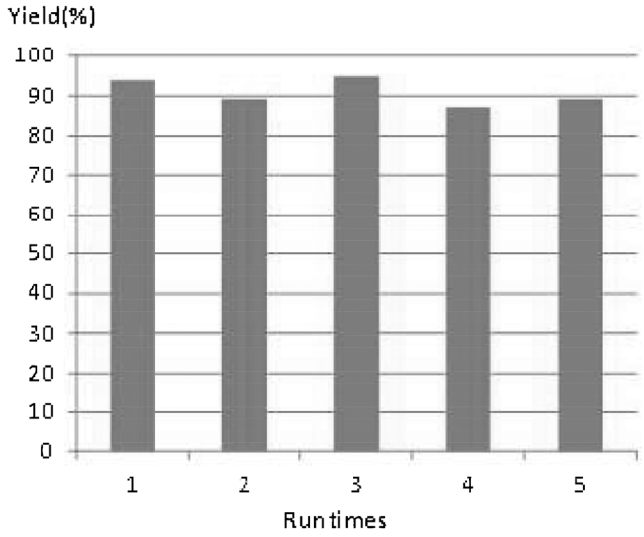

Figure 3. Recycling experiment of MNOS catalyst for the transamidation of benzamide with *n*-hexylamine. Yields were determined by GC analysis.

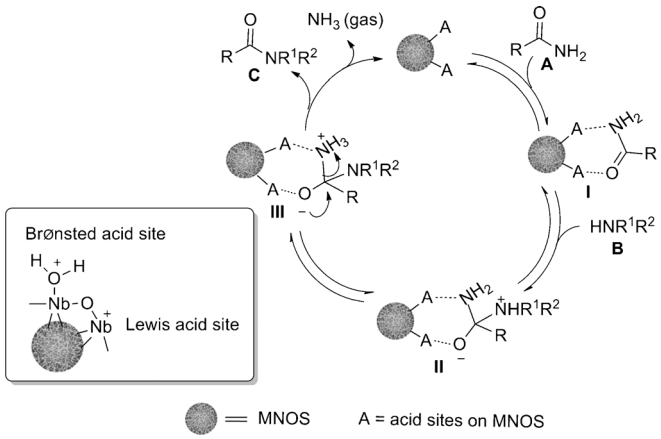

Figure 4. Proposed mechanism of the mesoporous niobium oxide spheres (MNOS)-catalyzed transamidation of primary amides with amines.

Conclusions

Mesoporous niobium oxide spheres, conveniently prepared by a novel antisolvent precipitation approach, have been shown to be a highly efficient catalyst for the transamidation of primary amides with amines. This transamidation catalyst is applicable to aliphatic, aromatic and heteroaromatic amides and a broad range of amines, providing a convenient access to *N*-alkyl amides in high yields. The reaction is compatible with several functional groups and can be carried out efficiently under solvent-free conditions without the formation of hazardous by-products. The MNOS catalyst is highly stable and reusable for five times with negligible loss of activity. The potential application of this transamidation catalyst has been demonstrated in a gram-scale synthesis of the antidepressant drug moclobemide.

Experimental Section

General Information

All reactions were carried out in oven-dried glassware under an inert atmosphere of dry argon or nitrogen. All primary amides and amines were obtained from commercial sources and used as received. $^{1}H/^{13}C$ NMR spectra were recorded at 400/100 MHz on a Bruker Advance III 400 spectrometer in $CDCl_3$ unless otherwise stated, using either TMS or the undeuterated solvent residual signal as the reference. Mass spectra were run with the electrospray ionization time-of-flight (ESI-TOF) mode on an Agilent 6210 mass spectrometer. Solvents for moisture sensitive reactions were obtained from a Glass Contour solvent purification system under nitrogen. GC analysis was performed on an Agilent 6890N GC system equipped with an HP-5 column using dodecane as an internal standard. Flash column chromatography purification of compounds was carried out by gradient elution using ethyl acetate (EA) in light petroleum ether (PE) unless otherwise stated. NH_3-TPD was performed on a TPDRO-1100 apparatus (Thermo Electron Corporation) equipped with a thermal conductivity detector as described previously.[12]

General Procedure for the Transamidation of Primary Amides with Amines using Mesoporous Niobium Oxide Catalyst

An oven-dried Radleys® carousel tube was charged with mesoporous niobium oxide spheres (prepared according to a reported protocol,[11] 26 mg, 5 mol%), a primary amide (2 mmol) and the amine (4 mmol, 2 equiv.). The tube was connected to an argon line and the reaction mixture was heated at the specified temperature for 24 h. After being cooled to room temperature, the crude product was purified by flash chromatography on silica gel to obtain the amide product.

Catalyst Recycling Experiments

Upon completion of the reaction (transamidation of benzamide with *n*-hexylamine, Table 2, entry 1), the mixture was diluted with methanol and chloroform (2 mL each). Dodecane (50 μL) was added and 0.2 μL was injected in the GC for analysis. The remaining solution was centrifuged to separate the catalyst by removing the supernatant liquid. The solid residue was washed with ethyl acetate and centrifuged to remove the solvent. This procedure was repeated for three times. The solid residue (catalyst) obtained was dried under vacuum before being used for another round of reaction.

Compound Characterization Data

***N*-Hexylbenzamide (3a):**[12d] White solid; yield: 380 mg (92%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.79–7.73$ (m, 2H),

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7.52–7.45 (m, 1H), 7.45–7.38 (m, 2H), 6.15 (s, 1H), 3.45 (td, $J=7.2$, 5.9 Hz, 2H), 1.69–1.55 (m, 3H), 1.45–1.25 (m, 6H), 0.90 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 167.6, 135.1, 131.4, 128.7, 127.0, 40.3, 31.6, 29.8, 26.8, 22.7, 14.1; HR-MS (ESI): $m/z=228.1361$ $[M+Na]^+$, calcd. for $C_{13}H_{19}NNaO$: 228.1364.

***N*-Hexyl-4-chlorobenzamide (3b):**[16] White solid; yield: 460 mg (96%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.76$–7.63 (m, 2H), 7.43–7.31 (m, 2H), 6.28 (s, 1H), 3.48–3.33 (m, 2H), 1.67–1.48 (m, 2H), 1.41–1.24 (m, 6H), 0.97–0.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=166.6$, 137.6, 133.4, 128.9, 128.4, 40.4, 31.6, 29.7, 26.8, 22.7, 14.1; HR-MS (ESI): $m/z=$ 262.0978 $[M+Na]^+$, calcd. for $C_{13}H_{18}ClNNaO$: 262.0975.

***N*-Hexyl-4-methylbenzamide (3c):**[12d] White solid; yield: 335 mg (76%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.59$–7.49 (m, 2H), 7.11 (dd, $J=7.6$, 1.4 Hz, 2H), 6.05 (s, 1H), 3.36–3.26 (m, 2H), 2.27 (s, 3H), 1.54–1.44 (m, 2H), 1.31–1.17 (m, 6H), 0.84–0.74 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 167.6, 141.7, 132.2, 129.3, 126.9, 40.2, 31.6, 29.8, 26.8, 22.7, 21.5, 14.1; HR-MS (ESI): $m/z=242.1507$ $[M+Na]^+$, calcd. for $C_{14}H_{21}NNaO$: 242.1521.

***N*-Hexyl-4-methoxybenzamide (3d):**[16] White solid; yield: 343 mg (73%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.80$–7.66 (m, 2H), 6.98–6.85 (m, 2H), 6.09 (s, 1H), 3.83 (s, 3H), 3.42 (td, $J=7.3$, 5.7 Hz, 2H), 1.66–1.51 (m, 2H), 1.40–1.26 (m, 6H), 0.93–0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 167.2, 162.2, 128.7, 127.3, 113.8, 55.5, 40.2, 31.7, 29.9, 26.8, 22.7, 14.1; HR-MS (ESI): $m/z=258.1456$ $[M+Na]^+$, calcd. for $C_{14}H_{21}NNaO_2$: 258.1470.

***N*-Hexyl-2-hydroxy-2-phenylacetamide (3e):** White solid; yield: 348 mg (74%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.42$–7.30 (m, 5H), 6.01 (s, 1H), 5.01 (s, 1H), 3.25 (dd, $J=13.4$, 6.9 Hz, 2H), 1.55–1.37 (m, 3H), 1.40–1.14 (m, 8H), 0.94–0.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=172.1$, 139.8, 129.1, 128.8, 127.0, 74.3, 39.8, 31.5, 29.5, 26.5, 22.6, 14.1; HR-MS (ESI): $m/z=258.1475$ $[M+Na]^+$, calcd. for $C_{14}H_{21}NNaO_2$: 258.1470.

***N*-Hexylhexanamide (3f):**[16] White solid; yield: 359 mg (90%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.36$ (s, 1H), 3.30–3.18 (m, 2H), 2.21–2.09 (m, 2H), 1.70–1.60 (m, 2H), 1.54–1.43 (m, 2H), 1.40–1.19 (m, 10H), 0.97–0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=173.2$, 39.7, 37.1, 31.6, 29.8, 26.7, 25.7, 22.7, 22.6, 14.1, 14.1; HR-MS (ESI): $m/z=$ 222.1830 $[M+Na]^+$, calcd. for $C_{12}H_{25}NNaO$: 222.1834.

***N*-Hexylthiophene-2-carboxamide (3g):**[17] White solid; yield: 330 mg (78%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.47$ (dt, $J=9.8$, 4.6 Hz, 2H), 7.06 (dt, $J=8.6$, 3.6 Hz, 1H), 6.13 (s, 1H), 3.51–3.34 (m, 2H), 1.68–1.53 (m, 2H), 1.42–1.25 (m, 6H), 0.97–0.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 162.0, 139.4, 129.7, 127.9, 127.6, 40.2, 31.6, 29.8, 26.7, 22.7, 14.1; HR-MS (ESI): $m/z=234.0935$ $[M+Na]^+$, calcd. for $C_{11}H_{17}NNaOS$: 234.0929.

***N*-Hexylfuran-2-carboxamide (3h):**[18] White solid; yield: 367 mg (94%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.42$ (dd, $J=1.7$, 0.8 Hz, 1H), 7.09 (dd, $J=3.5$, 0.7 Hz, 1H), 6.49 (dd, $J=3.5$, 1.8 Hz, 1H), 6.32 (s, 1H), 3.48–3.36 (m, 2H), 1.66–1.51 (m, 2H), 1.47–1.19 (m, 6H), 0.89 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=158.5$, 148.4, 143.8, 114.0, 112.2, 39.3, 31.6, 29.8, 26.7, 22.7, 14.1; HR-MS (ESI): $m/z=$ 218.1150 $[M+Na]^+$, calcd. for $C_{11}H_{17}NNaO_2$: 218.1157.

***N*-Hexylnicotinamide (3i):**[19] White solid; yield: 371 mg (90%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.97$ (d, $J=1.7$ Hz, 1H), 8.68 (dd, $J=4.8$, 1.5 Hz, 1H), 8.11 (dt, $J=7.9$, 1.9 Hz, 1H), 7.42–7.31 (m, 1H), 6.48 (s, 1H), 3.45 (dd, $J=13.1$, 7.1 Hz, 2H), 1.60 (dd, $J=14.7$, 7.6 Hz, 2H), 1.45–1.21 (m, 6H), 0.88 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=165.7$, 152.0, 147.8, 135.4, 130.8, 123.7, 77.5, 77.2, 76.8, 40.4, 31.6, 29.7, 26.8, 22.6, 14.1; HR-MS (ESI): $m/z=$ 229.1322 $[M+Na]^+$, calcd. for $C_{12}H_{18}N_2NaO$: 229.1317.

***N*-Benzylbenzamide (3j):**[12d] White solid; yield: 325 mg (77%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.79$ (dd, $J=5.3$, 3.3 Hz, 2H), 7.54–7.47 (m, 1H), 7.47–7.39 (m, 2H), 7.39–7.32 (m, 4H), 7.32–7.27 (m, 1H), 6.42 (brs, 1H), 4.65 (d, $J=$ 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=167.5$, 138.3, 134.6, 131.7, 128.9, 128.7, 128.1, 127.8, 127.1, 44.3; HR-MS (ESI): $m/z=234.0899$ $[M+Na]^+$, calcd. for $C_{14}H_{13}NNaO$: 234.0895.

***N*-(4-Chlorobenzyl)benzamide (3k):**[9] White solid; yield: 374 mg (76%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.89$–7.74 (m, 2H), 7.57–7.48 (m, 1H), 7.49–7.40 (m, 2H), 7.34–7.28 (m, 4H), 6.57 (s, 1H), 4.62 (d, $J=5.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=167.5$, 137.0, 134.3, 133.5, 131.8, 129.3, 129.0, 128.8, 127.1, 43.5; HR-MS (ESI): $m/z=$ 268.0514 $[M+Na]^+$, calcd. for $C_{14}H_{12}ClNNaO$: 268.0505.

***N*-(4-Fluorobenzyl)benzamide (3l):**[20] White solid; yield: 311 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.83$–7.75 (m, 2H), 7.55–7.47 (m, 1H), 7.46–7.38 (m, 2H), 7.36–7.27 (m, 2H), 7.07–6.98 (m, 2H), 6.52 (s, 1H), 4.60 (d, $J=5.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=167.5$, 162.4 (d, $J=$ 244 Hz, C-F coupling), 134.4, 134.2 (d, $J=4$ Hz, C-F coupling), 131.8, 129.7 (d, $J=8$ Hz, C-F coupling), 128.7, 127.1, 115.7 (d, $J=21$ Hz, C-F coupling) 43.5; HR-MS (ESI): $m/z=252.0809$ $[M+Na]^+$, calcd. for $C_{14}H_{12}FNNaO$: 252.0801.

***N*-(4-Methoxybenzyl)benzamide (3m):**[9] White solid; yield: 324 mg (67%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.85$–7.72 (m, 2H), 7.54–7.38 (m, 3H), 7.31–7.26 (m, 2H), 6.97–6.80 (m, 2H), 6.55–6.23 (m, 1H), 4.57 (d, $J=5.5$ Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=167.4$, 159.3, 134.6, 131.6, 130.4, 129.4, 128.7, 127.1, 114.3, 55.4, 43.8; HR-MS (ESI): $m/z=264.1003$ $[M+Na]^+$, calcd. for $C_{15}H_{15}NNaO_2$: 264.1000.

***N*-(1-Phenylethyl)benzamide (3n):**[21] White solid; yield: 299 mg (66%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.85$–7.72 (m, 2H), 7.52–7.45 (m, 1H), 7.45–7.32 (m, 6H), 7.32–7.26 (m, 1H), 6.42 (brs, 1H), 5.34 (dt, $J=14.3$, 7.0 Hz, 1H), 1.61 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=166.7$, 143.3, 134.8, 131.6, 128.9, 128.7, 127.6, 127.1, 126.4, 49.4, 21.9. HR-MS (ESI): $m/z=248.1061$ $[M+Na]^+$, calcd. for $C_{15}H_{15}NNaO$: 248.1051.

***N*-(Heptan-2-yl)benzamide (3o):**[22] White solid; yield: 330 mg (75%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.80$–7.70 (m, 2H), 7.47–7.36 (m, 3H), 5.93 (brs, 1H), 4.26–4.11 (m, 1H), 1.62–1.44 (m, 2H), 1.44–1.26 (m, 6H), 1.22 (dd, $J=6.6$, 2.0 Hz, 3H), 0.88 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=166.9$, 135.3, 131.3, 128.6, 126.9, 45.9, 37.2, 31.8, 25.9, 22.7, 21.2, 14.1; HR-MS (ESI): $m/z=242.1505$ $[M+Na]^+$, calcd. for $C_{14}H_{21}NNaO$: 242.1521.

***N*-(5-Hydroxypentyl)benzamide (3p):**[12b] White solid; yield: 359 mg (87%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.75$ (dd, $J=5.3$, 3.3 Hz, 2H), 7.52–7.46 (m, 1H), 7.46–7.39 (m, 2H), 6.18 (s, 1H), 3.67 (t, $J=6.4$ Hz, 2H), 3.48 (dd, $J=12.9$, 6.9 Hz, 2H), 1.72–1.58 (m, 4H), 1.53–1.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=167.8$, 134.9, 131.5, 128.7,

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127.0, 62.8, 40.1, 32.4, 29.6, 23.3; HR-MS (ESI): m/z = 230.1165 $[M+Na]^+$, calcd. for $C_{12}H_{17}NNaO2$: 230.1157.

***N*-[2-(Diethylamino)ethyl]benzamide (3q):**[23] White solid; yield: 406 mg (92%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.74 (m, 2H), 7.51–7.35 (m, 3H), 7.01 (s, 1H), 3.47 (dd, J = 6.3, 5.5 Hz, 2H), 2.67–2.62 (m, 2H), 2.56 (q, J = 7.1 Hz, 4H), 1.03 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 134.9, 131.3, 128.6, 127.0, 51.5, 46.9, 37.4, 12.0; HR-MS (ESI): m/z = 243.1479 $[M+Na]^+$, calcd. for $C_{13}H_{20}N_2NaO$: 243.1473.

***N*-Benzoyl-4-benzylpiperazine (3r):**[24] White solid; yield: 503 mg (90%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 5H), 7.34–7.31 (m, 5H), 3.79 (brs, 2H), 3.54 (s, 2H), 3.43 (s, 2H), 2.61–2.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 136.0, 129.8, 129.3, 128.7, 128.6, 128.5, 127.5, 127.2, 63.0, 52.9, 47.8, 42.3; HR-MS (ESI): m/z = 303.1468 $[M+Na]^+$, calcd. for $C_{18}H_{20}N_2NaO$: 303.1473.

***N*-Benzoyl-(*S*)-prolinol (3s):**[25] White sticky solid; yield: 312 mg (76%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (dd, J = 7.4, 1.8 Hz, 2H), 7.40 (t, J = 6.2 Hz, 3H), 4.39 (d, J = 6.5 Hz, 1H), 3.94 (s, 1H), 3.85–3.63 (m, 2H), 3.60–3.34 (m, 2H), 2.23–2.07 (m, 1H), 1.96–1.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 136.8, 130.3, 128.7, 128.5, 127.1, 67.3, 61.6, 51.2, 28.6, 25.1; HR-MS (ESI): m/z = 228.1006 $[M+Na]^+$, calcd. for $C_{12}H_{15}NNaO_2$: 228.1000.

***N*-(5-Hydroxypentyl)nicotinamide (3t):** White solid; yield: 409 mg (98%); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.96 (dd, J = 2.1, 0.6 Hz, 1H), 8.64 (dd, J = 3.4, 1.2 Hz, 1H), 8.16–8.06 (m, 1H), 7.35 (ddd, J = 7.8, 4.9, 0.6 Hz, 1H), 7.02 (d, J = 15.6 Hz, 1H), 3.63 (t, J = 6.1 Hz, 2H), 3.47–3.44 (m, 2H), 2.47–2.44 (m, 2H), 1.72–1.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 152.0, 147.9, 135.5, 130.7, 123.7, 62.4, 40.2, 32.1, 29.2, 23.3; HR-MS (ESI): m/z = 231.1105 $[M+Na]^+$, calcd. for $C_{11}H_{16}N_2NaO$: 231.1109.

***N*-[2-(Diethylamino)ethyl]nicotinamide (3u):**[12d] White solid; yield: 420 mg (95%); ^1H NMR (400 MHz, $CDCl_3$): δ = 9.00–8.93 (m, 1H), 8.69 (dd, J = 4.8, 1.6 Hz, 1H), 8.15–8.08 (m, 1H), 7.36 (ddd, J = 7.9, 4.8, 0.8 Hz, 1H), 7.11 (s, 1H), 3.48 (dd, J = 6.1, 5.5 Hz, 2H), 2.70–2.62 (m, 2H), 2.56 (q, J = 7.1 Hz, 4H), 1.03 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 152.2, 148.1, 135.2, 130.5, 123.6, 51.3, 46.9, 37.4, 12.1; HR-MS (ESI): m/z = 222.1603 $[M+H]^+$, calcd. for $C_{12}H_{20}N_3O$: 222.1606.

***N*-(Phenylethyl)nicotinamide (3v):**[26] White solid; yield: 389 mg (86%); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.85 (s, 1H), 8.75–8.57 (m, 1H), 8.12–7.97 (m, 1H), 7.39–7.27 (m, 3H), 7.26–7.14 (m, 3H), 6.36 (brs, 1H), 3.82–3.64 (m, 2H), 3.05–2.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 152.2, 147.8, 138.8, 135.2, 130.5, 128.9, 126.8, 123.6, 41.3, 35.7; HR-MS (ESI): m/z = 249.1001 $[M+Na]^+$, calcd. for $C_{14}H_{14}N_2NaO$: 249.1004.

***N*-Phenylnicotinamide (3w):**[17] White solid; yield: 332 mg (84%); ^1H NMR (400 MHz, $CDCl_3$): δ = 9.06 (dd, J = 2.4, 1.0 Hz, 1H), 8.68 (dd, J = 4.9, 1.7 Hz, 1H), 8.61 (s, 1H), 8.16 (dt, J = 7.9, 1.9 Hz, 1H), 7.65–7.57 (m, 2H), 7.40–7.28 (m, 3H), 7.19–7.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 152.3, 148.0, 137.7, 135.7, 131.0, 129.2, 125.1, 123.8, 120.8; HR-MS (ESI): m/z = 221.0690 $[M+Na]^+$, calcd. for $C_{12}H_{10}N_2NaO$: 221.0691.

***N*-(4-Chlorobenzyl)hexanamide (3x):**[10e] White solid; yield: 461 mg (96%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.24 (m, 2H), 7.20–7.13 (m, 2H), 5.99 (s, 1H), 4.36 (d, J = 5.9 Hz, 2H), 2.22–2.14 (m, 2H), 1.68–1.57 (m, 2H), 1.34–1.24 (m, 4H), 0.91–0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 137.2, 133.3, 129.2, 128.9, 42.9, 36.8, 31.6, 25.5, 22.5, 14.0; HR-MS (ESI): m/z = 240.1139 $[M+H]^+$, calcd. for $C_{13}H_{19}ClNO$: 240.1155.

***N*-(4-Fluorobenzyl)hexanamide (3y):** White solid; yield: 424 mg (95%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.20 (m, 2H), 7.06–6.91 (m, 2H), 5.85 (s, 1H), 4.38 (d, J = 5.8 Hz, 2H), 2.25–2.14 (m, 2H), 1.71–1.57 (m, 2H), 1.37–1.23 (m, 4H), 0.94–0.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 162.9 (d, J = 244 Hz, C-F coupling), 134.5 (d, J = 4 Hz, C-F coupling), 129.6 (d, J = 8 Hz, C-F coupling), 115.6 (d, J = 21 Hz, C-F coupling), 42.9, 36.8, 31.6, 25.6, 22.5, 14.0; HR-MS (ESI): m/z = 246.1272 $[M+Na]^+$, calcd. for $C_{13}H_{18}FNNaO$: 246.1270.

***N*-(4-Methoxybenzyl)hexanamide (3z):**[10c] White solid; yield: 347 mg (74%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.16 (m, 2H), 6.90–6.82 (m, 2H), 5.69 (s, 1H), 4.36 (d, J = 5.5 Hz, 2H), 3.79 (s, 3H), 2.23–2.13 (m, 2H), 1.70–1.59 (m, 2H), 1.37–1.26 (m, 4H), 0.92–0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 159.2, 130.7, 129.3, 114.2, 55.4, 43.2, 36.9, 31.6, 25.6, 22.5, 14.1; HR-MS (ESI): m/z = 236.1657 $[M+H]^+$, calcd. for $C_{14}H_{22}NO_2$: 236.1651.

***N*-(1-Phenylethyl)hexanamide (3aa):**[27] White solid; yield: 399 mg (91%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.19 (m, 5H), 5.78 (brs, 1H), 5.16 (dt, J = 15.1, 7.1 Hz, 1H), 2.18 (dd, J = 8.2, 7.1 Hz, 2H), 1.71–1.59 (m, 2H), 1.50 (d, J = 6.9 Hz, 3H), 1.39–1.26 (m, 4H), 0.95–0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 143.5, 128.7, 127.4, 126.3, 48.7, 37.0, 31.6, 25.6, 22.5, 21.8, 14.0; HR-MS (ESI): m/z = 242.1525 $[M+Na]^+$, calcd. for $C_{14}H_{21}NNaO$: 242.1521.

***N*-Phenethyl-2-propylpentanamide (3ab):**[28] White solid; yield: 75 mg (15%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 2H), 7.25–7.17 (m, 3H), 5.41 (s, 1H), 3.59–3.49 (m, 2H), 2.87–2.77 (m, 2H), 1.99–1.87 (m, 1H), 1.62–1.48 (m, 2H), 1.38–1.12 (m, 6H), 0.86 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0, 139.1, 128.9, 128.7, 126.6, 47.9, 40.4, 36.1, 35.4, 20.9, 14.2; HR-MS (ESI): m/z = 248.2012 $[M+H]^+$, calcd. for $C_{16}H_{26}NO$: 248.2014.

1,3-Diphenethylurea (3ac):[29] White solid; yield: 418 mg (78%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, J = 7.3 Hz, 4H), 7.25–7.19 (m, 2H), 7.19–7.13 (m, 4H), 3.41 (t, J = 6.9 Hz, 4H), 2.79 (t, J = 6.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 139.2, 129.0, 128.8, 126.6, 41.8, 36.5; HR-MS (ESI): m/z = 291.1479 $[M+Na]^+$, calcd. for $C_{17}H_{20}N_2NaO$: 291.1473.

4-Chloro-*N*-(2-morpholinoethyl)benzamide (moclobemide, 3ad):[12c] White solid; yield: 484 mg (90%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.68 (m, 2H), 7.44–7.37 (m, 2H), 6.78 (s, 1H), 3.76–3.69 (m, 4H), 3.54 (dd, J = 11.4, 5.5 Hz, 2H), 2.60 (t, J = 6.0 Hz, 2H), 2.53–2.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 137.8, 133.1, 129.0, 128.5, 67.1, 57.0, 53.5, 36.2; HR-MS (ESI): m/z = 291.0882 $[M+Na]^+$, calcd. for $C_{13}H_{17}ClN_2NaO_2$: 291.0876.

Gram-Scale Synthesis of Moclobemide (3ad)

4-Chlorobenzamide (**1b**, 0.93 g, 6 mmol), 2-morpholinoethan-1-amine (**2n**, 1.17 g, 9.0 mmol) and MNOS catalyst (80 mg, 0.30 mmol, 5 mol%) were added to a Radleys® carousel tube. The mixture was heated at 155–160 °C in an oil bath with stirring under an argon atomsphere until the start-

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ing material was consumed (12 h as judged by TLC). The mixture was allowed to cool and EA (10 mL) was added just before the precipitation occurred. The pale yellow suspension was allowed to settle, the supernantant was decanted and the solid residues were washed with EA (2× 5 mL). The combine organic layer was washed with water (2×10 mL) (to remove the excess amine) and brine. After drying and evaporation of the solvent, the crude product was recrystallized from ethyl acetate in hexane (2:3) to provide moclobemide as a white solid; yield: 1.38 g (86%). The characterization data were in agreement with those reported above for **3ad**.

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References

[1] a) T. Cupido, J. Tulla-Puche, J. Spengler, F. Albericio, *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 768; b) J. W. Bode, *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 765; c) J. M. Humphrey, A. R. Chamberlin, *Chem. Rev.* **1997**, *97*, 2243; d) A. K. Ghose, V. N. Viswanadhan, J. J. Wendoloski, *J. Comb. Chem.* **1999**, *1*, 55.

[2] a) R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, **1999**; b) S.-Y. Han, Y.-A. Kim, *Tetrahedron* **2004**, *60*, 2447; c) C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827; d) E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606.

[3] For selected reviews, see: a) S. Roy, G. W. Gribble, *Tetrahedron* **2012**, *68*, 9867; b) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405; c) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471; d) C. Cheng, S. H. Hong, *Org. Biomol. Chem.* **2011**, *9*, 20; e) E. Ekoue-Kovi, C. Wolf, *Chem. Eur. J.* **2008**, *14*, 6302.

[4] For examples, see: a) L. J. Gooßen, D. M. Ohlmann, P. P. Lange, *Synthesis* **2009**, 160; b) B. S. Jursic, Z. Zdravkovski, *Synth. Commun.* **1993**, *23*, 2761; c) A. Truchan, J. B. Davidson, (for nicotinamide synthesis), U.S. Patent 2,993,051, **1961**; d) J. A. Mitchell, E. E. Reid, *J. Am. Chem. Soc.* **1931**, *53*, 1879.

[5] a) S. E. Eldred, D. A. Stone, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* **2003**, *125*, 3422; b) D. A. Kissounko, L. A. Guzei, S. H. Gellman, S. S. Stahl, *Organometallics* **2005**, *24*, 5208; c) J. M. Hoerter, K. M. Otte, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 5177; d) D. A. Kissounko, J. M. Hoerter, I. A. Guzei, Q. Cui, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* **2007**, *129*, 1776; e) J. M. Hoerter, K. M. Otte, S. H. Gellman, Q. Cui, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 647; f) N. A. Stephenson, J. Zhu, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* **2009**, *131*, 10003.

[6] T. A. Dineen, M. A. Zajac, A. G. Myers, *J. Am. Chem. Soc.* **2006**, *128*, 16406.

[7] a) C. L. Allen, B. N. Atkinson, J. M. J. Williams, *Angew. Chem.* **2012**, *124*, 1412; *Angew. Chem. Int. Ed.* **2012**, *51*, 1383; b) B. N. Atkinson, A. R. Chhatwal, H. V. Lomax, J. W. Walton, J. M. J. Williams, *Chem. Commun.* **2012**, *48*, 11626.

[8] M. Zhang, S. Imm, S. Bahn, L. Neubert, H. Neumann, M. Beller, *Angew. Chem.* **2012**, *124*, 3971; *Angew. Chem. Int. Ed.* **2012**, *51*, 3905.

[9] S. N. Rao, D. C. Mohan, S. Adimurthy, *Org. Lett.* **2013**, *15*, 1496.

[10] a) R. Vanjari, B. K. Allam, K. N. Singh, *RSC Adv.* **2013**, *3*, 1691; b) T. B. Nguyen, J. Sorres, M. Q. Tran, L. Ermolenko, A. Al-Mourabit, *Org. Lett.* **2012**, *14*, 3202; c) M. Tamura, T. Tonomura, K. Shimizu, A. Satsuma, *Green Chem.* **2012**, *14*, 717; d) P. Starkov, T. D. Sheppard, *Org. Biomol. Chem.* **2011**, *9*, 1320; e) M. Shi, S.-C. Cui, *Synth. Commun.* **2005**, *35*, 2847; f) S. C. Alimsiz, M. A. Lipton, *J. Org. Chem.* **2005**, *70*, 6218; g) R. M. Lanigan, P. Starkov, T. D. Sheppard, *J. Org. Chem.* **2013**, *78*, 4512; h) R. M. Lanigan, T. D. Sheppard, *Eur. J. Org. Chem.* **2013**, 7453.

[11] C. C. Li, J. Dou, L. Chen, J. Lin, H. C. Zeng, *ChemCatChem* **2012**, *4*, 1675.

[12] a) S. C. Ghosh, J. S. Y. Ngiam, C. L. L. Chai, A. M. Seayad, D. T. Tuan, A. Chen, *Adv. Synth. Catal.* **2012**, *354*, 1407; b) S. C. Ghosh, J. S. Y. Ngiam, A. M. Seayad, D. T. Tuan, C. L. L. Chai, A. Chen, *J. Org. Chem.* **2012**, *77*, 8007; c) T. T. Dang, Y. Zhu, S. C. Ghosh, A. Chen, C. L. L. Chai, A. M. Seayad, *Chem. Commun.* **2012**, *48*, 1805; d) T. T. Dang, Y. Zhu, J. S. Y. Ngiam, S. C. Ghosh, A. Chen, A. M. Seayad, *ACS Catal.* **2013**, *3*, 1406.

[13] For selected reviews, see: a) V. Lacerda Jr, D. A. dos Santos, L. Carlos da Silva-Filho, S. J. Greco, R. B. dos Santos, *Aldrichimica Acta* **2012**, *45*, 19; b) Y. Zhao, X. Zhou, L. Ye, S. C. E. Tsang, *Nano Reviews* **2012**, 3:17631. DOI: 10.3402/nano.v3i0.17631; c) Y. C. Sharma, B. Singh, J. Korstad, *Biofuels, Bioprod. Bioref.* **2011**, *5*, 69; d) M. O. Guerrero-Pérez, A. E. Lewandowska, M. A. Bañares, *Recent Patents on Chemical Engineering* **2008**, *1*, 201; e) M. O. Guerrero-Pérez, M. A. Bañares, *Catal. Today* **2009**, *142*, 245; f) K. Tanabe, *Catal. Today* **2003**, *78*, 65; g) P. Carniti, A. Gervasini, S. Biella, A. Auroux, *Chem. Mater.* **2005**, *17*, 6128.

[14] a) L. Shi, Y. Yang, Z.-L. Li, Z.-W. Zhu, C.-H. Liu, H.-L. Zhu, *Bioorg. Med. Chem.* **2010**, *18*, 1659; b) R. W. Pero, A. Olsson, T. Ekberg, A. Schwartz, D. Chaplin, *PCT WO* 97/32576, **1997**.

[15] a) U. Bonnet, *CNS Drug Rev.* **2002**, *8*, 283; b) U. Bonnet, *CNS Drug Rev.* **2003**, *9*, 97.

[16] T. Ohshima, Y. Hayashi, K. Agura, Y. Fujii, A. Yoshiyama, K. Mashima, *Chem. Commun.* **2012**, *48*, 5434.

[17] J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 8612; *Angew. Chem. Int. Ed.* **2007**, *46*, 8460.

[18] S. Kegnaes, J. Mielby, U. V. Mentzel, T. Jensen, P. Fristrup, A. Riisager, *Chem. Commun.* **2012**, *48*, 2427.

[19] A. J. A. Watson, A. C. Maxwell, J. M. J. Williams, *J. Org. Chem.* **2011**, *76*, 2328.

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[20] D. Dube, A. A. Scholte, *Tetrahedron Lett.* **1999**, *40*, 2295.
[21] R. Vanjari, T. Guntreddi, K. N. Singh, *Org. Lett.* **2013**, *15*, 4908.
[22] C. Chen, S. H. Hong, *Org. Lett.* **2012**, *14*, 2992.
[23] S. K. Shannon, M. J. Peacock, S. A. Kates, G. Barany, *J. Comb. Chem.* **2003**, *5*, 860.
[24] M. Zhu, K. Fujita, R. Yamaguchi, *J. Org. Chem.* **2012**, *77*, 9102.
[25] A. Boto, D. Hernandez, R. Hernandez, A. Montoya, E. Suarez, *Eur. J. Org. Chem.* **2007**, 325.
[26] C. M. Boehner, D. M. Marsden, H. F. Sore, D. Norton, D. R. Spring, *Tetrahedron Lett.* **2010**, *51*, 5930.
[27] J. Tian, W.-C. Gao, D. M. Zhou, C. Zhang, *Org. Lett.* **2012**, *14*, 3020.
[28] E. Behar, H. Astroug, T. Netzeva, *Acta Pharm.* **1999**, *49*, 21.
[29] J. C. Anderson, R. B. Moreno, *Org. Biomol. Chem.* **2012**, *10*, 1334.

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