Preparation of Nd/Na heterogeneous catalyst from bench-stable and inexpensive Nd salt for an *anti*-selective catalytic asymmetric nitroaldol reaction

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ABSTRACT

A Nd/Na heterobimetallic complex prepared from an amide-based chiral ligand, Nd alkoxide, and NaHMDS is a highly efficient heterogeneous catalyst for an *anti*-selective catalytic asymmetric nitroaldol reaction. Nd alkoxide is sensitive to moisture, expensive, and scarce, making it difficult to use the Nd/Na catalyst in large-scale applications. Herein we describe a new protocol that allows for catalyst preparation from bench-stable and inexpensive $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$ with comparable catalytic activity.

The nitroaldol (Henry) reaction, a carbon-carbon bond-forming reaction of nitroalkanes and carbonyl compounds (typically aldehydes), offers expeditious access to vicinal amino alcohols after reducing the nitro group.^{1,2} Given the ready availability of these substrates and the established synthetic utility of vicinal amino alcohols, particularly for medicinal chemistry,³ the nitroaldol reaction is one of the most widely used C–C bond-forming reactions in the organic reaction toolbox (Scheme 1). Since our first report rendering this reaction in a catalytic and asymmetric manner with *syn*-diastereoselectivity,⁴ major challenges in this field have been simultaneous control of the diastereo- and enantioselectivity, allowing for stereoselective access to one of the four vicinal nitroalkanol.⁵ Shortly after Ooi's report on the catalytic *anti*-selective and enantioselective nitroaldol reaction,⁶ we disclosed an Nd/Na heterobimetallic complex as an effective heterogeneous catalyst for producing *anti*-nitroaldol products with a broad substrate scope (Scheme 2).^{7,8} The Nd/Na catalyst was readily prepared using an amide-based ligand **1**, $\text{NdO}_{1/5}(\text{O}^i\text{Pr})_{13/5}$, and NaHMDS in THF/ EtNO_2 ; self-assembly of **1**/Nd/Na proceeded with incorporation of EtNO_2 to give the powdered heterogeneous catalyst.^{7b,9} Catalyst preparation in the presence of multi-walled carbon nanotubes (MWNT) allowed for self-assembly in the fibrous matrix of the MWNT, thereby affording a MWNT-confined catalyst with smaller catalyst clusters that enabled higher catalytic efficiency, catalyst reuse, and reactions in a continuous-flow platform.¹⁰

An inherent problem, however, remained unsolved– the instability and limited availability of $\text{NdO}_{1/5}(\text{O}^i\text{Pr})_{13/5}$. This Nd alkoxide is 1) expensive;¹¹ 2) unstable to moisture; 3) and requires handling in a glove box under an inert atmosphere, which hampers widespread use of this particularly useful catalyst. Herein we report a new catalyst preparation procedure

using an alternative bench-stable and inexpensive $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$ as the Nd

Scheme 1. Overview of nitroaldol (Henry) reaction.

salt. The previously required NaHMDS as a Na source was also replaced with more common and less expensive Na alkoxides. The newly formed catalyst was characterized by XRD and STEM, and exhibited catalytic activity comparable to that of $\text{NdO}_{1/5}(\text{O}^i\text{Pr})_{13/5}$.

We selected $\text{NdO}_{1/5}(\text{O}^i\text{Pr})_{13/5}$ as the Nd salt of choice due to its high solubility in the preferred reaction solvent, e.g., THF, and its basic character is suitable for self-assembly with phenolic ligand **1**. Based of these criteria, $\text{Nd}(\text{HMDS})_3$ was an appropriate alternative that produced a similar reaction outcome as $\text{NdO}_{1/5}(\text{O}^i\text{Pr})_{13/5}$ in the nitroaldol reaction of benzaldehyde (**2a**) and EtNO_2 (**3**). The cost and instability, however, remained comparable, and thus further modifications were needed (Table 1,

issue: moisture sensitive, expensive,
limited availability of $\text{NdO}_{1.5}(\text{O}^i\text{Pr})_{13/5}$

Scheme 2. Overview of the previously developed Nd/Na heterobimetallic heterogeneous catalyst for *anti*-selective nitroaldol reaction.

Table 1. Screening of Nd salts^a

A For entries 1–3

Nd salt	ligand 1	NaHMDS	30 mM
3 mol% in THF	3 mol%	6 mol%	rt

B For entries 4–9

Nd salt	NaHMDS	ligand 1	NaHMDS
3 mol% in THF	9 mol%	3 mol%	6 mol%

60 °C, 12 h

30 mM, rt

THF, -40°C , 20 h

Entry	Nd salt	ambient conditions	€/g-Nd ^b	prepn	Yield ^c [%]	<i>anti</i> / <i>syn</i> ^d	<i>ee</i> ^e [%]
1 ^f	$\text{NdO}_{1.5}(\text{O}^i\text{Pr})_{13/5}$	–	239	A	99	>20/1	92
2	$\text{Nd}(\text{HMDS})_3$	–	240	A	>99	>20/1	94
3	$\text{Nd}(\text{OH})_3$	+	17	A	<5	1.7/1	nd ^g
4	$\text{Nd}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$	+	3.3	B	<5	2.7/1	nd ^g
5	$\text{Nd}(\text{OAc})_3 \cdot \text{H}_2\text{O}$	+	1.8	B	<5	1.7/1	nd ^g
6	NdF_3	+	0.9	B	<5	1.2/1	nd ^g
7	NdCl_3	+	11	B	99	>20/1	93
8	$\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$	+	1.6	B	<5	1.9/1	nd ^g
9	NdBr_3	+	40	B	42	6.8/1	33

^a2a: 0.4 mmol, 3: 4.0 mmol. ^bCited references are described in ESI. ^cDetermined by ^1H NMR analysis of the crude mixture with DMF as an internal standard. ^dDetermined by ^1H NMR analysis of the crude mixture. ^eEe of *anti* diastereomer. Determined by chiral stationary-phase HPLC analysis. ^fData from ref 7b. Nd salt in THF was mixed into ligand 1/THF. ^gnd: not determined.

procedure A, entries 1,2). We searched for bench-stable and neutral Nd salts to prepare the catalyst with a greater amount of NaHMDS to compensate for the basicity and facilitate self-assembly. Because potentially basic $\text{Nd}(\text{OH})_3$ was ineffective for catalyst preparation, likely due to insolubility in THF (entry 3), in situ preparation of $\text{Nd}(\text{HMDS})_3$ from various readily available and inexpensive Nd salts was examined with a 3-fold excess of NaHMDS (Table 1, procedure B).¹² The highly cost-effective Nd salts, e.g., $\text{Nd}(\text{OAc})_3 \cdot 6\text{H}_2\text{O}$, $\text{Nd}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$, and NdF_3 , barely afforded the catalysts sufficiently active to promote the nitroaldol reaction (entries 4–6). In contrast to NdF_3 , the catalyst prepared from NdCl_3 produced a nearly similar reaction outcome to that obtained using $\text{NdO}_{1.5}(\text{O}^i\text{Pr})_{13/5}$ (entry 1 vs entry 7). NdBr_3 delivered less effective catalyst to afford product 4a with an inferior yield and stereoselectivity (entry 9). Although the hydrate form of NdCl_3 was much less expensive, the use of $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$ in the identical catalyst preparation procedure afforded only trace amount of product 4a (entry 8).

Given the lower cost of NdCl_3 (11 euro/1g-Nd) compared with $\text{NdO}_{1.5}(\text{O}^i\text{Pr})_{13/5}$ (239 euro/1g-Nd),¹¹ we directed our attention to establishing a reliable and cost-effective protocol based on its hydrate form, $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$ (1.6 euro/1g-Nd) (Table

2).¹¹ Pre-incubation of NdCl_3 and 3-fold excess of NaHMDS could be omitted for operational simplicity; mixing 6-fold excess of NaHMDS with NdCl_3 /ligand 1 in THF gave a similar result (Table 1, entry 7 vs Table 2, procedure A, entry 1). This simplified procedure was valid for $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$, presumably due to the presence of ligand 1 upon contact with Nd and Na salts, which reduced the negative effect of the hydrates (entry 2). NaHMDS (35 euro/1g-Na) was also replaced with less expensive and more readily available NaO^iBu (0.6 euro/1g-Na) under more concentrated conditions (40 mM in ligand 1) at a higher temperature (60 °C),¹¹ affording the nitroaldol product 4a without any detrimental effects on the reaction outcome (entry 3).¹³

Table 2. Screening of Na salts^a

A For entries 1–3,5–8

Nd salt	ligand 1	Na salt	y [mM]	z [°C]
3 mol% in THF	3 mol%	x mol%	300	rt

B For entry 4

Nd salt	Na salt	ligand 1
3 mol% in THF	x mol%	3 mol%

60 °C, 12 h

30 mM, rt

THF, -40°C , 20 h

Entry	Nd salt	Na salt	€/g-Nd ^b	€/g-Na ^b	prepn	Yield ^c [%]	<i>anti</i> / <i>syn</i> ^d	<i>ee</i> ^e [%]
1	NdCl_3	NaHMDS	18	11	35	A 30 rt	93	>20/1 93
2	$\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$	NaHMDS	18	1.6	35	A 30 rt	97	>20/1 95
3	$\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$	NaO^iBu	18	1.6	0.6	A 40 60	98	>20/1 93
4	$\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$	NaO^iBu	18	1.6	0.6	B 40 60	<5	5.2 nd ^g
5	$\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$	NaO^iBu	12	1.6	0.6	A 40 60	40	>20/1 95
6	$\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$	NaO^iAm	18	1.6	2.7	A 40 60	98	>20/1 94
7	$\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$	NaOEt	18	1.6	0.3	A 40 60	>99	>20/1 93
8 ^f	$\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$	NaO^iBu	18	1.6	0.6	A 40 60	97	>20/1 93

^a2a: 0.4 mmol, 3: 4.0 mmol. ^bCited references are described in ESI. ^cDetermined by ^1H NMR analysis of the crude mixture with DMF as an internal standard. ^dDetermined by ^1H NMR analysis of the crude mixture. ^eEe of *anti* diastereomer. Determined by chiral stationary-phase HPLC analysis. ^f18 mg of MWNT was added before adding EtNO_2 (3a). ^gnd: not determined.

Scheme 3. Schematic representation of new preparation protocol of the Nd/Na heterogeneous catalyst. The solid white object is a magnetic stirring bar.

Formation of the Nd/Na heterogeneous catalyst under these conditions is delineated in Scheme 3.¹⁴ Unexpectedly, pre-incubation of $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$ and NaO^iBu in the absence of ligand 1 under otherwise identical conditions gave a solid material with almost no catalytic activity (procedure B, entry 4), presumably because $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$ and NaO^iBu produced an insoluble aggregate and therefore no productive complexation with 1 proceeded. The amount of base was also important; reducing NaO^iBu to 4-fold excess reduced the catalytic efficiency (entry 5).¹⁵ Other Na alkoxides under otherwise identical conditions produced similar reaction outcomes (entries 6,7). Under the optimized conditions for catalyst preparation, mixing the MWNT before adding EtNO_2 produced MWNT-confined catalyst for

potential use in a flow reaction (*vide infra*). The MWNT-confined catalyst had increased durability, was easily filtered for recovery, and produced similar reaction outcome in a batch system (entry 8). Replacing the Nd and Na salts from $\text{NdO}_{1/5}(\text{O}^i\text{Pr})_{13/5}/\text{NaHMDS}$ to $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}/\text{NaO}^i\text{Bu}$ resulted in a ca. 120-fold cost reduction.

The Nd/Na heterobimetallic heterogeneous catalysts prepared by the original ($\text{NdO}_{1/5}(\text{O}^i\text{Pr})_{13/5}/\text{NaHMDS}$)^{7b} and new ($\text{NdCl}_3 \cdot 6\text{H}_2\text{O}/\text{NaO}^i\text{Bu}$) protocol were analyzed by powder XRD analysis.¹⁶ As expected based on the comparable reaction outcomes in the nitroaldol reaction, we observed nearly identical diffraction patterns. Several unique peaks observed for the new

Figure 1. STEM image of MWNT-confined catalyst prepared by new protocol ($\text{NdCl}_3 \cdot 6\text{H}_2\text{O}/\text{NaO}^i\text{Bu}$). (a) STEM image; (b) merged image of STEM and EDS mapping for Nd, F, and Cl; (c) EDS mapping analysis for Nd detection; (d) EDS mapping analysis for F detection; (e) EDS mapping analysis for Cl detection.

catalyst were assigned as peaks derived from NaCl. STEM and EDS mapping images of the MWNT-confined catalyst confirmed that the catalyst clusters were trapped in the fibrous network of the MWNT (Fig. 1); characteristic X-ray areas of fluorine (derived from ligand **1**), chlorine, and Nd were superimposed with the catalyst image. Chloride anions derived from $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$, which is absent in the original method, located uniformly in the catalyst and had no negative effect on the catalyst activity.

The Nd/Na catalyst prepared via the new protocol was evaluated using various substrates in comparison with the catalyst prepared via the original protocol (Table 3). The results of the original catalyst using the same catalyst loading (based on Nd) are shown in parentheses,^{7b} and almost identical reaction outcomes were obtained for a series of aldehydes (entries 1–10). *Ortho*-substituent, electron-donating and -withdrawing substituents were tolerated to afford the nitroaldol products in high yield, *anti*-selectivity, and enantioselectivity (entries 2–5), albeit with a little erosion in stereoselectivity for 4-nitrobenzaldehyde (**2f**) (entry 6). Although the reaction with

cinnamaldehyde (**2g**) as an archetypal α,β -unsaturated aldehyde afforded reasonable yield and stereoselectivity without forming a 1,4-adduct (entry 7), lower diastereoselectivity was generally observed for aliphatic aldehydes (entries 8–10). A branched aldehyde, e.g., cyclohexanecarboxaldehyde (**2h**) exhibited better stereoselectivity (entry 8) and self-condensation of aliphatic aldehydes was barely detected (entries 8–10).

The MWNT-confined Nd/Na heterobimetallic catalyst prepared via the new protocol was applied to a continuous-flow reaction (Scheme 4).¹⁷ The MWNT-confined catalyst was suspended in THF with dried Celite and packed in a stainless steel column with end-capping disk frits (2 μm) (62.2 μmol based on Nd). Benzaldehyde (**2a**) (0.1 M/THF) and EtNO_2 (**3**) (1.0

Table 3. Substrate generality of the nitroaldol reaction promoted by the Nd/Na heterobimetallic catalyst via new protocol ($\text{NdCl}_3 \cdot 6\text{H}_2\text{O}/\text{NaO}^i\text{Bu}$)^a

$\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$ 3 mol%
 ligand **1** 3 mol%
 NaO^iBu 18 mol%
 EtNO_2 (**3**) 300 mol%

precipitate
 THF, -40°C , 20 h

Entry	aldehyde 2 $\text{R}^1 =$	4	Yield [%] ^{b,c}	<i>anti/syn</i> ^{c,d}	<i>ee</i> [%] ^{e,e}	
1	Ph	2a	4a	96 (99)	>20/1 (>20/1)	93 (92)
2	2,4-Me ₂ C ₆ H ₃	2b	4b	95 (99)	>20/1 (>20/1)	99 (98)
3	4-BnOC ₆ H ₄	2c	4c	87 (89)	>20/1 (>20/1)	99 (97)
4	4-NCC ₆ H ₄	2d	4d	91 (88)	19/1 (15/1)	97 (94)
5 ^f	4-MeO ₂ CC ₆ H ₄	2e	4e	92 (99)	>20/1 (>20/1)	96 (96)
6	4-NO ₂ C ₆ H ₄	2f	4f	92 (99)	6.5/1 (5.7/1)	88 (86)
7	(<i>E</i>)-PhCH=CH	2g	4g	95 (96)	>20/1 (>20/1)	98 (97)
8 ^{g,h}	^c Hex	2h	4h	90 (92)	6.8/1 (8.3/1)	94 (95)
9 ^g	PhCH ₂ CH ₂	2i	4i	94 (99)	4.4/1 (4.9/1)	82 (77)
10 ^g	ⁿ C ₈ H ₁₇	2j	4j	90 (93)	3.3/1 (3.4/1)	85 (87)

^a**2a**: 0.4 mmol, **3a**: 4.0 mmol. ^bData in parentheses are obtained from the catalyst prepared from the original protocol ($\text{NdO}_{1/5}(\text{O}^i\text{Pr})_{13/5}/\text{NaHMDS}$).^{7b} ^cIsolated yield of diastereomixture. ^dDetermined by ¹H NMR analysis of the crude mixture. ^eEe of *anti* diastereomer. Determined by chiral stationary-phase HPLC analysis. ^fRun for 14 h. ^gDME was used as solvent with 6 mol% of catalyst. ^hRun for 22 h.

Scheme 4. Nitroaldol reaction in a continuous-flow platform with MWNT-confined Nd/Na heterogeneous catalyst prepared via new protocol.

M/THF) were introduced in separate streams at 4.2 mL/h using syringe pumps and **2a** was passed through an MS3A column and a NaHCO_3 column to remove trace amount of water and acidic

impurities. The two streams merged in a mixer and the resulting substrate mixture was precooled to -40°C before entering the catalyst column. The flow system was operated for 24 h with high conversion and stereoselectivity to afford 1.63 g of product **4a** (90% yield, *anti/syn* = 20/1, 90% ee, TON = 145). The flow system is advantageous because 1) the heterogeneous catalyst was prepared by simple mixing without any covalent linkage;¹⁸ 2) no work-up procedure was required and evaporation of the eluent gave the crude product; 3) the cooling volume was significantly reduced to decrease the electric power required for cryogenic conditions. The nitro product of **4a** can be readily reduced to give (–)-norephedrine.^{8c}

In conclusion, we established a new preparation protocol for an Nd/Na heterobimetallic heterogeneous catalyst. Replacing of $\text{NdO}_{1.5}(\text{O}^i\text{Pr})_{13.5}/\text{NaHMDs}$ with $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}/\text{NaO}^i\text{Bu}$ allowed us to prepare the catalyst under ambient conditions with a ca. 120-fold reduction in the cost. The catalyst prepared via the new protocol was characterized by XRD and STEM, which indicated the catalyst was essentially identical to that prepared with the original protocol, a finding supported by the similar reaction outcomes in nitroaldol reactions. The new protocol was compatible with MWNT confinement and the MWNT-confined catalyst was operative in a continuous-flow platform.

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- Grinded $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$ was used to reduce the fluctuation depending on the production lot.
- Representative experimental procedure: To a flame dried test tube (20 mL) equipped with a magnetic stirring bar and a 3-way glass stopcock was charged with $\text{NdCl}_3 \cdot 6\text{H}_2\text{O}$ (4.3 mg, 0.012 mmol), and dried under vacuum at room temperature. Ar was backfilled (evacuation/backfill was repeated for several times) to the test tube, and THF (100 μL) and ligand **1** (200 μL , 0.012 mmol, 0.6 M/THF) were added successively by well-dried syringes and needles at room temperature. After stirring the resulting slightly cloudy solution at 60°C for 30 min, NaO^iBu (36 μL , 0.072 mmol, 2.0 M/THF) was added dropwise at the same temperature. After stirring the resulting mixture at 60°C for 1 h (white precipitate appeared), the mixture was cooled to room temperature and nitroethane (**3**) (86 μL , 1.2 mmol) was added (the precipitate was partly dissolved). Self-assembly of Nd/Na catalyst initiated in a few minutes and the resulting mixture was stirred at room temperature for 12 h to give a thick white suspension. The whole suspension was transferred to an Eppendorf tube and the tube was centrifuged at ca. 10^4 rpm for 30 sec. The supernatant was decanted and dry THF (1.2 mL) was added to the precipitate. The tube was agitated using a vortex mixer for 30 sec and the resulting tube was centrifuged again, then the supernatant was decanted (washing process). The resulting precipitate was agitated with dry THF (1.6 mL) and the resulting suspension was transferred to a flame-dried test tube (20 mL) for the nitroaldol reaction.
- Although the use of 5-fold excess of NaO^iBu is sufficient for complexation (3-fold for trivalent Nd and 2-fold for two phenolic protons of **1**), 6-fold excess of NaO^iBu is recommended for higher reproducibility.
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- Recent selected examples of noncovalent immobilization of asymmetric catalysts: (a) Yasukawa, T.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, 134, 16963; (b) Tan, Y.-X.; He, Y.-P.; Zhang, J. *Chem. Mater.* **2012**, 24, 4711; (c) Jin, R.; Liu, K.; Xia, D.; Qian, Q.; Liu, G.; Li, H. *Adv. Synth. Catal.* **2012**, 354, 3265; (d) Li, Z.-H.; Zhou, Z.-M.; Hao, X.-Y.; Zhang, J.; Dong, Z.; Liu, Y.-Q. *Chirality* **2012**, 24, 1092; (e) Xu, Y.; Cheng, T.; Long, J.; Liu, K.; Qian, Q.; Gao, F.; Liu, G.; Li, H. *Adv. Synth. Catal.* **2012**, 354, 3250; (f) Miyamura, H.; Kobayashi, S. *Acc.*

Graphical Abstract

Preparation of Nd/Na heterogeneous catalyst from bench-stable and inexpensive Nd salt for an *anti*-selective catalytic asymmetric nitroaldol reaction

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