#### Heterogeneous Catalysis

## A Carbon Nanotube Confinement Strategy to Implement Homogeneous Asymmetric Catalysis in the Solid Phase

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**Abstract:** A readily recyclable asymmetric catalyst has been developed based on the self-assembly of a homogeneous catalyst in a fibrous network of multiwalled carbon nanotubes (MWNTs). Dimerization of an amide-based chiral ligand with a suitable spacer allows for the efficient formation of a heterogeneous catalyst by self-assembly on addition of Er(OiPr)<sub>3</sub>. The self-assembly proceeds in the MWNT fibrous network and small clusters of assembled catalyst are confined in the MWNTs, producing an easily handled solid-phase catalyst. The resulting MWNT-confined catalyst exhibits a good catalytic performance in a catalytic asymmetric Mannich-type reaction, which can be conducted in a repeated batch system and in a continuous-flow platform.

The development of heterogeneous catalysts is a continuous area of research because of their value in industrial applications.<sup>[1,2]</sup> In contrast to the broad availability and intensive use of achiral heterogeneous catalysts, their chiral counterparts, which enable enantioselective catalysis, have been less explored because of the inherent difficulty of rendering stereochemical differentiation by catalysts in the solid phase. A commonly exploited approach to producing heterogeneous chiral catalysts involves utilization of the covalent linkage of the chiral elements used in homogeneous catalysis, e.g., chiral organocatalysts or chiral ligands for metal-based catalysts, to a given solid phase material. However, a decrease in catalytic activity and/or stereoselectivity frequently arises, and is associated with the distinct chemical environment of the catalytically active sites in the solid phase.

Therefore, robust and reliable chiral heterogeneous catalysts are still underdeveloped, and are in high demand for prospective use in continuous-flow platforms in the chemical and pharmaceutical industries.<sup>[3,4]</sup> Recently, we reported the use of multiwalled carbon nanotubes (MWNTs) as suitable solid sup-

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ports for heterogeneous Nd/Na catalysts for the *anti*-selective nitroaldol reaction.<sup>[5]</sup> An insoluble Nd/Na catalyst was formed through self-assembly<sup>[6]</sup> of the catalyst component ligand **1**, NdO<sub>1/5</sub>(O/Pr)<sub>13/5</sub>, and sodium hexamethyldisilazide (NaHMDS; Scheme 1 a).<sup>[5a,b]</sup> When the self-assembly was conducted in the



**Scheme 1.** a) Confinement of the heterogeneous Nd/Na catalyst; b) modification of the chiral ligand for the production of new MWNT-confined catalyst.

presence of MWNTs, the formation of catalyst clusters occurred within the minute MWNT fibrous network. The assembled catalyst was effectively confined within the MWNTs, thereby producing a more stable and readily recoverable catalyst.<sup>[5c,d]</sup> The confinement in MWNT bestowed an extended lifetime to the less stable insoluble catalyst and the thus-obtained recyclable solid-phase asymmetric catalyst was applied to a continuous-flow reaction.<sup>[5e]</sup>

Although MWNT confinement is easily achieved, just by mixing, and no covalent linkage is required,<sup>[7,8]</sup> this methodology is only valid for heterogeneous complexes. We anticipated that linking chiral ligands would lead to heterogeneity on complexation with metals, and a similar MWNT-confined catalyst would be produced. We reasoned that the chiral amide-based ligand **2a** would be well-suited for this study because: (1) Several catalytic asymmetric reactions have been developed using **2a** and rare earth (RE) metal catalysts,<sup>[9]</sup> and (2) **2a**, containing amide functionalities, is prone to form insoluble material on addition of RE cations. Herein, we report on a strategic modification of an amide-based chiral ligand to generate a heteroge

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neous catalyst by self-assembly with  $Er(OiPr)_3$  that was confined in an MWNT network. The confined catalyst could be used repeatedly and was applied to a continuous-flow reaction.

Among the asymmetric catalysts based on **2** a/RE complexes, we focused on a catalytic asymmetric Mannich-type reaction to revisit for the development of our solid-phase catalyst.<sup>[10]</sup> The **2** a/Er catalyst used had been developed by our group as a homogeneous catalyst to promote the Mannich-type reaction of  $\alpha$ -cyanoketones **3** and *N*-Boc imines **4** in a highly stereoselective manner (Scheme 2).<sup>[11,12]</sup> Heterogeneity on com-



Scheme 2. Catalytic asymmetric Mannich-type reaction of  $\alpha$ -cyanoketone 3 and *N*-Boc imine 4 with 2 a/Er catalyst.

plexation with an Er source was essential to render the confinement of an asymmetric catalyst in the MWNTs. In our study, we set out by designing the linked amide-based ligands. We evaluated their heterogeneity on addition of Er(OiPr)<sub>3</sub> and their catalytic performance in the asymmetric Mannich-type reaction. As the simplest strategy was to produce insoluble catalysts by increasing the number of amide functionalities, we envisaged synthesizing a series of dimeric and trimeric ligands **2b-h** (Table 1). A representative synthetic procedure of the dimeric ligand **2e**, having an undecyl linker, is outlined in Scheme 3.<sup>[13]</sup> A linker needed to be installed away from the chiral center and the two aromatic rings located on both sides of **2a** were preferable positions.

For the convergence of the synthetic route, a salicylic acid section was more suitable for installing the linker than the opposite aminophenol moiety, and the chiral intermediate **13** 



was shared for the synthesis of all the linked ligands 2b-h in the later stages (Scheme 3). Synthesis of the requisite linked salicylic acid 10 commenced with the diethynylation of 1,7-dibromoheptane (6) with a lithium acetylide ethylenediamine complex to give undec-1,9-diyne (7). Sonogashira coupling of



Scheme 3. Representative synthetic procedure for 2e: a) Lithium acetylide ethylenediamine complex, DMSO, 0°C, 2 h, 93%; b) Cul, [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>], Et<sub>3</sub>N, DMF, RT, 4 h, 71%; c) Pd(OH)<sub>2</sub>, H<sub>2</sub>, THF, RT, 5 h, >99%; d) KOH (aq.), 100°C, 3 h, 93%; e) pivaloyl chloride, Et<sub>3</sub>N, toluene, 0°C, 0.5 h, then 12, RT, 1 h; f) 4 N HCl/1,4-dioxane, RT, 11 h, 89% (2 steps); g) EDCl-HCl (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride), HOBt-H<sub>2</sub>O, Et<sub>3</sub>N, DMF, RT, 3 h, 95%; h) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 3 h, 81%.

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Figure 1. Catalytic asymmetric Mannich-type reaction promoted by the MWNT-confined 2e/Er catalyst in a continuous-flow platform

methyl 4-iodo-2-methoxybenzoate (8) and diyne 7 gave linked compound 9, which was subjected to hydrogenation of triple bonds and basic hydrolysis of the methyl ester to afford the linked salicylic acid 10. The requisite chiral unit 13 was obtained as a hydrochloride salt by amide formation via mixed anhydride and Boc deprotection without chromatographic purification. Two chiral units of 13 were attached to the linked salicylic acid 10 via amide formation to give 14 in 95% yield. Final deprotection of the four methyl ether groups by BBr<sub>3</sub> furnished linked tetraamide 2e. Other linked amides with different number of methylene groups (2b-f), a 1,4-diethylbenzene linker (2g), or a trident linker (2h), were synthesized in a similar manner and evaluated in the Mannich-type reaction of 3a and 4a (Table 1). In contrast to ligand 2a, all the linked ligands 2b-h produced an insoluble white suspension after addition of an equimolar amount of Er(OiPr)<sub>3</sub> in ether, although their catalytic performance (the catalyst used was a mixture of precipitate and supernatant) differed significantly.

Ligand **2b**, with the shortest C2 linker, afforded the product **5a** in approximately 1:1 diastereomeric ratio with moderate enantioselectivity, which was a far worse stereochemical outcome than that obtained using the original catalyst **2a**/Er (Table 1, entries 1 and 2). The stereoselectivity improved gradually by increasing the linker length (Table 1, entries 2–6), and the highest *syn* selectivity, as well as enantioselectivity, was observed with ligand **2e**, having a C11 linker (Table 1, entry 5). Dimeric and trimeric ligands **2g** and **2h**, having a benzene core, gave the product with eroded stereoselectivity was observed with the trimeric ligand **2h**, presumably because the closely located catalytically active sites gave rise to negative interference (Table 1, entry 8).

The confinement of the insoluble Er complex of most effective ligand 2e in the MWNTs was then examined (Scheme 4). To a homogeneous 0.04  $\mbox{m}$  THF solution of 2e were sequentially added MWNT (250 wt% based on 2e) and a 0.2  $\mbox{m}$  THF solution of Er(OiPr)<sub>3</sub>, executing the self-assembly process of 2e/Er within the minute MWNT network. In contrast to catalyst preparation in the absence of MWNTs, a white suspension was not observed after 1 h of stirring at room temperature, which was indicative of self-assembly and confinement of the 2e/Er complex in the MWNT network. The thus-obtained black solid material was centrifuged and washed with THF. Quantitative analysis of the supernatant and washings revealed that 72.5% of ligand 2e and 92.7% of  $Er^{3+}$  were incorporated within the MWNT.<sup>[14]</sup> The isolated and washed solid-phase MWNT-confined catalyst exhibited similar catalytic performance to 2a/Er in the Mannich-type reaction of 3a and 4a.

The durability and robustness of the MWNT-confined catalyst were examined by repeated use in the Mannich-type reactions of several substrates (Table 2). 5 mol% of the MWNT-confined catalyst was suspended in an ethereal solution of representative substrates **3a** and **4a** at 0 °C (Table 2, entry 1). After 3 h, the mixture was diluted with ether and centrifuged (ca. 3000 rpm, 30 s), and the resulting supernatant was extracted using a syringe. Ether was added to suspend the MWNT-



Scheme 4. Catalyst preparation procedure for the MWNT-confined catalyst and its catalytic performance. White solid objects in the pictures are Tefloncoated magnetic stirring bars.

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<b>Table 2.</b> Repeated use of the MWNT-confined catalyst in asymmetric Mannich-type reaction of <b>3 a</b> and $4^{[a]}$										
o	CN +	BocN	M c	WNT-co atalyst (2 5 mol	O NHBoc					
	) /	H AI	E	t <sub>2</sub> O, 0 °C	c, 1.5 h		vr.			
3a 4 5										
Entry	Ar	4	Product	Cycle	Yield [%] <sup>[b]</sup>	syn/anti <sup>[c]</sup>	ee <sup>[d]</sup> [%]			
	_			1	98	94:6	96			
				2	99	92:8	97			
1 <sup>[e]</sup>	Ph	4a	5 a	3	99	91:9	96			
				4	99	89:11	95			
				5	99	87:13	94			
				1	99	97:3	95			
			5 b	2	99	98:2	94			
2	2-naph	4b		3	98	97:3	93			
				4	96	96:4	92			
				5	99	95:5	91			
				1	00	07.2	00			
				1	99	97:3	98 09			
3	2-MeC H	4.0	50	2	99	97.5	90			
	2-mec <sub>6</sub> n <sub>4</sub> +c	40	50	4	99	97:3	98			
				5	99	96:4	98			
				1	99	94:6	97			
	4-MeC <sub>6</sub> H <sub>4</sub> 4			2	99	92:8	96			
4		4 d	5 d	3	98	90:10	96			
				4	99	89:11	95			
				5	99	89:11	95			
				1	99	97:3	97			
				2	99	95:5	95			
5	2-CIC <sub>6</sub> H <sub>4</sub> <b>4</b> e	4e	5 e	3	99	93:7	94			
				4	99	92:8	93			
			5	99	90:9	92				
				4	00	07.2	02			
	4-CIC <sub>6</sub> H <sub>4</sub> 4 f			ו כ	90 85	97:3 97:3	93 87			
6		4 f	5 f	∠ 3	96	96:4	86			
ľ		••	5.	4	94	94:6	82			
			5	93	93:7	78				
	4-MeOC <sub>6</sub> H <sub>4</sub> <b>4 g</b>									
				1	99	94:6	93			
			_	2	99	94:6	95			
7		4 g	5 g	3	99	95:5	97 07			
				4	99 99	94:0 94:6	97 97			
					77	54.0	91			
[a] Cat	talyst loading	was d	esignated	based	on the amo	ount of Er(	O <i>i</i> Pr)₃			
used t	to prepare th	e cataly	st; [b] dete	ermined	I by 'H NMR	spectrosco	py of			
the crude reaction mixture with DMF as an internal standard; [c] deter-										
minea by "H NMK spectroscopy; [a] the <i>ee</i> of the <i>syn</i> isomer, determined										
by chiral stationary-phase HPLC analysis; [e] reaction time was 3 h.										

confined catalyst, and the centrifugation/extraction was repeated. After this washing process, another batch of substrates in ether was introduced to the remaining MWNT-confined catalyst to run the next reaction. The collected supernatants were concentrated to give the crude product without any workup procedure. A high catalytic activity was observed, even after five cycles of use, albeit with a slight loss in stereoselectivity. A high catalytic activity was maintained with repeated use for other substrates (Table 2, entries 2–7). The *N*-Boc imines **4**,

bearing various substituents with varying steric and electronic properties, could be employed to produce similar reaction outcomes to those of the reactions promoted by the original 2a/ Er catalyst, showing that 2e provided a nearly identical chiral environment to 2a with a high heterogeneity. The synthetic utility of the MWNT-confined 2e/Er catalyst culminated with a catalytic asymmetric reaction in a continuous-flow platform (Figure 1).  $^{\left[ 15\right] }$  The freshly prepared catalyst, using 0.1 and 0.1 mmol of 2e and Er(OiPr)<sub>3</sub>, respectively, was suspended in THF with dried Celite and transferred to two empty stainless steel columns ( $\phi$  10×30 mm each, total inner volume = 4.7 mL) equipped with stainless steel frits (2 µm) for end-capping. Ether was passed through the column at 15 mLh<sup>-1</sup> to wash out any incomplete complexes. Quantitative analysis of the collected initial washings indicated that 71.1% of 2e and 88.8% of Er<sup>3+</sup> were incorporated in the MWNTs (0.089 mmol on  $Er^{3+}$ ).<sup>[14]</sup>  $\alpha$ -Cyanoketone **3a** and *N*-Boc imine **4a** were separately supplied as ethereal solutions using syringe pumps at 7.5 mLh<sup>-1</sup>. The two streams connected at a T-shaped mixer junction before the catalyst column, and were cooled to 0°C. To remove the trace amounts of water and acidic impurities, 4a was passed through MS 3A and NaHCO<sub>3</sub> columns before the T-junction. The continuous elution of product 5a was monitored every 8 h. The flow system was operated for 56 h and the collected crude product was purified to afford 6.27 g of 5a (96% average conversion) with syn/anti ratio = 93:7 and 94% ee, which corresponded to a turnover number (TON) of 225. The significantly reduced cooling volume (4.7 mL) is advantageous for large-scale implementation, as the volume of the reaction mixture for a standard batch system to give an identical amount of **5** a is as high as 199 mL.<sup>[16]</sup>

In conclusion, a solid-phase catalyst 2e/Er was developed for an asymmetric Mannich-type reaction of  $\alpha$ -cyanoketone and *N*-Boc imines by a strategic modification of the ligand structure. Self-assembly of 2e and  $Er(OiPr)_3$  proceeded in an MWNT network to give a heterogeneous MWNT-confined catalyst that allowed repetitive use and gram-scale reaction in a continuous-flow platform. Further generalization of our MWNT confinement strategy to produce synthetically useful solid phase catalysts is ongoing.

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**Keywords:** asymmetric catalysis · carbon nanotubes · erbium · heterogeneous catalysis · Mannich reaction

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- [16] Standard conditions (0.1 M) to produce 6.27 g of 5a (19.9 mmol) requires 199 mL solvent and a corresponding container in a batch system.

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# COMMUNICATION

### Heterogeneous Catalysis

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A Carbon Nanotube Confinement Strategy to Implement Homogeneous Asymmetric Catalysis in the Solid Phase



A readily recyclable asymmetric catalyst was developed based on the self-assembly of a homogeneous catalyst in a fibrous network of multiwalled carbon nanotubes (MWNTs). The resulting MWNT-confined catalyst exhibited a high catalytic performance in a catalytic asymmetric Mannich-type reaction, which could be conducted in a repeated batch system and in a continuous-flow platform.