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Self-Supported Chiral Titanium Cluster (SCTC) as a Robust Catalyst for the Asymmetric Cyanation of Imines under Batch and Continuous Flow at Room Temperature

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Abstract: A robust heterogeneous selfsupported chiral titanium cluster (SCTC) catalyst and its application in the enantioselective imine-cyanation/ Strecker reaction is described under batch and continuous processes. One of the major hurdles in the asymmetric Strecker reaction is the lack of availability of efficient and reusable heterogeneous catalysts that work at room temperature. We exploited the readily hydrolyzable nature of titanium alkoxide to synthesize a self-supported chiral titanium cluster (SCTC) catalyst by the controlled hydrolysis of a preformed chiral titanium-alkoxide complex. The isolated SCTC catalysts were remarkably stable and showed up to 98% enantioselectivity (*ee*) with complete conversion of the imine within 2 h for a wide variety of imines at room temperature. The heterogeneous catalysts were recyclable more than 10 times without any loss in activity or selectivity. The robustness, high performance, and recyclability of the catalyst enabled it to be used in a packed-bed reactor to carry out the cyanation under continu-

Keywords: amino alcohols • asymmetric synthesis • cluster compounds • continuous-flow reactions • Strecker reaction

Introduction

Natural and unnatural α -amino acids^[1] are essential for life and are frequently used as food additives and as chiral auxiliaries for the synthesis of drugs,^[2] catalysts,^[3] and polymers.^[4]

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ous flow. Up to 97% ee and quantitative conversion with a throughput of 45 mg h⁻¹ were achieved under optimized flow conditions at room temperature in the case of benzhydryl imine. Furthermore, а three-component Strecker reaction was performed under continuous flow by using the corresponding aldehydes and amines instead of the preformed imines. A good product distribution was obtained for the formation of amino nitriles with ee values of up to 98%. Synthetically useful ee values were also obtained for challenging α -branched aliphatic aldehyde by using the three-component continuous Strecker reaction.

The synthesis of amino acids has traditionally been dominated by biocatalytic or enzymatic methods.^[5] Although the chemical synthesis of chiral a-amino acids from the asymmetric cyanation of imines (modified Strecker reaction) has been known since 1996 on a laboratory scale,^[6] the technology has not been scaled-up for large-scale preparations. Recently, Jacobsen and co-workers^[7] reported the synthesis of N-Boc-protected unnatural α -amino acids on a 3–14 g scale by using the cyanation of preformed imines with thioureabased catalysts at low temperatures (-30 to 0 °C). The major hurdles that still need to be overcome in the enantioselective three-component Strecker reaction or the cyanation of imines^[8,9] are the requirement of low temperature to achieve high enantioselectivity (ee) and the lack of availability of simple, inexpensive, and readily available chiral catalysts.

In an effort to address these issues, we recently reported^[10] a simple catalyst system that was derived from partially hydrolyzed titanium alkoxide (PHTA) and chiral *N*-salicyl- β -amino-alcohol ligands as a highly enantioselective catalyst for the cyanation of imines by using TMSCN or HCN under homogeneous reaction conditions at room temperature. We rationalized that the development of heterogeneous chiral catalysts^[11] for the Strecker reaction would be highly desirable for industrial applications in view of the ease of separa-

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tion of the product and the reusability of the catalyst. For this purpose, we took advantage of the readily hydrolyzable nature of titanium alkoxides and their tendency to form supramolecular assemblies.^[12] Herein, we report a class of robust chiral heterogeneous self-supported catalysts^[13] for the asymmetric cyanation of imines that gave high enantioselectivities at room temperature. The catalyst was easy to separate and was recycled efficiently. This system was also placed in a packed-bed reactor to demonstrate the asymmetric Strecker reaction under continuous flow, which has not yet been reported.

Results and Discussion

Catalyst synthesis: The formation of a μ^3 -oxo-bridged tetranuclear titanium cluster by the partial hydrolysis of monocomplex [Ti(binolato)(OiPr)₂], which was formed from titanium alkoxide and chiral binol as a bidentate ligand, has been reported previously.^[14] This soluble complex was reported to catalyze the enantioselective aldol and carbonylene reactions. By adopting a similar procedure to that of Mikami et al.,^[14] we attempted the synthesis of a self-supported chiral titanium cluster (SCTC) by using the tridentate amino-alcohol ligand, H₂L. Various chiral catalysts (SCTC 1-7) were synthesized from 1:1 complexes of titanium alkoxide (Ti(OnBu)₄/Ti(OiPr)₄) and chiral N-salicyl- β amino alcohol ligands (H₂L) by hydrolysis using 0.5-1.0 equivalent of water at 90 °C for 2 h (Scheme 1).^[15] Interestingly, the solubility of the SCTC compounds in common organic solvents mainly depended on the R¹ substituent at the stereogenic center of the chiral ligand. For example, the obtained SCTC compound was completely soluble in toluene when $R^1 = iPr$ (2) and partially soluble when $R^1 = tBu$ (3, 4). Completely insoluble materials were obtained when $R^1 = Bn$ (5, 6) and 3-Me-indyl (7). All of these isolated SCTC compounds were air- and moisture stable and had long shelf-lives.

The soluble and partially soluble clusters (1-4)showed broad ¹H NMR signals that corresponded to oligomeric cluster-type structures. IR absorptions in the region $400-650 \text{ cm}^{-1}$ suggested the presence of Ti-O-Ti structural units.^[16] ESI and MALDI-TOF MS showed complex patterns for soluble clusters 1–4 (see the Supporting Information), with m/zvalues of up to 1500, which suggested that the clusters may have consisted of more than one titanium atom with repeated OTi(L) basic units (Scheme 1). SEM surface-characterization (Figure 1) showed distinct morphologies for the SCTC compounds with different \mathbf{R}^1 groups at the stereogenic center: Soluble SCTC material **2** ($\mathbf{R}^1 = i\mathbf{Pr}$) had a sheet-like morphology, which was formed by the aggregation of nanosized particles. Partially soluble SCTC 4 $(\mathbf{R}^1 = t\mathbf{B}\mathbf{u})$ aggregated as irregular microsized units of various shapes. In the case of insoluble SCTC 6 $(\mathbf{R}^1 = \mathbf{Bn})$, the nanoparticles aggregated to form



Scheme 1. Preparation of self-supported chiral titanium cluster (SCTC) catalysts.

larger microsized particles. Regular microsized particles of $3-5 \,\mu\text{m}$ were formed when $R^1=3$ -Me-indyl (SCTC 7). TGA analysis showed that the SCTC compounds were robust and the weight loss was not significant until 300 °C (see the Supporting Information).

Cyanation of imines: SCTC materials **1–7** were evaluated for the asymmetric cyanation of benzhydryl- (**9a**) and benzyl imines (**9b**) under the optimized conditions reported previously by ourselves for titanium-based homogeneous catalysts.^[10] Very high enantioselectivities (up to 99%) and quantitative yields were observed for the cyanation of compound **9a** in 1 h with 1.5 equivalents of TMSCN and 10 mg of the SCTC catalyst in the presence of *n*-butanol as a proton source in toluene at room temperature (Table 1). Interestingly, the catalyst loading could be lowered to 1 mg without a significant loss in the conversion and *ee* value (Table 1, entry 3). With benzhydryl imine (**9a**) as the substrate, no significant difference in the catalytic performance

Table 1. Cyanation of imines using SCTC catalysts.

	N ^{.PG}	TMSCN — (1.5 equiv) t	SCTC catal -butanol (1.0 oluene (0.70 RT, 2 h	equiv) mL)	HN ^{PG}	
	9 (a , b) (0.20 mmol)				10 (a, b)	
Entry	Catalyst [mg] ^[a]	PG		<i>t</i> [h]	Conv. [%] ^[b]	ее [%] ^[c]
l	SCTC 1 (10)	CHPh	n ₂ (9 a)	1	98	99
2	SCTC 1 (5)	CHPł	1 ₂ (9 a)	2	99	98
3	SCTC 1 (1)	CHPł	n ₂ (9 a)	2	99	97
1	SCTC 2 (1)	CHPł	n ₂ (9 a)	2	99	96
5	SCTC 4 (1)	CHPł	n ₂ (9 a)	2	99	96 ^[d]
5	SCTC 6 (1)	CHPł	n ₂ (9 a)	2	99	97 ^[d]
7	SCTC 7 (1)	CHPł	1 ₂ (9a)	2	98	94
3	SCTC 1 (1)	CH_2P	h (9b)	1	99	72
)	SCTC 4 (1)	CH_2P	h (9b)	1	99	86
10	SCTC 6 (1)	CH_2P	h (9b)	1	99	64

[a] The catalysts were prepared as described in Scheme 1. [b] Determined by 1H NMR spectroscopy. [c] Determined by HPLC. [d] Similar results were obtained with SCTC **3** and SCTC **5**.

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SCTC-2



SCTC-4



SCTC-6

Figure 1. SEM images of the SCTC catalysts.

was observed between the SCTC catalysts, whereas SCTC **4** was the best catalyst for benzyl-protected imine **9b** (Table 1, entry 9). A number of solvents were tested as the reaction medium with 1.0 mg catalyst loading. Conversions and *ee* values for the cyanation of compound **9a** in Et₂O (99%, 88% *ee*), methyl *tert*-butyl ether (98%, 86% *ee*), THF (80%, 60% *ee*), and 1,4-dioxane (79%, 66% *ee*) were all inferior to those in toluene.

The substrate scope for the imine in the cyanation reaction was examined with SCTC **4** as the representative catalyst (Scheme 2). Benzhydryl-protected imines **9c–9f** gave very high *ee* values (94–98%) of the corresponding amino nitriles **10c–10f**. Moderate *ee* values (86–89%) were achieved in the case of benzyl-protected amino nitriles **10g–10i**. The stereochemistry of the amino nitriles were assigned in comparison with the reported optical rotation values.^[7,8] The amino nitriles were readily converted into their corresponding α -amino acids by hydrolysis, as reported previously.^[9]



SCTC-8



Scheme 2. Substrate scope for the cyanation of imines.

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Scheme 3. A) Catalyst-recycling study and B) catalyst-leaching study.

Recycling and leaching studies: In contrast to SCTCs 1–4, catalysts 5–7 were completely insoluble in the reaction medium and could easily be recovered and recycled. The recyclability of the catalysts was examined by using 5.0 mg of SCTCs 5 and 6 in the cyanation of compound 9a under the optimized conditions (Scheme 2). Interestingly, both catalysts were efficiently recycled more than 10 times without any significant loss in catalytic performance (Scheme 3 A). After each run, the reaction mixture was centrifuged to recover the catalyst, which was Table 2 washed with toluene before charging with a fresh reaction mixture.

To understand the heterogeneous nature of the SCTC catalysts, leaching experiments were performed (Scheme 3B). SCTC 6 was stirred with imine 9a and *n*-butanol in toluene for 2 h in the absence of TMSCN. The catalyst was separated by centrifugation and TMSCN was added to the clear solution and stirred for 2 h. Only 20% conversion was observed, with the formation of racemic amino nitrile. On the other hand, the recovered SCTC 6 catalyzed the cyanation of imine 9a with 99% conversion and 96% ee when a fresh reaction mixture (9a, TMSCN, and *n*-butanol) was added. These observations indicated that no appreciable amount of chiral catalyst had leached into the solution and that the enantioselectivity originated from the solid catalyst.

Cyanation of imines under continuous flow: The robustness and efficient recyclability of the SCTC catalyst encouraged us to use it as a solid-phase catalyst for the continuous-flow asymmetric cyanation reaction, which has not been reported previously.^[17]

The interest in developing technologies for organic reactions under continuous flow^[18] has increased in recent years owing to its many advantages, such as low mass-transfer limitations, the safe and easy handling of large amounts of hazardous reagents, uniform reaction conditions throughout the reaction, easy scale-up, etc. We expected that packing the catalyst together with some inert materials would be more practical than packing the catalyst alone in a column reactor. To select a suitable inert material, 5.0 mg of SCTC **6** was independently mixed with equal amounts (by weight) of silica gel, alumina, powdered molecular sieves, and celite, and the catalytic performance was evaluated for the cyanation of imine **9b** under the batch conditions described in Scheme 2 (see the Supporting Information).

When the catalyst was mixed with silica and alumina, complete conversion into compound 10b was obtained with only 10% ee. On the other hand, mixing the catalyst with either molecular sieves or celite did not affect the ee value, whilst higher conversion was obtained with celite. Hence, a mixture of SCTC 6 (250 mg) and celite (250 mg) was packed into a fixed-bed tubular reactor (4 mm×80 mm) and used as a catalyst for the continuous-flow asymmetric cyanation reaction. Toluene solutions of compound 9b (0.25 M), nbutanol (0.25 M), and TMSCN (0.37 M, 1.50 equiv)^[19] were infused through the catalyst cartridge at the flow of $10 \,\mu \text{Lmin}^{-1}$ of each reagent by using high-pressure syringe pumps. However, only 81% conversion was obtained with very a low ee value of 17% (Table 2, entries 1 and 2), which may have been due to the formation of HCN during the hydrolysis of TMSCN in the presence of excess n-butanol.^[20]

Table 2. Flow-rate optimization for the cyanation of imines.



Entry	PG	Flow rate $[\mu L \min^{-1}]$			t	Conv.	ee
		Imine	TMSCN	n-Butanol	[h] ^[a]	[%] ^[b]	[%] ^[c]
1	CH ₂ Ph (9b)	10	10	10	1	81	17
2	CH ₂ Ph (9b)	10	10	10	2	83	16
3	CH_2Ph (9b)	10	10	5	1	>99	54
4	CH_2Ph (9b)	10	10	5	2	>99	63
5	CH ₂ Ph (9b)	10	10	5	3	>99	65
6	CH_2Ph (9b)	10	10	2.5	1	86	37
7	CH ₂ Ph (9b)	10	10	2.5	2	91	40
8	CH_2Ph (9b)	10	8	5	2	>99	63
9	CH_2Ph (9b)	10	8	5	3	>99	64
10	$CHPh_2$ (9a)	10	8	5	1	92	98
11	CHPh ₂ (9 a)	10	8	5	2	92	97
12	$CHPh_2$ (9a)	5	4	2.5	2	80	97
13	$CHPh_2$ (9a)	5	4	2.5	4	91	97
14	CHPh ₂ (9 a)	10	10	5	1	99	97
15	$CHPh_2$ (9a)	10	10	5	2	99	97

[a] Time at which the sample was taken and analyzed. [b] Determined by ¹H NMR spectroscopy. [c] Determined by HPLC.

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We anticipated that this hydrolysis could be minimized by reducing the amount of *n*-butanol. Interestingly, reducing the flow rate of *n*-butanol to $5 \,\mu\text{Lmin}^{-1}$ (0.5 equiv with respect to the imine) improved both the conversion (>99%) and *ee* value (65%) (Table 2, entry 5) to values that were comparable to those from the batch reaction (Table 1, entry 10). Further decrease in the flow rate of *n*-butanol had a negative effect on both the conversion and *ee* value (Table 2, entries 6 and 7). It would also be desirable to reduce the amount of excess TMSCN whilst maintaining the conversion and *ee* value. Accordingly, the flow rate of TMSCN was reduced to $8 \,\mu\text{Lmin}^{-1}$ (1.2 equiv with respect to the imine) without a significant change in the catalytic performance (Table 2, entries 9 and 10).

Next, the cyanation of compound **9a**, which was less-reactive towards cyanide addition than compound **9b**, was carried out under the above-optimized flow rates. Lower conversions were obtained (Table 2, entries 10 and 11), although the *ee* values were comparable to those in the batch reaction. Increasing the flow rate of TMSCN to 10 μ Lmin⁻¹ was necessary to drive the conversion to 99% (Table 2, entries 14 and 15). Under the optimized conditions, the cyanation of compound **9a** was carried out for 85 h without a significant loss in activity or enantioselectivity (Figure 2). This



Figure 2. Conversion and ee value for the continuous-flow cyanation of compound 9a for 85 h.

system afforded a throughput of 45.0 mg h^{-1} with a residence time of 40 min. Excess cyanide was quenched by bubbling through a saturated solution of Fe(SO₄)₂. The amino nitrile product (**10a**) did not contain any cyanide impurities and no significant leaching of the titanium catalyst was noticed. In an independent experiment, the collected amino nitrile (**10a**) was mixed with imine **9a** and the ratio was determined to be 33:67 (**9a/10a**, 98% *ee*) by NMR spectroscopy. TMSCN and *n*-butanol were added to the above mixture, which was stirred for 12 h at room temperature and then analyzed. The ratio only changed to 24:76 (**9a/10a**, 92% *ee*). Thus, the lower *ee* value and increased amount of compound **10a** suggested the presence of an uncatalyzed background reaction.

Three-component Strecker reaction under continuous flow: To make this process more practical, a three-component

asymmetric Strecker reaction was carried out by using the corresponding aldehydes and amines instead of the preformed imines. Quantitative imine formation is necessary to carry out the three-component Strecker reaction under continuous flow. Often, this reaction leads to the formation of a cyanohydrin side-product from the addition of cyanide to the aldehyde. In principle, the imine can be obtained by infusing the aldehyde and amine through a column that is filled with any dehydrating agent or an acid catalyst. Therefore, for our initial experiments, the column $(4 \text{ mm} \times 50 \text{ mm})$ was packed with MgSO₄, and 0.5 M solutions of benzaldehyde and benzhydryl amine in toluene were infused at a flow rate of 5.0 µLmin⁻¹. Only 46% of the aldehyde was converted into the corresponding imine. Similar results were obtained when the column was packed with powdered molecular sieves and sulfamic acid. Interestingly, when TiO₂ (MC 150) was added to the column as a catalyst, complete conversion was obtained with a residence time of 25 min. However, the imine began to precipitate inside the tube at low flow rates.

To avoid this problem, we carried out the imine formation at elevated temperature by using a stainless steel coil reactor without any packing material (Figure 3). Imine formation was successfully achieved by passing 0.5 M solutions of the aldehydes and benzhydryl amine in toluene through a stainless steel coil that was preheated to 70°C (residence time, 50 min). The in-situ-formed imine^[21] and TMSCN^[22] were passed through a cartridge that was filled with catalyst SCTC 6 and celite. No n-butanol was added because the water that had formed during the imine formation was sufficient to act as a proton donor.^[23] A similar throughput (45.0 mg h^{-1}) was achieved with the exclusive formation of amino nitrile; no cyanohydrin side-product was observed. In the three-component Strecker reaction, the flow of TMSCN was optimized to 1.3 equivalents with respect to the imine without compromising the yield. The three-component reaction proceeded well with good product distribution for the formation of amino nitriles from their corresponding aldehydes. Synthetically useful ee values were obtained (Table 3, entries 3-8) when benzhydryl amine was used as the amine partner. Interestingly, in the case of more-challenging α branched aldehydes, such as 3-phenylacetaldehyde, an improved ee value of 87% was achieved for the formation of compound 100 under the optimized flow conditions compared to that of the batch reaction (70% ee). This methodology paves the way for the Strecker reactions of relatively less stable imines.

Conclusion

A highly active and robust heterogeneous self-supported chiral titanium cluster catalyst was developed for the enantioselective Strecker reaction at room temperature. The catalyst was successfully recycled more than 10 times without any significant loss in the catalytic performance. The robustness and ease of recovery of the heterogeneous catalyst

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Figure 3. Customized flow reactor for the three-component Strecker reaction.

Table 3. Continuous-flow three-component Strecker reaction using benzaldehyde and benzhydryl amine.



1	PhCHO	benzyl amine ^[a]	<1	2	>97 (61), 10b
2	PhCHO	PMP amine ^[a]	absent	< 2	>98 (47), 10 j
3	PhCHO	benzhydryl amine	<1	1	>98 (97), 10 a
4	F CHO	benzhydryl amine	<1	<1	>99 (93), 10 k
5	H ₃ C	benzhydryl amine	<1	<1	>99 (97), 10 d
6	Н₃СО СНО	benzhydryl amine	1	3	96 (86), 101
7	CHO	benzhydryl amine	<1	1	>99 (98), 10 m
8	CHO N	benzhydryl amine	<1	9	>90 (97), 10 n
9	СССНО	benzhydryl amine ^[a]	absent	1	>99 (87), ^[b] 10 o

[a] Temperature for imine formation was 60 °C. [b] 70% *ee* was obtained under batch reaction conditions with SCTC **6**.

from the reaction mixture is attractive for the large-scale synthesis of α -aryl and α -alkyl amino nitriles. The continuous-flow asymmetric Strecker reaction reported herein offers operational advantages over batch processes, such as increased atom-efficiency and safer handling of toxic and

hazardous cyanide reagents. To the best of our knowledge, this is the first heterogeneous catalyst that shows high activity and enantioselectivity at room temperature for the cyanation of imines and the three-component asymmetric Strecker reaction under continuous flow.

Experimental Section

General procedure for the synthesis of the SCTC catalyst: Ti-(OnBu)₄ (0.68 g, 2.00 mmol) or Ti(OiPr)₄ (0.59 g, 2.00 mmol) was added to a flame-dried two-necked flask and dry toluene (60 mL) was added. The ligand (2.00 mmol) was added in portions under a flow of argon. After stirring the contents for 1 h at room temperature, H₂O (18.0 μ L, 1.00 mmol in 1.00 mL THF) was added dropwise using a syringe. The reaction mixture was heated to 90 °C and stirred for 2 h. The volatile compounds were removed by distillation to obtain the SCTC catalyst. The catalyst was washed with cold toluene (2×10 mL), dry *n*-hexane (2×10 mL), and the solid was dried under reduced pressure. SCTC catalysts 6 and 7 precipitated during the heating at 90°C and were filtered as solids from a hot toluene solution.

(b) 10 a General procedure for the cyanation of imines: To the SCTC catalyst (1.0 mg), toluene (0.7 mL), imine (0.20 mmol), trime-thylsilyl cyanide (TMSCN, 41 μL, 0.30 mmol),^[23] and *n*-butanol (18 μL, 0.20 mmol) were added sequentially and the mixture was stirred at RT for 2 h. The reaction mixture was filtered through a plug of celite/silica gel, washed with CH₂Cl₂, and the volatile compounds were removed to obtain the amino nitriles. For the recycling experiments, the SCTC catalyst was recovered by centrifugation and added to a fresh reaction mixture.

Cyanation of imines under continuous flow: A 0.25 M solution of imine **9a** (0.29 g in 6.0 mL) or **9b** in toluene (0.41 g in 6.0 mL), *n*-butanol (92 µL in 6.0 mL, 0.25 M), and TMSCN (240 µL in 6.0 mL, 0.33 M, 1.50 equiv) were taken-up in separate syringe pumps. The three reagents

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were infused through the catalyst cartridge at a specified flow rate. The outlet was bubbled through saturated $FeSO_4$ solution to quench the excess cyanides. The product was collected and analyzed by NMR spectroscopy and HPLC.

Three-component Strecker reaction under continuous flow: 0.50 M solutions of the aldehyde and amine in toluene were infused through a preheated (60–70 °C) stainless steel coil. TMSCN (350 µL in 8 mL toluene, 0.33 M) was introduced after 60 min. Quenching of the reaction and analysis was carried out as described before.

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- [21] The quantitative formation of the imine was confirmed by on-line IR spectroscopy (see the Supporting Information).
- [22] Under the reaction conditions, TMSCN could be hydrolyzed to form extremely poisonous HCN gas. The reaction vial should be

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properly sealed. Proper safety precautions must be adhered to and appropriate safety equipment must be used, such as a cyanide detector and personal protection equipment. The reactions must be carried out in a well-ventilated fume-hood.

[23] We have previously observed that controlled quantities of water (up to 0.5 equiv) is also effective as a proton source instead of alcohols

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to obtain high *ee* values under batch conditions in the case of homogeneous titanium catalysts.

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