

INCORPORATION OF MOLECULAR NITROGEN INTO
ORGANIC COMPOUNDS. TITANIUM CATALYZED
NITROGENATION

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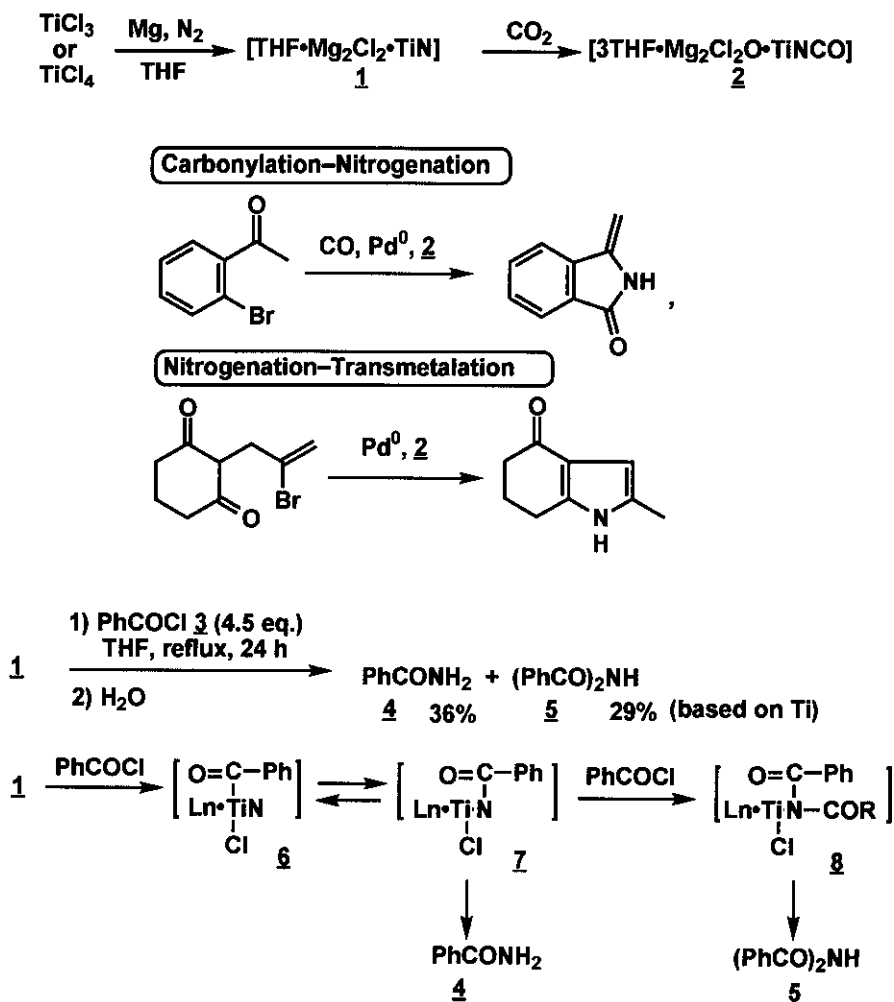
Abstract-----Incorporation of molecular nitrogen into organic compounds was realized using a catalytic amount of TiCl_4 in the presence of excess TMSCl and Li . Various imides were prepared from the corresponding acid anhydrides by use of this catalytic system.

The incorporation of molecular nitrogen into organic compounds is very challenging work. These processes would be realized by use of the transition metals. We have already reported the incorporation of molecular nitrogen into organic compounds¹ using the titanium nitrogen complex² and titanium isocyanate complex³ generated from molecular nitrogen, Mg , and TiCl_4 or TiCl_3 . By the reaction, many heterocycles such as isoindolinone,^{1b} quinazoline,^{1b} indole,^{1c} and quinoline derivatives^{1c} were synthesized in good yields. These reactions are very interesting, however, an equimolar amount of the titanium isocyanate complex (2) is required for the preparation of the heterocycle (Scheme1).

Thus, the next problem is to examine whether the reaction proceeds by a catalytic amount of the titanium nitrogen complex (1) or (2).⁴ In the case of the reaction of the titanium

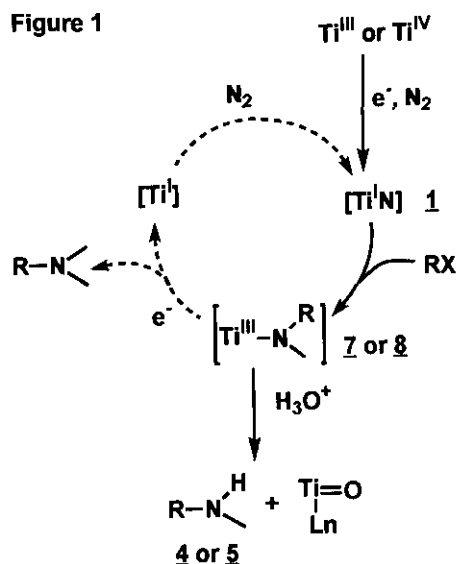
Dedicated to Dr. Arnold Brossi, Scientist Emeritus NIH, on the occasion of his 70th birthday.

nitrogen complex (1) with benzoyl chloride (3), we proposed the following reaction course: Oxidative addition of the low-valent titanium nitrogen complex(1) (1) occurs to produce the benzoyl titanium nitrogen complex(III) (6). Migration of the benzoyl group from titanium to nitrogen provides the amide complex (7). Benzoyl chloride further reacts with 7 to produce the imide complex (8). Hydrolysis of these complexes (7 and 8), afforded the amide (4) and the imide (5). Presumably, the oxidation state of the amide complex would be same as that of the imide complex (8) because benzoyl chloride would react with nitrogen on the titanium nitrogen complex (7).



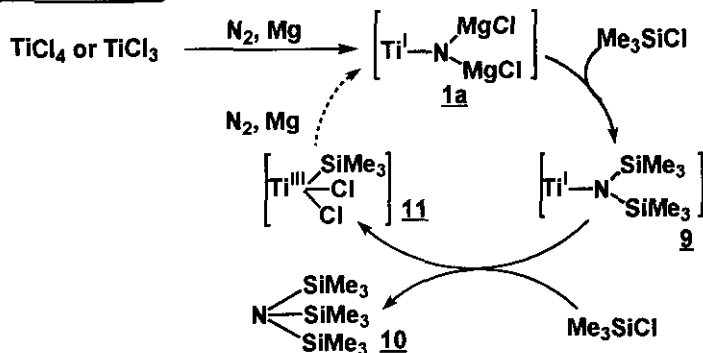
In order to make this reaction proceed using a catalytic amount of the titanium complex (1), the amide (7) or imide complex (8) must be reduced to the low-valent titanium complex (1) with an appropriate reducing agent (Figure 1). It was considered that excess Mg would reduce Ti^{III} to Ti^I because $TiCl_4$ or $TiCl_3$ was reduced to titanium nitrogen complex(I) with Mg under nitrogen.

Figure 1



The titanium nitrogen complex (1) can be considered to be (1a). If trimethylsilyl chloride (TMSCl) is added to this reaction, 1a would react with TMSCl to give the titanium silylamine complex (9). The TMSCl would then oxidatively add to 9 followed by transmetalation to afford tris(trimethylsilyl)amine (10) and the titanium complex (11). If excess Mg is present, the titanium complex (11) would be reduced under nitrogen to the titanium nitrogen complex (1a).

Working Hypothesis



For the preliminary work, the reaction was carried out in the presence of TMSCl using the previously reported reaction conditions. Namely, a mixture of TiCl_4 , TMSCl, and Mg in THF was stirred under nitrogen at room temperature overnight, and then benzoyl chloride (**3**) was added to the mixture. The whole mixture was refluxed overnight. After the usual work up, the desired benzamide (**4**) and benzimide (**5**) were obtained. The total yields of the amide (**4**) and the imide (**5**) were same as that of the previous work (Table 1, runs, 1 and 2) and the reaction proceeded even at room temperature (run 3). When the reaction was carried out in excess Mg (50 eq.) and TMSCl (50 eq.) at room temperature, the yields were improved. On the other hand, the use of Li as a reducing agent afforded the same effect and the reaction conditions are moderate (runs 5, 6 and 7). In these cases, the yields of the desired product were improved, but the reaction did not proceed by a catalytic amount of TiCl_4 in each case.

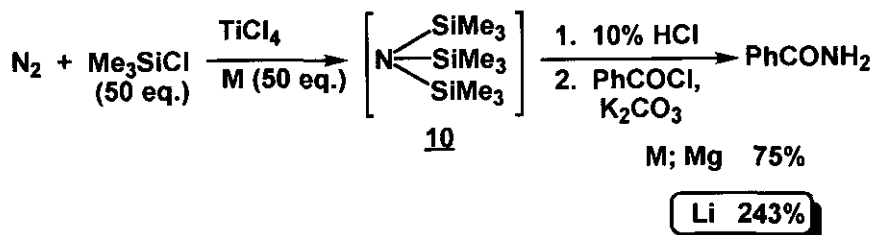
Table 1 Effect of Metals

$\text{TiCl}_4 + \text{N}_2 + \text{Metal}$ $\downarrow \text{Me}_3\text{SiCl}$ $\text{PhCOCl} \xrightarrow{\hspace{1.5cm}} \xrightarrow{\text{H}_2\text{O}} \text{PhCONH}_2 + (\text{PhCO})_2\text{NH}$							
run	Metal (eq.)		Me_3SiCl	Temp	Yields (%) [*]		
					<u>4</u>	<u>5</u>	Total
1	Mg	(4)	none	reflux	27	1	28
2	Mg	(4)	5 eq.	reflux	23	6	29
3	Mg	(4)	5 eq.	rt ^{**}	13	9	22
4	Mg	(50)	50 eq.	rt ^{**}	36	20	56
5	Li	(50)	50 eq.	rt ^{**}	42	17	59
6	Li	(50)	50 eq.	0 °C	21	11	32
7	Li	(50)	50 eq.	reflux	33	6	39

* based on Ti

^{**} room temperature

It is considered that tris(trimethylsilyl)amine (**10**) can not react with benzoyl chloride. In order to get all of the incorporated nitrogen, hydrolysis of the reaction products with 10% HCl was tried. Titanium nitrogen complex, which was prepared from TiCl_4 , TMSCl and reducing agent under nitrogen in THF, was hydrolyzed with 10% HCl. The aqueous solution was made basic with K_2CO_3 and then the benzene solution of benzoyl chloride was added. The whole solution was stirred vigorously. After usual work up, we obtained benzamide in 75% yield when Mg was used as a reducing agent. On the other hand, when Li was used as a reducing agent, benzamide was obtained in 243% yield based on the titanium.



Using Li as a reducing agent, we examined the various forms of Li. Each form of Li [wire (243%), granular (250%), and powder (147%)] was an effective reducing agent. However, the longer reaction time decreased the yield of the desired product (run 2).

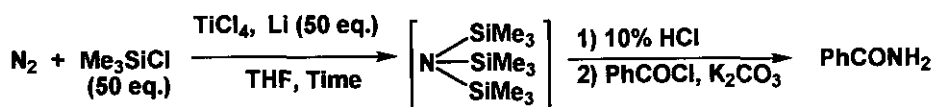


Table 2 Nitrogenation of PhCOCl

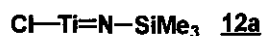
Run	Shape of Li	Time (h)	Yield (%) [*]
1	wire	24	243
2	wire	48	189
3	granular	24	250
4	powder	24	147

^{*} Based on titanium complexes.

The reaction mechanism is not clear at present. Thus, the ratio of Li or TMSCl to TiCl₄ was changed. The results are shown in Table 3. In the absence of TMSCl, the desired product was not obtained and the use of 4 eq. of Li and 5 eq. of TMSCl did not afford the product (Table 3, runs 1 and 2). When 10 eq. of Li was used for this reaction, the desired product was obtained in 79% yield, and increasing the amount of Li raised the yield of the desired product.

Table 3 The effect of Li and Me₃SiCl

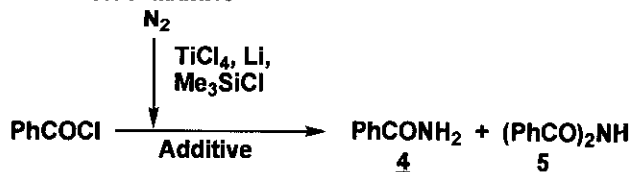
run	Li (eq.)	Me ₃ SiCl (eq.)	Yield (%)
1	4	—	—
2	4	5	—
3	10	10	79
4	10	50	83
5	20	20	142
6	30	30	202
7	50	50	250



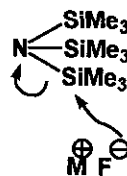
Shiina reported⁵ the reductive silylation of molecular nitrogen *via* fixation to tris(trimethylsilyl)amine. He described that using CrCl_3 for the metal afforded 5.4 eq. mol. of tris(trimethylsilyl)amine (**10**) but TiCl_4 afforded only 0.8 eq. mol. of **10**. In our reaction, we obtained 250% of benzamide. Thus, other nitrogen sources, such as the titanium nitrogen complex (**12a** or **12b**), should be produced.⁶

Next, in order to remove the silyl group of titanium-nitrogen complex, various reagents were added. The results are shown in Table 4. The addition of CsF increased the yield of the desired product (Table 4, run 2). However, other additives such as KF , $\text{KF}\cdot\text{HF}$, and Me_3SiOTf were not effective.

Table 4 Effect of additive



run	Additive (eq.)	Yields (%)		
		4	5	Total
1	none	42	17	59
2	CsF (10)	77	11	88
3	KF (10)	37	17	54
4	$\text{KF}\cdot\text{HF}$ (10)	39	—	39
5	Me_3SiOTf (0.1)	22	15	37



On the basis of these results, cyclic imide was synthesized using titanium catalyzed nitrogenation. To a solution of the nitrogen fixation products prepared from TMSCl (10 eq.), TiCl_4 (1 eq.), and Li (10 eq.) under nitrogen in THF, phthalic anhydride (**13**) (3 eq.) was added and the solution was stirred at room temperature overnight. Hydrolysis with H_2O followed by the usual work up gave the desired phthalimide (**14**) in 23% yield (Table 5, run 1). When the reaction was carried out in the presence of 50 eq. of Li and TMSCl , the yield of (**14**) raised to 51%. It was very surprising that when the THF solution was refluxed overnight in the presence of CsF , the desired phthalimide (**14**) was obtained in 204% yield (run 3). These results suggest that incorporation of molecular nitrogen into phthalic anhydride (**13**) can be achieved by titanium catalyzed nitrogenation.

Subsequently, various cyclic imides (**14b**, **14c** and **14d**) were prepared from the corresponding acid anhydrides, (**13b**, **13c** and **13d**). The results were shown in Scheme. The five membered imides (**14b** and **14c**) were obtained in 142% and 144% yields based on TiCl_4 , respectively. But this method is not effective for the formation of six membered ring.

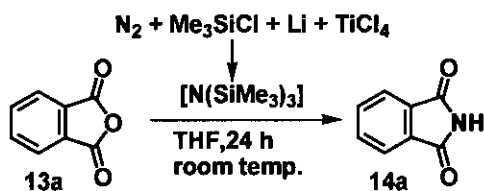
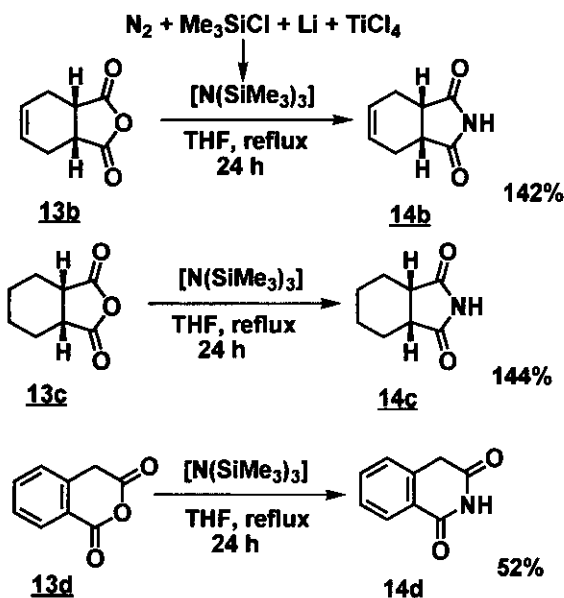


Table 5 Incorporation of N_2 into **13**

run	Li	Me_3SiCl	Additive	Yield
1	10 eq.	10 eq.	—	23%
2	50 eq.	50 eq.	—	51%
3	50 eq.	50 eq.	CsF	204%



The important characteristic of this reaction is as follows: The incorporation of molecular nitrogen proceeds using a catalytic amount of TiCl_4 in the presence of excess Li and TMSCl under mild conditions.⁷ The procedure for the nitrogen fixation is easy. The nitrogen

fixation products $[(\text{Me}_3\text{Si})_3\text{N}, \text{Ti}=\text{NSiMe}_3 \text{ or others}]$ can be easily converted to the cyclic imides in the presence of CsF in one pot. Further studies for the incorporation of molecular nitrogen into organic compounds are now in progress.

EXPERIMENTAL SECTION

General Experimental Procedure. All reactions were run under argon atmosphere except the preparation of the titanium nitrogen complex. Melting points were determined on a Yanagimoto No. 815 melting point apparatus or Ishii melting point apparatus and are uncorrected. Ir spectra were recorded on a JASCO A-300 spectrophotometer and PERKIN ELMER 1600 FTIR. ^1H Nmr spectra were measured on a JEOL FX-90Q at 90 MHz or JEOL FX-100 at 100 MHz and JEOL GX-270 and EX-270 at 270 MHz. EI-mass and high resolution mass spectra were recorded on a JEOL JMS DX-303 instrument.

General Procedure for the Preparation of Titanium-Nitrogen Complex. To a THF suspension of Li or Mg was added TiCl_4 (and TMSCl) at -78°C under nitrogen and the whole mixture was stirred at room temperature overnight. The undissolved material was filtered off under nitrogen and the filtrate was used as the titanium-nitrogen complex.

Reaction of Titanium-Nitrogen Complex with Benzoyl Chloride. To a THF solution of titanium-nitrogen complex, prepared from TiCl_4 (0.11 ml, 1.00 mmol) and Mg (97.0 mg, 3.99 mmol) in THF (3.0 ml) under nitrogen, was added benzoyl chloride (0.35 ml, 3.02 mmol) at -78°C and the solution was refluxed overnight. Water was added at 0°C and the solution was stirred overnight. The aqueous solution was extracted with ethyl acetate and the organic layer was washed with sat. NaHCO_3 solution, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane=1/4) to give benzamide (32.3 mg, 27%, mp 129°C) and benzimide (3.0 mg, 1%).

Reaction of Titanium-Nitrogen Complex with Benzoyl Chloride in the Presence of TMSCl . To a suspension of TiCl_4 (0.11 ml, 1.00 mmol) and Mg (97.0 mg, 3.99 mmol) in THF (3 ml) was added TMSCl (0.63 ml, 4.96 mmol) under nitrogen and the solution was

stirred overnight. The undissolved material was filtered off. To the THF solution was added benzoyl chloride (0.35 ml, 3.02 mmol) and the solution was refluxed overnight. After usual work up, benzamide (28.0 mg, 23%) and benzimide (14.3 mg, 6%) were obtained.

Titanium Catalyzed Nitrogenation. To a THF solution of titanium-nitrogen complex prepared from Li (granule, 186 mg, 26.8 mmol), TiCl_4 (0.055 ml, 0.50 mmol) and TMSCl (3.20 ml, 25.2 mmol) in THF under nitrogen overnight, was added 10% HCl and the solution was stirred overnight. The aqueous layer was separated and was made basic with K_2CO_3 . To the solution was added K_2CO_3 (1 g, 7.2 mmol) and benzoyl chloride (0.58 ml, 5.00 mmol) in benzene (30 ml) and the solution was stirred overnight. After usual work up, benzamide (151.4 mg, 250%) was obtained.

General Procedure for the Synthesis of Imide (14) from Acid Anhydride (13) Using Titanium Catalyzed Nitrogenation. A THF solution of titanium-nitrogen complex, prepared from Li (174 mg, 25.0 mmol), TiCl_4 (0.055 ml, 0.50 mmol) and TMSCl (3.20 ml, 25.2 mmol) in THF (7.5 ml) under nitrogen, was added a THF solution of the acid anhydride (4.91 mmol) and CsF (760 mg, 5.00 mmol) and the solution was refluxed overnight. After usual work up, the residue was purified by column chromatography on silica gel to give the imide.

Synthesis of Phthalimide (13a). The crude product, prepared from phthalic anhydride (727 mg, 4.91 mmol), CsF (760.2 mg, 25 mmol), Li (174 mg, 25.0 mmol), TiCl_4 (0.055 ml, 0.50 mmol) and TMSCl (3.20 ml, 25.2 mmol) in THF (7.5 ml) was purified by column chromatography (ethyl acetate/hexane=1/2) to give phthalimide (150.1 mg, 205%). mp 237-239 °C (from CH_2Cl_2 -hexane) (lit.,⁸ 238 °C); ν_{max} (KBr) 3200, 1770, 1740, 1600 cm^{-1} ; ^1H -nmr (CDCl_3) 7.60-8.00(m, 4H); mass m/z 147 (M^+), 104, 76.

Synthesis of cis-1,2,3,6-Tetrahydrophthalimide (13b). The crude product, prepared from *cis*-1,2,3,6-tetrahydrophthalic anhydride (756.1 mg, 5 mmol), CsF (760.2 mg, 25 mmol), Li (174 mg, 25.0 mmol), TiCl_4 (0.055 ml, 0.50 mmol) and TMSCl (3.20 ml, 25.2 mmol) in THF (7.5 ml), was purified by column chromatography (ethyl acetate/hexane=1/3) to give *cis*-1,2,3,6-tetrahydrophthalimide (107.8 mg, 142%). mp 132-135.5 °C (from CH_2Cl_2 -hexane) (lit.,⁹ 136.5-137.3 °C); ν_{max} (KBr) 3200, 1756, 1702, 1600 cm^{-1} ; ^1H -

nmr (CDCl₃) 2.19-2.27 (m, 2H), 2.57-2.67 (m, 2H), 3.10-3.16 (m, 2H), 5.94-6.00 (m, 2H), 8.13(br s, 1H); mass m/z 151 (M⁺), 122, 107, 79.

Synthesis of *cis*-Hexahydrophthalimide (13c). The crude product, prepared from *cis*-hexahydrophthalic anhydride (771.6 mg, 5 mmol), CsF (760.2 mg, 25 mmol), Li (174 mg, 25.0 mmol), TiCl₄ (0.055 ml, 0.50 mmol) and TMSCl (3.20 ml, 25.2 mmol) in THF(7.5 ml), was purified by column chromatography (ethyl acetate/hexane=1/3) to give *cis*-1,2,3,6-tetrahydrophthalimide (110.8 mg, 144%). mp 135-136 °C (from CH₂Cl₂-hexane) (lit.,⁹ 137°C); ir ν max (KBr) 3140, 1762, 1709 cm⁻¹; ¹H-nmr (CDCl₃) 1.42-1.51 (m, 4H), 1.74-1.91 (m, 4H), 2.87-2.96 (m, 2H), 7.98(br s, 1H); mass m/z 153 (M⁺), 138, 125, 111, 99.

Synthesis of Homophthalimide (13d). The crude product, prepared from homophthalic anhydride (810.5 mg, 5 mmol), CsF (760.0 mg, 25 mmol), Li (174 mg, 25.0 mmol), TiCl₄ (0.055 ml, 0.50 mmol) and TMSCl (3.20 ml, 25.2 mmol) in THF(7.5 ml), was purified by column chromatography (ethyl acetate/hexane=1/1) to give homophthalimide (42 mg, 52%). mp 234-238.5 °C (from EtOH) (lit.,¹⁰ 233°C); ir ν max (KBr) 3167, 1705, 1680, 1600 cm⁻¹; ¹H-nmr (CDCl₃) 3.94 (s, 2H), 7.23-7.27 (m, 1H), 7.36-7.41 (m, 1H), 7.51-7.58(m, 1H), 8.11-8.15 (m, 1H), 9.59 (br s, 1H); mass m/z 161 (M⁺), 118, 90.

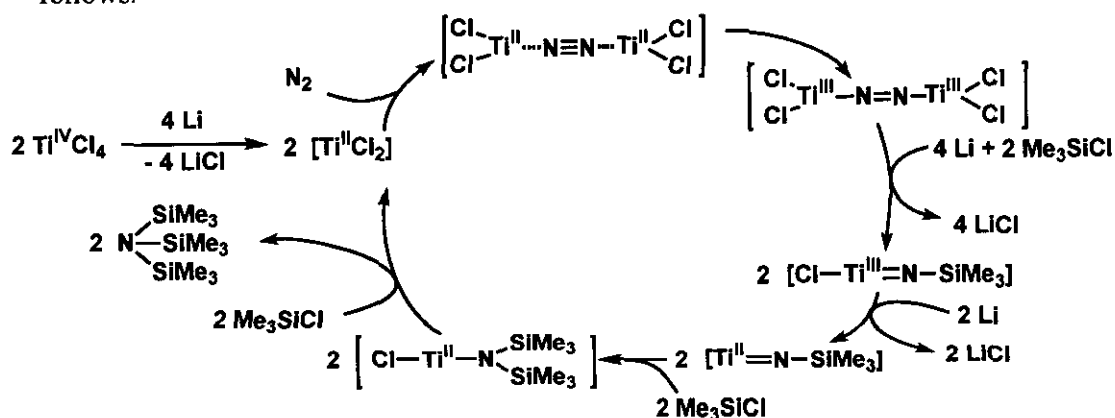
ACKNOWLEDGEMENT

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