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NITROGEN FIXATION USING TITANIUM COMPLEX: REINVESTIGAION OF THE REACTION CONDITIONS

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Abstract—The amounts of Li and TMSCl of a TiX_4-Li-TMSCl system for a nitrogen fixation method, previously reported by our group, were examined. As the results, the reactivity of titanium-nitrogen complexes prepared from 4 equiv. of Li and 6 equiv. of TMSCl for $Ti(OPr\text{-}i)_4$ (1 equiv.) under an atmosphere of nitrogen was same as that of titanium-nitrogen complexes reported previously.

Nitrogen fixation is a very interesting and attractive process.[1] We previously reported a novel nitrogen fixation method using a TiX_4-Li-TMSCl system.[2a,b] The procedure used for nitrogen fixation was very simple. A THF solution of $Ti(OPr\text{-}i)_4$ or $TiCl_4$ (1 equiv.) and TMSCl (10 to 16 equiv.) was stirred in the presence of Li (10 equiv.) at room temperature overnight under an atmosphere of nitrogen or dry air to produce titanium-nitrogen complexes (**1**).[2a] A substrate was then added to the THF solution, and the solution was stirred at an appropriate temperature. After the usual workup, nitrogen heterocycles were obtained in good to moderate yields. Using this method, we have synthesized many heterocycles[2] such as indole, quinoline, indolizine, quinolizine, and isoquinolone derivatives from compounds having a keto carbonyl or carboxyl groups in a tether,[2c,2d] and we have also synthesized natural products, such as

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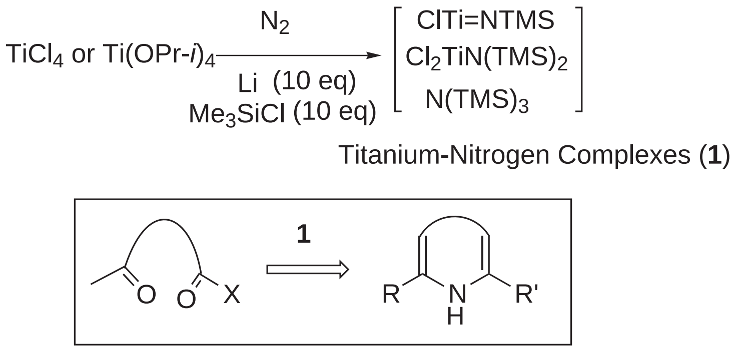
Dedicated to the memory of emeritus professor Yuichi Kanaoka (Hokkaido University)



Scheme 1. Novel Nitrogen Fixation Method

lycopodine,[2e] monomoline I,[2f] and pumiliotoxine C (Scheme 1).[2g] Using titanium-nitrogen complexes and a palladium catalyst, non-substituted anilines[3a] and amides[3b] were successively synthesized from aryl bromides.

We re-examined the reaction conditions because excess amounts of Li (10 equiv.) and TMSCl (10 or 16 equiv.) to TiX_4 were used for preparation of titanium-nitrogen complexes (**1**). The possible reaction course for formation of these complexes is shown in Figure 1.

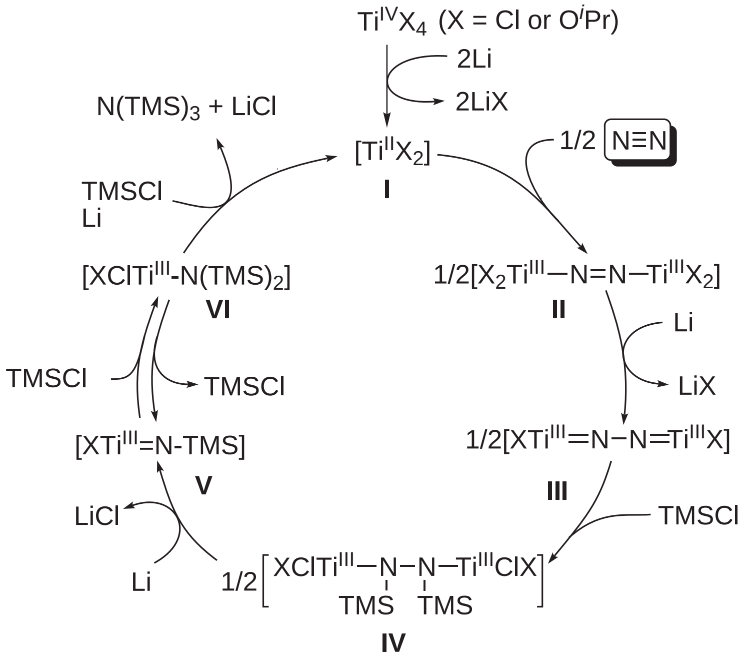


Figure 1. Generation of Titanium-Nitrogen Complexes

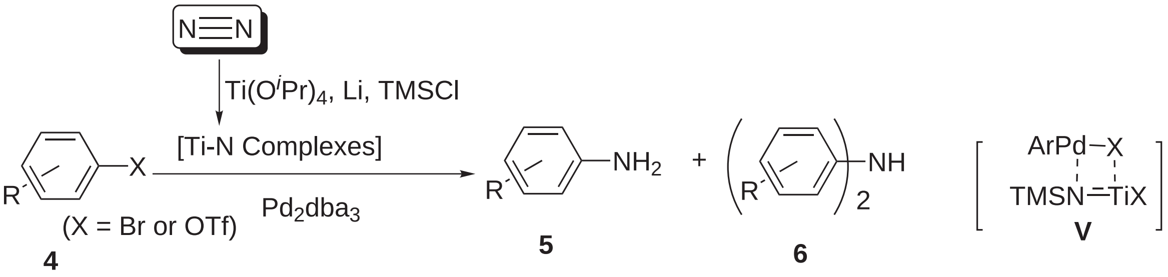
Divalent titanium complex TiX_2 (**I**), produced from TiX_4, would react with nitrogen to produce titanium-nitrogen complex (**II**), which is further reduced by Li to give complex (**III**). In the presence of TMSCl, complex (**III**) is converted into titanium nitrogen complex (**IV**). It is then reduced by Li to produce complex (**V**), which would be in a state of equilibrium with titanium nitrogen complex (**VI**) in the presence of TMSCl. Complex (**VI**) is further reduced by Li to give $N(TMS)_3$, and TiX_2 would be regenerated. As the result, a catalytic cycle is established.[3a]

Synthesis of a titanium-nitrogen complex from molecular nitrogen was first reported by Yamamoto,[4] and several groups have since reported the syntheses of various titanium-nitrogen complexes.[5-10] The structure of titanium-nitrogen complexes (**IIa**)[9] and (**IIb**)[10] were confirmed by X-Ray crystallography (Figure 2). The fact of the formation of these complexes would admit the formation of complex (**II**) shown in Figure 1.

IIa **IIb**

Figure 2. Titanium Nitrogen Complexes

Shiina reported the formation of $N(TMS)_3$ from transition metals and TMSCl in the presence of Li under a nitrogen atmosphere. Although a catalytic process was not established in the case of $TiCl_4$, $N(TMS)_3$ was formed from $TiCl_4$ and TMSCl.[11] This result would agree with the formation of $N(TMS)_3$ shown in Figure 1. On the other hand, we previously reported the synthesis of non-substituted anilines form aryl halide and titanium nitrogen complexes (**1**) and a palladium catalyst.[3a] In some cases, disubstituted anilines (**6**) were produced. Since it was clear that this reaction proceeds by transmetalation of an arylpalladium complex with a titanium-nitrogen complex,[3] disubstituted aniline (**6**) (and aniline (**5**)) should be produced from (**V**) *via* transmetalation (Scheme 2).



Scheme 2. Synthesis of Non-Substituted Aniline

Thus, the amounts of Li and TMSCl needed for the formation of each of the titanium-nitrogen complexes (**V**), **VI** and N(TMS)$_3$ were calculated (Table 1). Since LiOPr-*i* is produced when Ti(OPr-*i*)$_4$ is reduced by Li, a further 3 equiv. of TMSCl is needed. Namely, for the formation of complex (**V**) from Ti(OPr-*i*)$_4$, 4 equiv. of Li and 4 equiv. of TMSCl are required, and in the case of TiCl$_4$, 4 equiv. of Li and 1 equiv. of TMSCl are required.

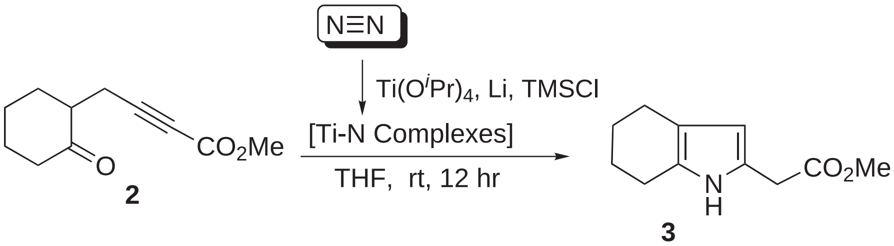
Table 1. Calculated Amounts of Li and TMSCl

Species		Li (eq.)	TMSCl (eq.)	
			TiCl$_4$[a]	Ti(O^{i}Pr)$_4$[b]
XTi=N-TMS	**(V)**	4	1	4
XClTi-N(TMS)$_2$	**(VI)**	4	2	5
N(TMS)$_3$		5	3	6

a) The amounts of TMSCl when TiCl$_4$ was used for nitrogen fixation.
b) The amounts of TMSCl when Ti(OPr-*i*)$_4$ was used for nitrogen fixation.

To determine the amounts of Li and TMSCl required for the formation of titanium-nitrogen complexes, synthesis of indole derivatives (**3**) from keto alkyne (**2**) and titanium nitrogen complexes (**1**) was chosen because the yield of **3** was good[2d] and the reaction proceeded at room temperature (Scheme 3).

At first, it was examined whether N(TMS)$_3$ is a nitrogenation agent or not for the formation of indole derivative (**3**). When a THF solution of **2** and N(TMS)$_3$ (2 equiv.) was stirred at room temperature for 16 h in the presence of CsF (6 equiv.), keto alkyne (**2**) was recovered in 94% yield. This means that N(TMS)$_3$ was not an active nitrogenation species for the synthesis of indole derivative (**3**). We then investigated the amounts of Li and TMSCl required for the formation of a titanium-nitrogen complex. A THF solution of titanium-nitrogen complexes prepared from Ti(OPr-*i*)$_4$ (1.25 equiv.), Li (10 equiv.) and TMSCl (16 equiv.) was added to a THF solution of keto alkyne (**2**) (1 equiv.) and CsF (6 equiv.), and the solution was stirred at room temperature for 12 h. After the usual workup, the desired indole derivative (**3**) was obtained in 77% yield based on the substrate (**2**) (Table 2, run 1). Thus, at first, the amount of Li was changed. When the amount of Li was decreased to 4 equiv. and the same amounts of TMSCl (16 equiv.), Ti(OPr-*i*)$_4$ (1 equiv.), and CsF (6 equiv.) were used for this reaction, the yield of **3** based on the substrate (**2**) was the same (run 2). This means that 4 equiv. of Li is enough to prepare complex (**V**) and/or (**VI**).



Scheme 3. Synthesis of Indole Derivatives.

Table 2.

run	Li (eq)	TMSCl (eq)	yield (%)[a]
1	10	16	77[b]
2	4	16	77[b]
3	4	16	60
4	4	8	54
5	4	6	49
6	4	4	5
7	3	8	40
8	4	6	65[b]

a) All reactions were carried out using Ti(O^{i}Pr)$_4$ (1.0 equiv.) and **2** (1.2 equiv.), and the yield was calculated based on Ti(O^{i}Pr)$_4$. b) The reaction was carried out using Ti(O^{i}Pr)$_4$ (1.2 equiv.), **2** (1.0 equiv.) and CsF (6 equiv.), and the yield was calculated based on **2**.

Next, the amount of TMSCl was examined. The reaction conditions were slightly modified: CsF was not used[12] and 1.0 equiv. of Ti(OPr-*i*)$_4$ and 1.2 equiv. of the substrate (**2**) were used, and the yield was calculated based on $Ti(OPr\text{-}i)_4$. When 4 equiv. of Li and 16 equiv. of TMSCl were used, indole derivative (**3**) was obtained in 60% yield (run 3). Then the amounts of TMSCl were decreased (runs 4-6). Although the use of 6 equiv. of TMSCl gave the desired compound (**3**) in 49% yield (run 5), 4 equiv. of TMSCl gave a trace amount of **3** (run 6). These results indicated that 4 equiv. of Li and 6 equiv. of TMSCl are needed for the synthesis of titanium-nitrogen complex (**V**) and/or (**VI**). When 3 equiv. of Li and an excess amount of TMSCl (8 equiv.) were used, a moderate yield of the desired compound (**3**) was obtained (run 7).[13] Finally, for the synthesis of indole derivative (**3**), when titanium-nitrogen complexes prepared from 1.2 equiv. of $Ti(Opr\text{-}i)_4$, 4.8 equiv. of Li and 7.2 equiv. of TMSCl were used for this reaction (ratio of titanium-nitrogen complexes to substrate: 1.2 to 1), the desired indole derivative (**3**) was obtained in 65% yield (run 8).[14]

These results suggested that for the synthesis of titanium-nitrogen complexes from $Ti(O^iPr)_4$, 4 equivalents of Li and 6 equivalents of TMSCl are required and the real species for this reaction would be **V** and/or **VI**.

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EXPERIMENTAL

All manipulations were performed under an argon atmosphere. $Ti(OPr\text{-}i)_4$ was distilled and stored under an argon atmosphere. THF was distilled from benzophenone and TMSCl was distilled from CaH_2.

Synthesis of 3. To a suspension of Li (14.5 mg, 2 mmmol) in THF were added $Ti(OPr\text{-}i)_4$ (0.15 mL, 0.5 mmol) and TMSCl (0.39 mL, 3 mmol) at -78 °C, and the suspension was degassed by a freeze-pump-thaw cycle. The argon atmosphere was changed to nitrogen gas, and the solution was stirred at rt under nitrogen (1 atm) for 24 h. The resultant black solution was added to the THF suspension of substrate (**2**) (78.2 mg, 0.4 mmol) at –78 °C, and the mixture was stirred at rt overnight. Saturated aqueous NaHCO$_3$ was added at 0 °C. The solution was stirred until the black precipitate had disappeared and was filtered through Celite, and the filtrate was extracted with Et$_2$O. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by chromatography on silica gel (hexane-ethyl acetate, 4/1, 1% NEt$_3$) to give a colorless oil of **3** (50.3 mg, 65%). IR (neat) 1734, 1604 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) □ 1.73 (tt, *J* = 6.1, 6.1 Hz, 2 H), 1.81 (tt, *J* = 6.1, 6.1 Hz, 2 H), 2.47 (t, *J* = 6.1 Hz, 2 H), 2.56 (t, *J* = 6.1 Hz, 2 H), 3.62 (s, 2 H), 3.72 (s, 3 H), 5.77 (br s, 1 H), 8.09 (br s, 1 H); ^{13}C NMR (CDCl$_3$, 125 MHz) □ 22.7, 22.8, 23.4, 23.8, 33.3, 52.1, 106.3, 11.69, 121.1, 127.1, 171.7; EI-LRMS *m/z* 193 (M$^+$), 134; EI-HRMS calcd for C$_{11}$H$_{15}$NO 193.1102, found 193.1086.

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12. The addition of CsF usually resulted in a slight increase in the yield of the product, but to simplify the reaction conditions, CsF was not added in each case (runs 3-8).

13. It was though that an excess amount of TMSCl would effectively act for formation of (**V**) or (**VI**).

14. The yield was slightly decreased compared with the result of run 1, because CsF was not used in this case.