

Activation of nitrogen for organic synthesis

Miwako Mori *

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

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Abstract

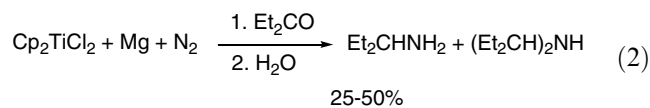
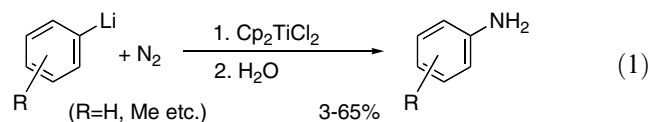
Nitrogen fixation using transition metals is a fascinating process. We have already reported the incorporation of molecular nitrogen into organic compounds using a titanium–nitrogen complex reported by Yamamoto. A novel titanium-catalyzed nitrogenation procedure was developed using TiCl_4 in the presence of an excess amount of Li and TMSCl. One atm pressure of nitrogen gas can be used in this reaction, and the reaction proceeds at room temperature. The procedure is very simple: a THF solution of TiCl_4 or $\text{Ti}(\text{O}i\text{Pr})_4$, Li, and TMSCl is stirred under an atmosphere of nitrogen at room temperature overnight to give titanium–nitrogen complexes. Although the structures of the titanium–nitrogen complexes have not been determined yet, the complexes are thought to consist of $\text{N}(\text{TMS})_3$, $\text{TiX}_2\text{N}(\text{TMS})_2$ and $\text{XTi}=\text{NTMS}$. To this solution was added a compound having a keto-carbonyl group and the solution was refluxed overnight to give heterocycles. Indole, quinoline, pyrrole, pyrrolizine, indolizine derivatives and lactams could be synthesized from molecular nitrogen in good to moderate yields by a one-pot reaction. Furthermore, nitrogen in an atmosphere could be fixed using this nitrogen fixation method. pumiliotoxin C and lycopodine could be synthesized from nitrogen in air as a nitrogen source. Transmetalation of nitrogen on a titanium–nitrogen complex to a palladium complex could be realized, and aniline, benzamide, allylamide and allylamine derivatives could be synthesized from titanium–nitrogen complexes, a palladium catalyst and the corresponding aryl or allyl halide in the absence or in the presence of carbon monoxide.

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1. Introduction

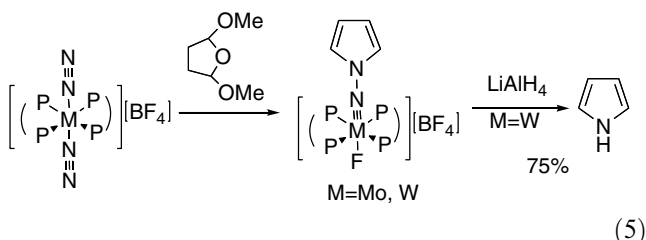
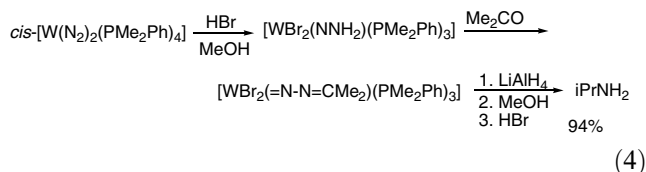
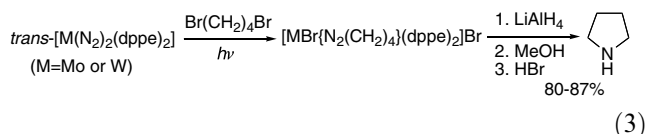
Since Vol'pin and Shur [1] discovered that molecular nitrogen could be fixed by transition metals and reducing agents under mild conditions, various systems of nitrogen fixation have been reported [2]. In 1967, Yamamoto reported the synthesis of a cobalt–nitrogen complex [3] and then a titanium–nitrogen complex [4]. Hidai [5] and Bercow [6] later reported the synthesis of a molybdenum–nitrogen complex and a zirconium–nitrogen complex, respectively. However, there have been few reports on incorporation of molecular nitrogen into organic compounds. In 1968, Vol'pin and Shur [7] reported the synthesis of aniline from Cp_2TiCl_2 and phenyl lithium under high pressure of nitrogen (Eq. (1)).

Later, van Tamelen and Rudler [8] succeeded in obtaining diethylamine and benzonitrile from diethylketone and benzoyl chloride, respectively using Cp_2TiCl_2 and Mg under nitrogen (Eq. (2)). In 1977, Chatt and co-workers [9] synthesized pyrrolizine and isopropylamine from 1,4-dibromobutane and acetone, respectively, using molybdenum or a tungsten–nitrogen complex (Eqs. (3) and (4)). Hidai et al. [10] synthesized pyrrole from a tungsten–nitrogen complex (Eq. (5)).

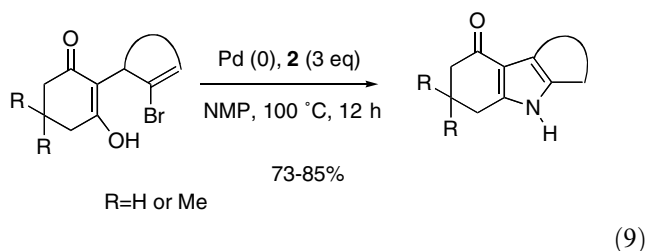
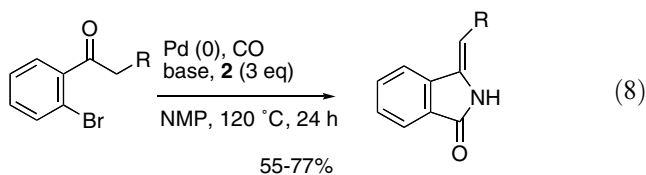
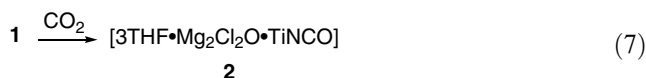
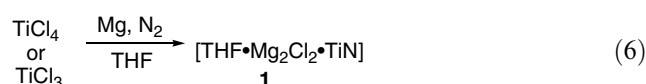


* Tel./fax: +81 11 706 4982.

E-mail address: mori@pharm.hokudai.ac.jp.



Yamamoto et al. [4] reported the synthesis of a very interesting titanium–nitrogen complex **1** from TiCl_4 or TiCl_3 and Mg as a reducing agent (Eq. (6)). In this reaction, the nitrogen–nitrogen triple bond was cleaved by a titanium complex and a reducing agent to give a Ti–N complex [11]. The result is very attractive for the synthesis of nitrogen heterocycles from molecular nitrogen because one nitrogen in molecular nitrogen is required for the synthesis of heterocycles. Sobota et al. [12] reported that the reaction of **1** with CO_2 gave a titanium–isocyanate complex **2** (Eq. (7)). Since the handling of complex **2** was easier than that of **1**, we used **2** as a nitrogenation agent and succeeded in synthesizing various heterocycles (Eqs. (8) and (9)) [13a–e]

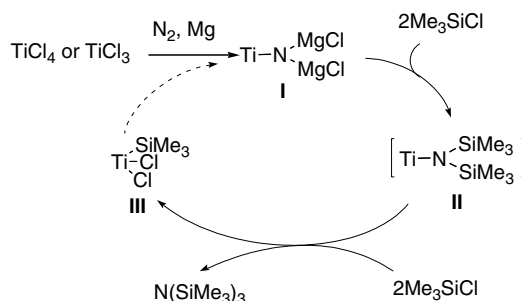


2. Development of titanium-catalyzed nitrogenation [14a,b]

Although the synthesis of heterocycles using titanium–nitrogen complex **2** was achieved, extension of this reaction to a catalytic reaction based on a transition metal was difficult because titanium–nitrogen complexes **1** and **2** were used after they had been isolated. To develop a titanium-catalyzed nitrogenation method, we thought that Yamamoto's complex should be described as structure **I**. If trimethylsilyl chloride (TMSCl) is added to this solution, **I** reacts with TMSCl to form **II**. If complex **II** further reacts with TMSCl, $\text{N}(\text{TMS})_3$ and complex **III** would be produced. To realize titanium-catalyzed nitrogenation, complex **III** must be converted into complex **I**. For that purpose, a reducing agent is required. Thus, we examined to synthesize alternative titanium–nitrogen complexes **3**, that is, nitrogen fixation reaction was carried out in the presence of TiCl_4 , excess amounts of reducing agents and TMSCl under an atmosphere of nitrogen (Scheme 1) [15].

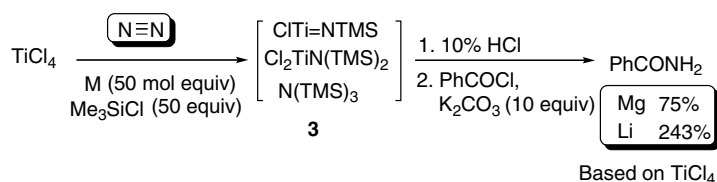
To measure the amount of fixed nitrogen, titanium–nitrogen complexes **3a**, prepared from TiCl_4 , Li, and TMSCl, were hydrolyzed with aq. HCl to be converted into NH_4Cl , which was reacted with benzoyl chloride to give benzamide. The amount of nitrogen fixed in this reaction was estimated by the yield of benzamide. A THF solution of TiCl_4 (1 equiv.) and excess amounts of TMSCl (50 equiv.) was stirred in the presence of a reducing agent (50 mol equiv.) under an atmosphere of nitrogen (1 atm) overnight, and the reaction mixture was hydrolyzed with 10% HCl. The solution was made basic with K_2CO_3 , and an excess amount of PhCOCl (10 equiv.) was added. The solution was then stirred at room temperature overnight to give benzamide. When magnesium was used for this reaction as a reducing agent, benzamide was obtained in 75% yield based on the amount of TiCl_4 . However, the use of Li gave benzamide in 243% yield. This means that the reaction proceeds catalytically based on TiCl_4 (Scheme 2) [16].

Working Hypothesis of Titanium-Catalyzed Nitrogenation



Scheme 1.

Titanium-Catalyzed Nitrogenation Using Excess Amounts of Reducing Agents



Scheme 2.

Table 1
Effects of titanium complexes and reducing agents for nitrogen fixation

Run	TiX_4	Reducing agent	PhCONH_2 (%)
1	TiCl_4	Li	96
2	Cp_2TiCl_2	Li	46
3	$\text{Ti}(\text{O}^i\text{Pr})_4$	$^i\text{PrMgCl}$	4
4	$\text{Ti}(\text{O}^i\text{Pr})_4$	Li	91

Subsequently, various titanium complexes and reducing agents were examined. The reaction conditions were changed to a stoichiometric reaction based on TiCl_4 ; that is, a THF solution of TiCl_4 (1 equiv.), Li (10 mol equiv.) and TMSCl (10 equiv.) was stirred under an atmosphere of nitrogen at room temperature overnight. After hydrolysis of the reaction mixture with aqueous HCl, benzamide was obtained in 96% yield based on TiCl_4 (Table 1, run 1). When Cp_2TiCl_2 was used as a titanium complex, nitrogen could be fixed, but the result was not satisfactory (run 2). A low-valent titanium complex prepared from $\text{Ti}(\text{O}^i\text{Pr})_4$ and Grignard reagent by Sato's method [17] gave only a small amount of benzamide (run 3). It was very interesting that titanium–nitrogen complexes **3b** prepared from $\text{Ti}(\text{O}^i\text{Pr})_4$ instead of TiCl_4 gave benzamide in 91% yield (run 4) [14f].

Since this procedure for nitrogen fixation is very simple, incorporation of molecular nitrogen into organic compounds was examined using these titanium–nitrogen complexes **3**, which is containing a mixture of titanium–imide complex, titanium–amide complex, $\text{N}(\text{TMS})_3$ and unreacted Li, and TMSCl .

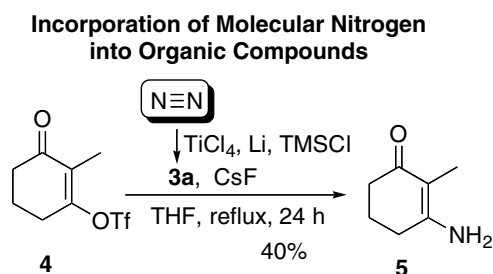
3. Synthesis of heterocycles using titanium–nitrogen complexes

3.1. Syntheses of pyrrole and indole derivatives

To determine whether nitrogen can be directly introduced into organic compounds, cyclohexadione derivative **4** was used as a model compound because if

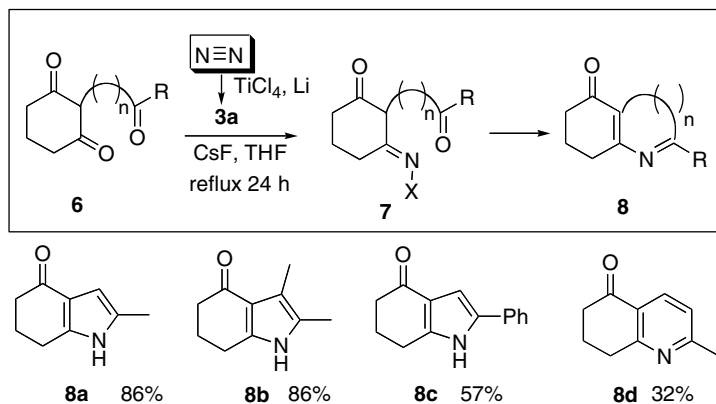
Michael addition proceeds using **3**, nitrogen would be introduced at the 3-position of cyclohexenone. To a THF solution of titanium–nitrogen complexes **3a**, which was prepared from TiCl_4 (1 equiv.), TMSCl (10 equiv.), and Li (10 mol equiv.) in THF under nitrogen, was added enol triflate **4b** and the whole solution was refluxed overnight. After the usual workup, enamino **5** was obtained in 35% yield. In this reaction, addition of CsF improved the yield of **5** to 40%. Presumably, fluoride anion attacks the silyl group on nitrogen of **3**. The results indicated that titanium–nitrogen complexes **3a** could react with **4**, and incorporation of molecular nitrogen into organic compounds is realized [14c] (see Scheme 3).

Subsequently, the synthesis of heterocycles from molecular nitrogen as a nitrogen source was examined. If 1,3-cyclohexadione **6** has a keto-carbonyl group in a tether, imine **7** should be formed, and the imine part should react with the keto-carbonyl group intramolecularly to give heterocycle **8** (Scheme 4). When to a THF solution of **3a** prepared from TiCl_4 , Li and TMSCl under nitrogen was added **6a** ($n = 1$, $\text{R} = \text{Me}$) and the solution was refluxed overnight, we were very pleased to find that indole derivative **8a** was obtained in 86% yield. Using this method, various indole derivatives **8b** and **8c** could be synthesized from the corresponding **6**. In a similar manner, quinoline derivative **8d** was obtained from **6d** ($n = 2$, $\text{R} = \text{Me}$) in 32% yield. In this case, dehydrogenation occurred during the workup. These results indicated that heterocycles could be synthesized from molecular nitrogen as a nitrogen source [14c].



Scheme 3.

Syntheses of Indole and Quinoline Derivatives from Cyclohexadione



Scheme 4.

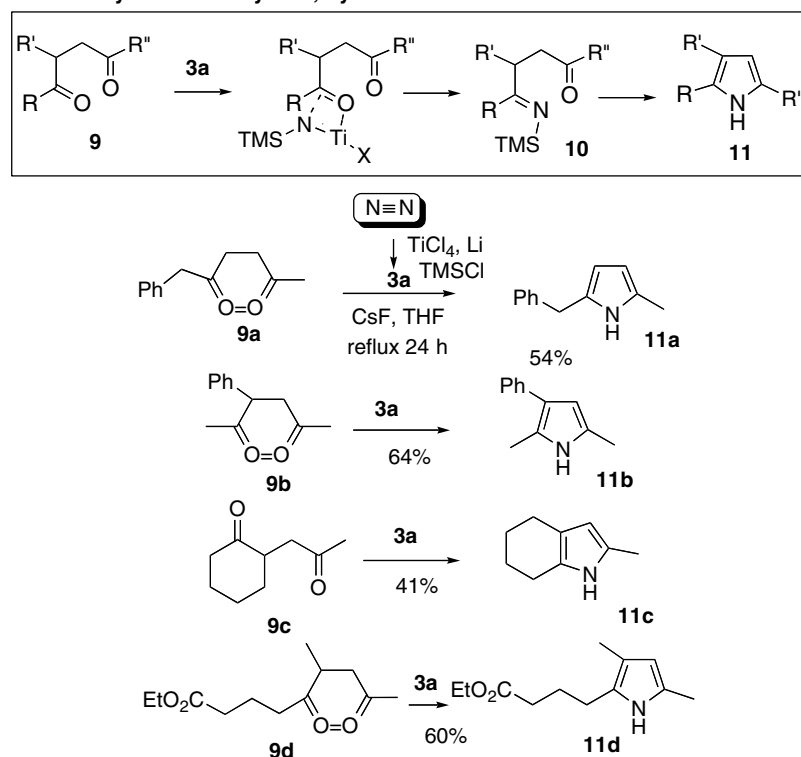
3.2. Synthesis of pyrrolizine and indolizine derivatives [14c]

If titanium–nitrogen complexes **3** react with the keto-carbonyl group to form imine, 1,4-diketones **9** should give pyrrole derivatives **11** via **10**. Thus, when diketone **9a** was reacted with **3a** upon heating in THF, pyrrole derivative **11a** was obtained in 54% yield. In a similar manner, various pyrrole derivatives **11b–d** could be synthesized from diketones **9b–d** (Scheme 5).

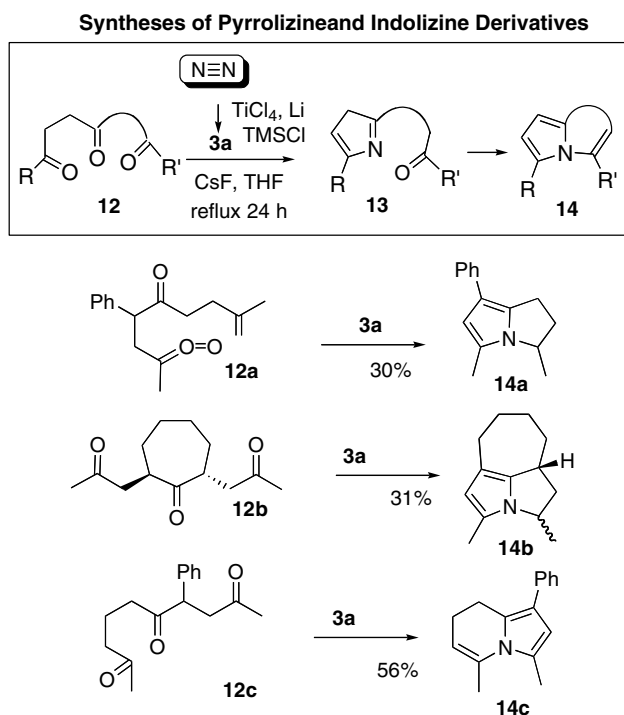
Since **3a** could react with diketone, it was thought that triketone **12** may be reacted with **3a** (Scheme 6). A THF solution of triketone **12a** was added to a solution of **3a**, and the solution was refluxed overnight. After the usual workup, the desired pyrrolizine derivative **14a** was obtained in 30% yield as a reduced form of **14**. In a similar treatment of **12b** and **12c**, pyrrolizine **14b** and indolizine **14c** derivatives could be synthesized.

Next, the natural product monomorine I [18] was synthesized from triketone **12d**. Our retrosynthetic analysis is shown in Scheme 7. To synthesize monomorine I

Syntheses of Pyrrole, Pyrrolizine and Indolizine Derivatives



Scheme 5.



from indolizine derivative **14d**, triketone **12d** is required, and the hydrogenation of the pyrrole ring of **14d** would afford monomoline I because hydrogen on the catalyst approaches from the backside of the methyl group. Ozonolysis of **15** [19] followed by treatment with Me_2S gave triketone **12d** in 85% yield. A THF solution of tri-

ketone **12d** and titanium–nitrogen complexes **3a** (2 equiv.), prepared from TiCl_4 , Li and TMSCl under nitrogen, was refluxed for 24 h. After the usual workup, the desired indolizine derivative **14d** was obtained in 30% yield. The use of Rh on alumina (20 atm) as a hydrogenation catalyst afforded monomoline I as a main product in 32% yield along with indolizidine 195B in 4% yield [20]. Thus, a short-step synthesis of monomoline I and indolizidine 195B was achieved using titanium–nitrogen complex **3a** as a nitrogen source [14d] (see Table 2).

3.3. Synthesis of lactams from keto-carboxylic acid derivatives

Since titanium–nitrogen complexes **3** could react with benzoyl chloride [14b], it was expected that keto-carboxyl chloride **16** should react with **3a** to give lactam **17**. Various keto-carboxylic acid derivatives **16**, such as chloride, mixed anhydride, phosphonate, ester and even carboxylic acid, could react with **3** and the desired lactams **17** were obtained in moderate yields (Table 1). The reactivity of titanium–nitrogen complexes **3b** prepared from $\text{Ti}(\text{O}^i\text{Pr})_4$ to **16** is superior to that of **3a** prepared from TiCl_4 (runs 3 and 4). Monocyclic lactams **17f** and **17g** could also be synthesized from keto-carboxyl phosphonates **16f** and **16g** [14f] (see Scheme 8).

3.4. Syntheses of indole and quinoline derivatives [14c]

It was expected that the keto-carbonyl group of **18** could react with titanium–nitrogen complexes to afford

Short Total Synthesis of Monomoline I Using Nitrogen Gas

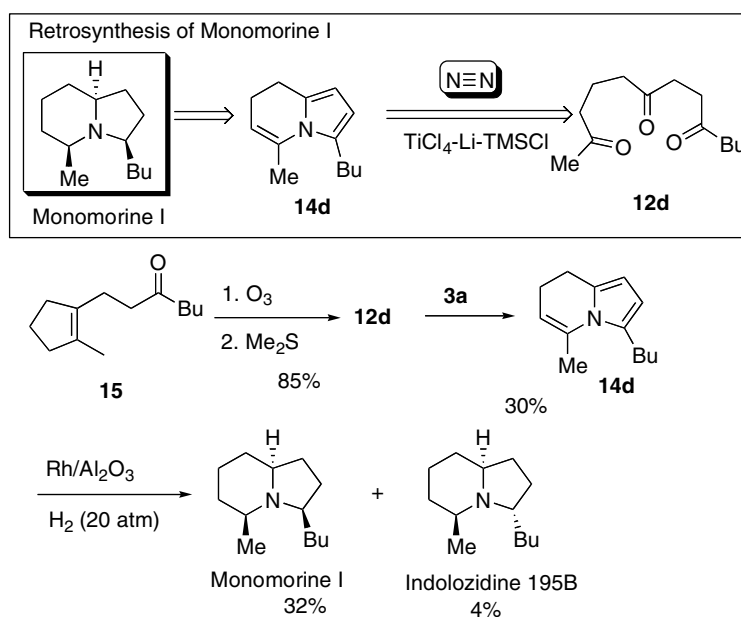
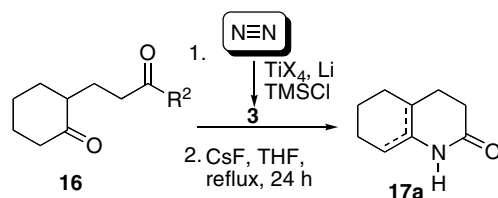
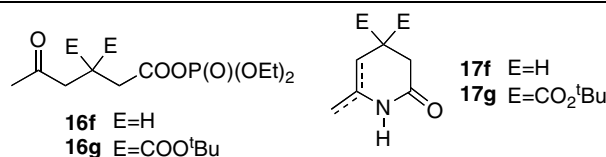
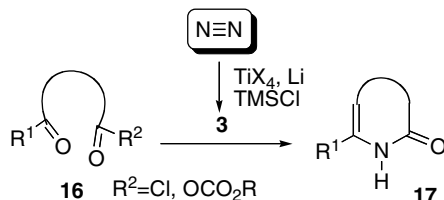


Table 2
Reaction of **16** with **3**

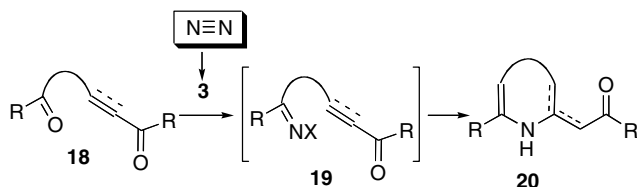
Run	16	R ²	TiX ₄	Product	Yield (%)
1	16a	Cl	TiCl ₄	17a	28
2	16a	Cl	Ti(O ^{<i>i</i>} Pr) ₄	17a	31
3	16b	OCO ₂ Et	Ti(O ^{<i>i</i>} Pr) ₄	17a	55
4	16b	OCO ₂ Et	TiCl ₄	17a	25
5	16c	OP(O)(OEt) ₂	Ti(O ^{<i>i</i>} Pr) ₄	17a	58
6	16d	OH	Ti(O ^{<i>i</i>} Pr) ₄	17a	53
7	16e	OEt	Ti(O ^{<i>i</i>} Pr) ₄	17a	50
8	16f		Ti(O ^{<i>i</i>} Pr) ₄	17f	24
9	16g		Ti(O ^{<i>i</i>} Pr) ₄	17g	51

Synthesis of Lactams from **3** and Keto-carboxylic Acid

Scheme 8.

imine **19**, which should react with α,β -unsaturated ester to give **20** (see Scheme 9).

When a THF solution of **18a** and **3a** prepared from TiCl₄, Li and TMSCl under nitrogen was refluxed overnight, surprisingly, the desired indole derivative **20a** was obtained in 90% yield (Table 3, run 1). The

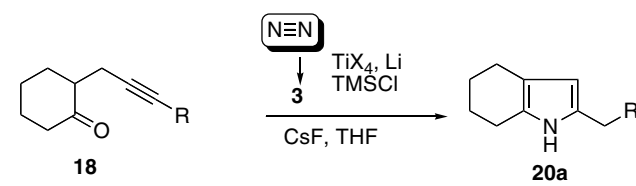
Reaction of Keto-Alkyne and **3**

Scheme 9.

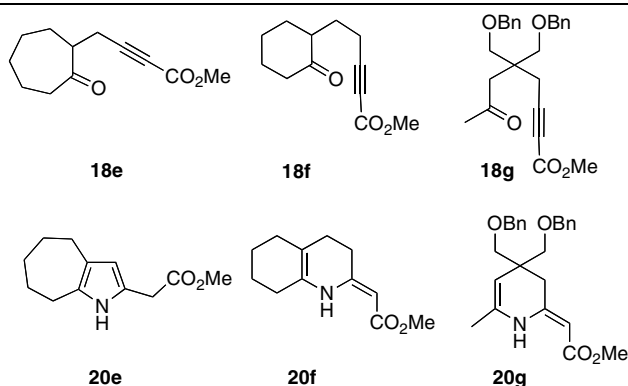
reaction of **18a** and **3b**, prepared from Ti(O^{*i*}Pr)₄, Li and TMSCl under nitrogen, proceeded smoothly at room temperature for 50 min to give **20a** in 82% yield. In a similar manner, indole derivative **20b** having a nitrile group could be synthesized from the corresponding keto-alkyne **18b** in high yield (run 3). In this reaction, an alkyl group on the alkyne did not give a good yield (run 4), but keto-alkyne having a phenyl group afforded the corresponding indole derivative in moderate yield (run 5). In a similar manner, keto-alkyne **18e** gave **20e** in 66% yield (run 6). Formation of six-membered ring compounds also smoothly proceeded and the desired compounds **20f** and **20g** were obtained from **18f** and **18g**, respectively, in high yields (runs 7 and 8).

The possible reaction course is shown in Scheme 10. There are two possible pathways. If the reaction of keto-alkyne **18** with N(TMS)₃ proceeds in the presence of CsF, imine **IV** would be formed. Then Michael addition of nitrogen of imine would afford **V**, which isomerizes to give **20** (path A). However, when **18** was reacted with N(TMS)₃ in the presence of CsF at room temperature for 16 h, no cyclized product was formed, indicating that N(TMS)₃ in titanium–nitrogen complexes **3b** is not an active species. Thus, the active species in this reaction would be titanium–imide complex [XTi=N(TMS)] or titanium–amide complex [X₂Ti–N(TMS)₂], and the complex reacts with the carbonyl carbon to give imine **IV** via **VI** [21]. Then the Michael

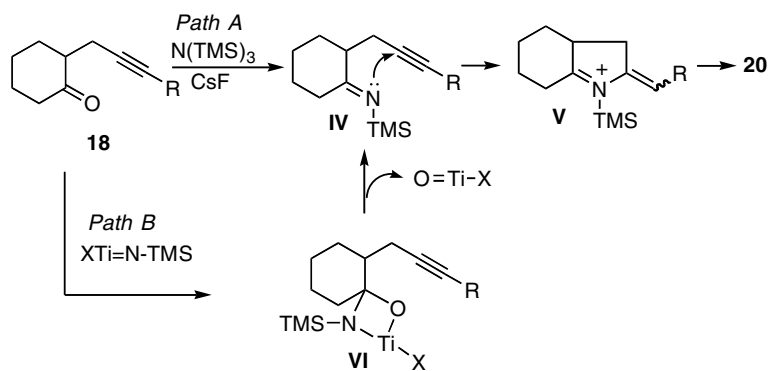
Table 3
Syntheses of indole derivatives



Run	TiX ₄	Substrate	R	Conditions	Yield (%)
1	TiCl ₄	18a	CO ₂ Me	Reflux, 17 h	90
2	Ti(O ⁱ Pr) ₄	18a	CO ₂ Me	r.t., 50 min	82
3	Ti(O ⁱ Pr) ₄	18b	CN	r.t., 12 h	92
4	Ti(O ⁱ Pr) ₄	18c	Me	Reflux, 20 h	3
5	Ti(O ⁱ Pr) ₄	18d	Ph	Reflux, 20 h	35
6	Ti(O ⁱ Pr) ₄	18e		r.t., 24 h	72
7	Ti(O ⁱ Pr) ₄	18f		r.t., 24 h	66
8	Ti(O ⁱ Pr) ₄	18g		r.t., 24 h	63



Possible Reaction Course



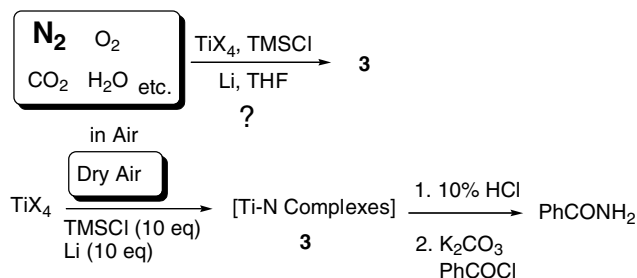
Scheme 10.

addition of nitrogen to α,β -unsaturated ester gives **20**. The mechanism of this reaction is similar to that of the synthesis of a pyrrole derivative by Arcadi, who obtained a pyrrole derivative from keto-alkyne and primary amine [22]. As an alternative mechanism, [2+2] cycloaddition of titanium-imide complex and alkyne may be considered [23].

4. Nitrogen fixation using dry air [14f]

It is well known that nitrogenase catalyzes the reduction of atmospheric nitrogen to NH_3 . We were therefore interested in whether nitrogen in air can be fixed directly. Nitrogen accounts for 80% of the gases in air, the other gases being oxygen and carbon dioxide. Early

Nitrogen Fixation in Air



Scheme 11.

Table 4
Nitrogen fixation using dry air

Run	TiX ₄	TMSCl, Li (equiv.)	Time (h)	Yield (%) ^a	
				Air	N ₂
1	TiCl ₄	10	24	89	96
2	Ti(O ⁱ Pr) ₄	10	24	80	91
3	Ti(O ⁱ Pr) ₄	50	48	356	496

^a Based on TiX₄.

transition metals are not so sensitive to oxygen but are very sensitive to water. Thus, we used *dry air* passed through a calcium chloride tube and a molecular sieve tube (see Scheme 11).

Table 5
Nitrogen fixation using nitrogen gas and dry air

Run	Substrate	Product	TiX ₄	Yield ^a	
1	 6a	 8a	TiCl ₄	Air	56%
				N ₂	86%
2	 9d	 11d	TiCl ₄	Air	37%
				N ₂	60%
3	 18a	 20a	Ti(O ⁱ Pr) ₄	Air	72%
				N ₂	82%
4	 18f	 20f	Ti(O ⁱ Pr) ₄	Air	54%
				N ₂	66%
5	 18g	 20g	Ti(O ⁱ Pr) ₄	Air	61%
				N ₂	63%
6	 16c	 17a	Ti(O ⁱ Pr) ₄	Air	58%
				N ₂	60%
7	 16g E=CO ₂ ^t Bu	 17g	Ti(O ⁱ Pr) ₄	Air	50%
				N ₂	51%

^a Titanium–nitrogen complexes **3** were prepared by reaction of TiX₄ (1.25 equiv.), Li (12.5 mol equiv.) and TMSCl (12.5 equiv.) in THF under dry air or nitrogen gas at room temperature for 24 h. All reactions were carried out using **3** in the presence of CsF (6 equiv.) in THF upon heating for 24 h. Yields are based on the substrate.

To determine whether nitrogen in air can be fixed by TiX_4 , Li and TMSCl, titanium–nitrogen complexes **3** prepared from dry air were converted into PhCONH_2 as a nitrogen fixation product. A THF solution of TiCl_4 (1.0 equiv.) and TMSCl (10.0 equiv.) was stirred in the presence of Li (10 mol equiv., porous) under *dry air* passed through a calcium chloride tube and a molecular sieve tube at room temperature for 24 h. The solution turned black with a green tinge. After hydrolysis of the reaction mixture, we were very pleased to find that benzamide could be isolated in 89% yield (Table 4, run 1). The use of nitrogen gas in a similar manner gave benzamide in 96% yield. The result obtained using a $\text{Ti}(\text{O}^i\text{Pr})_4$ –Li–TMSCl system under *dry air* was the same as that obtained using a TiCl_4 –Li–TMSCl system (run 2). It has already been shown that this nitrogen fixation reaction proceeds catalytically based on TiCl_4 [14a,14b]. Thus, an experiment was carried out to determine whether the nitrogen fixation reaction using *dry air* proceeds catalytically. Titanium–nitrogen complexes were synthesized from $\text{Ti}(\text{O}^i\text{Pr})_4$ (1 equiv.), excess amounts of Li (50 mol equiv.) and TMSCl (50 equiv.) under *dry air* for 2 days. After the solution had been treated in the usual manner, benzamide was obtained in 356% yield based on an amount of $\text{Ti}(\text{O}^i\text{Pr})_4$. (run 3).

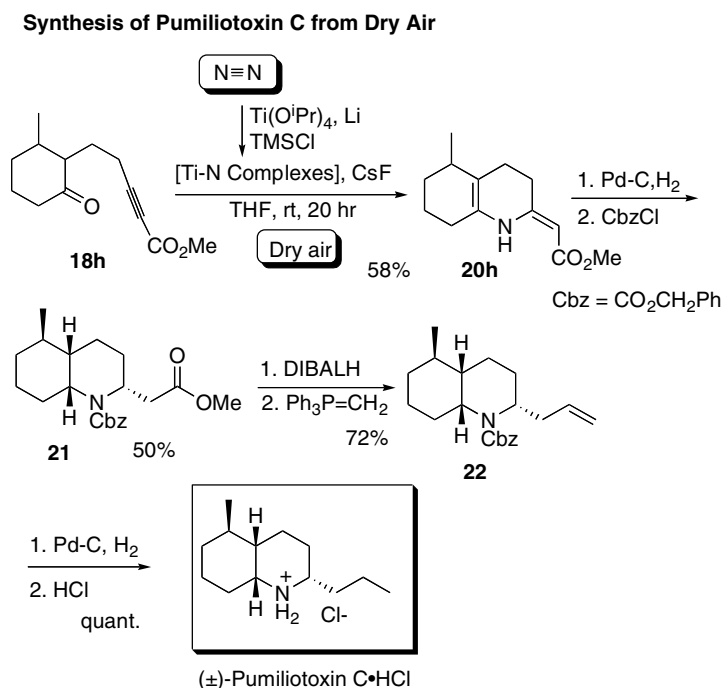
The results indicated that nitrogen in air could be fixed as titanium–nitrogen complexes **3**.

Subsequently, an experiment was carried out to determine whether various heterocycles could be synthesized from *dry air* as a nitrogen source. To a THF solution of cyclohexadione derivative **6a** and CsF was

added a THF solution of **3a** prepared from TiCl_4 , Li, and TMSCl under *dry air*, and the whole solution was refluxed overnight. After the usual workup, indole derivative **8a** was obtained in 56% yield based on cyclohexadione **6a** (Table 5, run 1). Using molecular nitrogen for this reaction, **8a** was obtained in 86% yield. By a similar treatment of diketone **9d**, pyrrole derivative **11d** was obtained in moderate yield (run 2). Various heterocycles were synthesized using titanium–nitrogen complexes **3** prepared from *dry air*, TiX_4 , Li, and TMSCl, and in each case, the desired heterocycles were obtained in good yields. The results are shown in Table 5. The yield obtained from *dry air* was slightly lower than that obtained using nitrogen gas in each case.

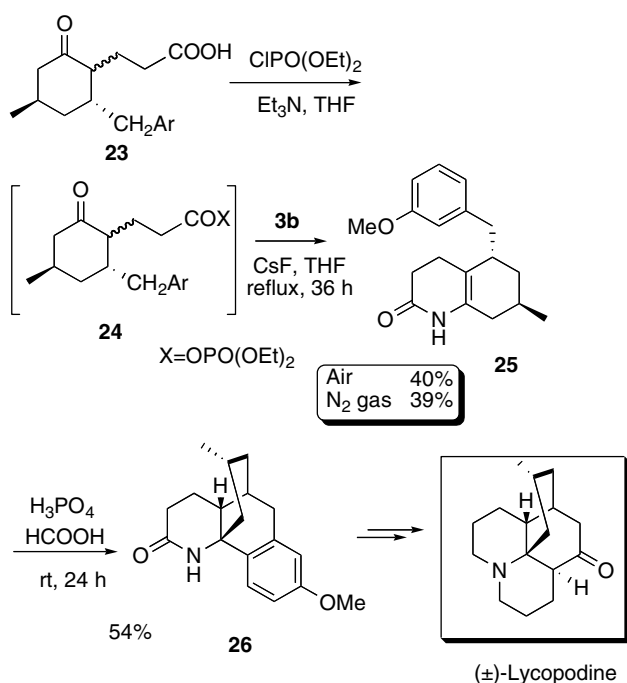
Since quinoline derivative **20f** could be synthesized from *dry air* in good yield (run 5), pumiliotoxin C [24] was synthesized from *dry air* as a nitrogen source. When a THF solution of **3b**, which was prepared from *dry air*, and keto-alkyne **13g** was stirred in the presence of CsF at room temperature for 20 h, quinoline derivative **14g** was obtained in 58% yield. Hydrogenation of **14g** with palladium on charcoal followed by protection of nitrogen gave **21**, which after treatment with DIBALH followed by Wittig reaction gave compound **22**. Hydrogenation of **22** followed by treatment with $\text{Et}_2\text{O} \cdot \text{HCl}$ afforded (\pm)-pumiliotoxin C hydrochloride [14g] (see Scheme 12).

Furthermore, the total synthesis of (\pm)-lycoperidine [25] was achieved using this method. In 1968, Stork [26a] and Ayer [26b] independently succeeded in the first



Scheme 12.

Formal Total Synthesis of (±)-Lycopodine



Scheme 13.

total synthesis of lycopodine. Stork achieved the synthesis of lycopodine from lactam **25** by a very ingenious method [26a]. Carboxylic acid **23** was synthesized and was converted into carboxyl phosphonate **24**. When a THF solution of **24** and titanium–nitrogen complexes **3b**, prepared from dry air, was refluxed for 36 h, lactam **25** was isolated in 40% yield. Conversion of **25** into **26** proceeded smoothly according to Stork's procedure. The melting point and spectral data of **25** and the spectral data of **26** are in complete agreement with those reported in the literature [26a]. Thus, the formal total synthesis was achieved using dry air as the nitrogen source (see Scheme 13).

5. Synthesis of nitrogen-containing compounds using transmetalation of titanium–nitrogen complexes to palladium catalysts

5.1. Synthesis of aniline derivatives [27a]

Since Migita and co-workers [28] Succeeded in synthesizing a disubstituted aniline derivative from an aryl-palladium complex and dialkylstannane, a method for synthesizing mono- and di-substituted aniline derivatives from aryl halides using a palladium catalyst has been established by the ingenious studies of Buchwald and co-workers [29]. However, synthesis of non-substituted aniline derivatives from an arylpalladium complex was not achieved because NH_3 must be used for that

purpose [30]. These results have stimulated us to synthesize non-substituted aniline derivatives **28** by a one-step reaction from arylpalladium complex **29** and titanium–nitrogen complexes **3** prepared from nitrogen gas and the TiCl_4 – or $\text{Ti}(\text{O}^i\text{Pr})_4$ –Li–TMSCl system. If titanium–nitrogen complexes **3** can be transmetalated with aryl palladium complex **29**, arylpalladiumamide complex **30** would be formed, and this should be followed by reductive elimination to give non-substituted aniline derivative **28** (see Scheme 14).

When a THF solution of titanium–nitrogen complexes **3b** (2.0 equiv.), which was prepared from $\text{Ti}(\text{O}^i\text{Pr})_4$ (2.0 equiv.), Li (20 mol equiv.), and TMSCl (20 equiv.) in THF under an atmosphere of nitrogen at room temperature for 8 h, was added to a THF solution of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (2.5 mol%), $\text{P}(o\text{-tolyl})_3$ (10 mol%), and NaO^iBu (2.8 equiv.) and the solution was refluxed overnight, no nitrogen-containing products were produced and a dehalogenation product was obtained along with the starting material (Table 6, run 1). Since it is known that THF is not the best solvent for palladium-catalyzed amination [29a,b], the solvent was changed from THF to toluene and the reaction was carried out in a similar manner to give 4-aminobiphenyl **28a** in 32% yield along with secondary aniline **31a** in 11% yield (run 2). Various ligands were used for this reaction, and the results are shown in Table 6. It seems likely that the bidentate ligand predominantly gave primary aniline **28a** (runs 4–7).

Aryl triflate **32a** can be used for this reaction, but the slow addition of the substrate was important for preventing the formation of *p*-phenylphenol [29d,e], and the use of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and DPPF gave a good result (see Scheme 15).

Formation of **31a** indicates that this reaction would proceed via transmetalation. In this reaction, nitrogen on imide complex **VII** is transmetalated to a palladium complex to give **VIII**. Reductive elimination from **VIII** gives complex **IX**. Then further transmetalation of **IX** into an arylpalladium complex gives complex **X**. Reductive elimination from **X** affords secondary amine **31a** (Scheme 16).

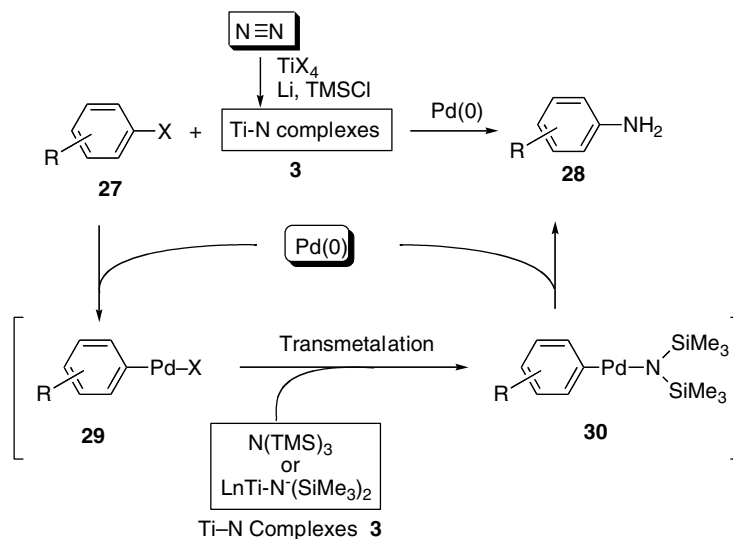
Various aryl bromides **27** and triflates **32** were used for this reaction and non-substituted aniline derivatives **28** were obtained in good yields (see Table 7).

5.2. Synthesis of benzamide derivatives [27b]

Next, incorporation of carbon monoxide and nitrogen into aryl halide was planned. If the nitrogen on titanium–nitrogen complexes **3** can be transmetalated to an acylpalladium complex derived from aryl halide, carbon monoxide and palladium complex, benzamide should be formed (Scheme 17).

When the reaction of **27f** and **3b** was carried out using the best conditions for the synthesis of aniline

Plan for Synthesis of Aniline Derivatives by Transmetalation



Scheme 14.

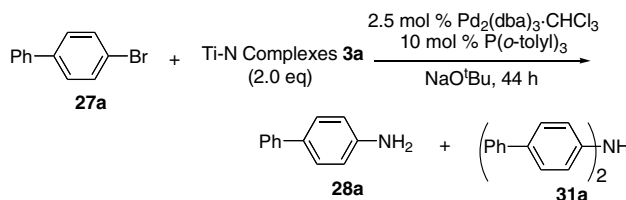
derivatives under carbon monoxide, amide **33f** was obtained in 12% yield along with imide **34f** and aniline derivatives **28f** in 6% and 22% yields, respectively (Scheme 18). The reaction procedure is shown in Fig. 1.

When the reaction was carried out in DMF, the desired amide **33a** was obtained in 37% yield along with

formylamide **35a** and amidine **36a** in 16% and 18% yields, respectively. The latter compounds were treated with K_2CO_3 in MeOH, and benzamide **33a** was obtained in high yields (Scheme 19). These results indicated that carbon monoxide and nitrogen could be introduced into aryl halide using a palladium catalyst and titanium–nitrogen complexes **3b**.

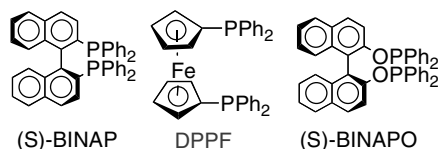
Table 6

Ligand effects on palladium-catalyzed amination

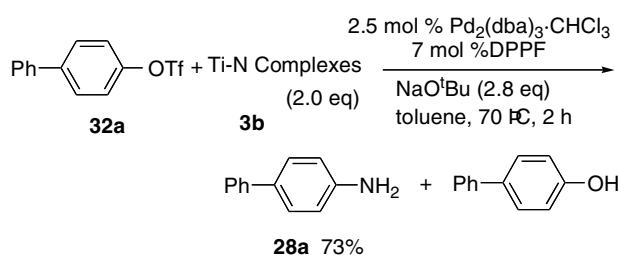


Run	Ligand	Solvent	Time (h)	Yields (%)	
				28a	31a
1	P(<i>o</i> -tolyl) ₃	THF	24	0	0
2	P(<i>o</i> -tolyl) ₃	Toluene	4	32	11
3	P(<i>o</i> -tolyl) ₃	Toluene	44	23	28
4	(<i>S</i>)-BINAP	Toluene	40	39	4
5	DPPF	Toluene	21	30	0
6	DPPP	Toluene	23	14	0
7	(<i>S</i>)-BINAPO	Toluene	21	15	0

All reactions were carried out in the presence of 2.5 mol% $Pd_2(dba)_3 \cdot CHCl_3$, 5–10 mol% ligand, 2 eq Ti–N complexes, and 2.8 equiv. NaO'Bu in toluene at 90 °C.

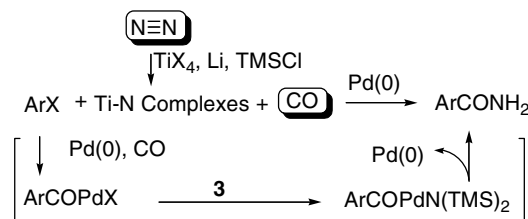


Synthesis of Aniline Derivatives from Aryl Triflate



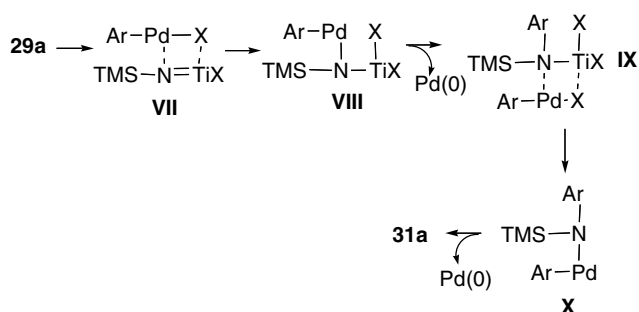
Scheme 15.

Plan for Synthesis of Amide



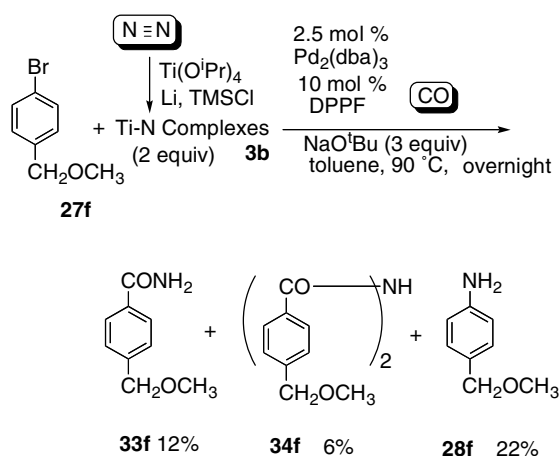
Scheme 17.

Reaction Course for Formation of Disubstituted Anilines



Scheme 16.

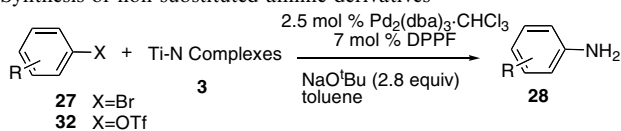
Palladium-Catalyzed Carbonylation



Scheme 18.

Table 7

Synthesis of non-substituted aniline derivatives



Substrate	Aniline	Yield
Ph-X	Ph-NH ₂	28a X=Br 77% X=OTf 73%
NC-X	NC-NH ₂	28b X=Br 39% X=OTf 44%
ROH ₂ C-X	ROH ₂ C-NH ₂	28c 58%
R = TBDMS		
		28d X=Br 74% X=OTf 80%
		28e 47%

Various benzamide derivatives **33** were synthesized from the corresponding aryl halide **27**, and the results are shown in Table 8. In some cases, a fair amount of benzonitriles **37** were formed.

The reaction is presumed to proceed by transmetalation of nitrogen on titanium–nitrogen complexes **3b** to acylpalladium complex **38** to give **39** (Scheme 20). Then **39** is converted into amide–titanium complex **40** by reductive elimination, and it reacts with DMF to give **41**, which is converted into formylamide **35** and amidine **36**. On the other hand, carbonyl oxygen of **39** coordinates intramolecularly with titanium metal, and then nitrile **37** would be produced via **42**.

Usually, *N*-substituted benzamide is prepared from aryl halide and primary or secondary amine under carbon monoxide in the presence of a palladium catalyst. However, non-substituted benzamide cannot be synthesized from aryl halide by palladium-catalyzed carbonylation because the nucleophilicity of NH₃ is low and handling of gaseous NH₃ is difficult.

These reactions are summarized in Scheme 21. When the reaction of aryl halides **27** and titanium–nitrogen complexes **3b** is carried out in the presence of a palladium catalyst in toluene under argon gas, we could obtain non-substituted anilines **28**. When the same reaction is carried out in DMF under carbon monoxide, the desired amide **33** could be obtained.

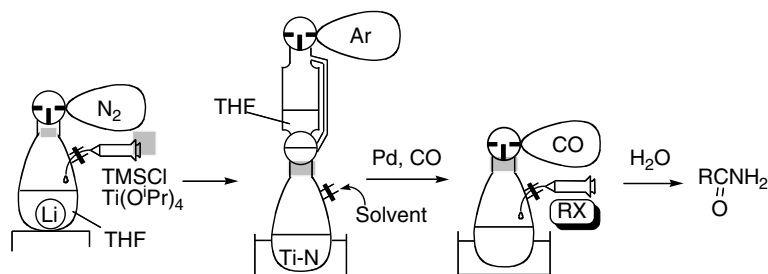
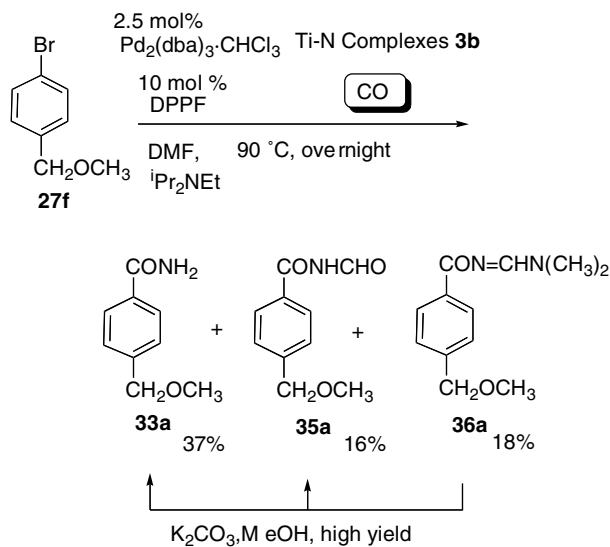


Fig. 1. Reaction procedure.

Palladium-Catalyzed Carbonylation in DMF



Scheme 19.

5.3. Transmetalation to π -allylpalladium complex [27c]

Next, we tried to introduce nitrogen and carbon monoxide into allyl halide (Scheme 22). If nitrogen from titanium–nitrogen complexes **3** can transmetalate [31] to a σ -acylpalladium complex **46** generated from a π -allylpalladium complex **45** and carbon monoxide, σ -acylpalladiumamide complex **47** would be formed. Reductive elimination from **47** should give an allylamide complex **48**, which should give an amide **44** after hydrolysis.

A toluene solution of **3b** (1.25 equiv.) was added to a toluene solution of allyl chloride **43a** (1 equiv.), Pd(OAc)₂ (5 mol%), PPh₃ (20 mol%), K₂CO₃ (3 equiv.) and HMPA (2.3 equiv.) [31] and then the whole solution was stirred at room temperature overnight. However, no nitrogen-containing product was obtained after hydrolysis, and only a mixture of the dimeric compounds **50** of allyl chloride **43a** was obtained in 86% yield. Thus, various ligands were used for transmetalation. P^tBu₃ gave a good result, and the desired allylamide **44a** was obtained in 59% yield along with allyl cyanide **49a** in 3% yield. The phosphonate gave a similar result (**44a**, 59% yield).

Table 8

Synthesis of amide by palladium-catalyzed carbonylation via transmetalation

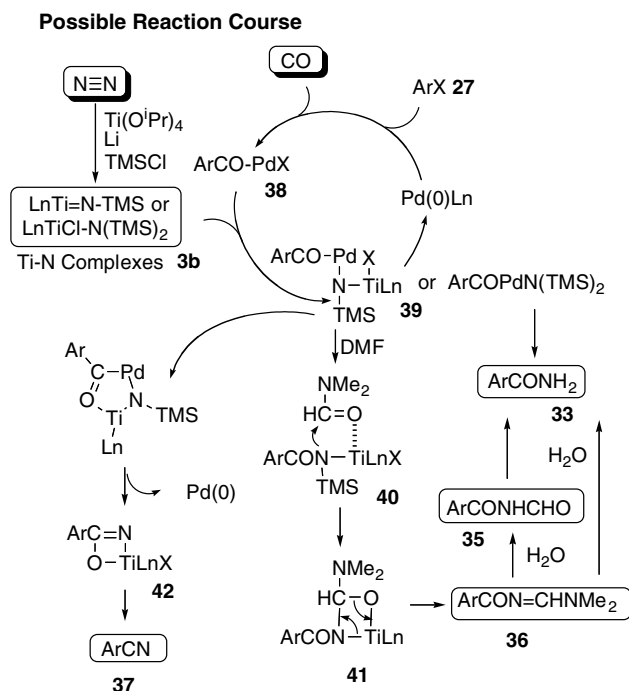
ArBr		Pd(0), CO				
27		Ti-N 3b				
		ArCONH ₂	ArCONHCHO	ArCON=CHNMe ₂	ArCN	
		33	35	36	37	
		Yield (%)				
Run	Substrate	33	35	36	37	Total ^a
1	MeOH ₂ C-	14	5	41	27	87
2	Ph-	47	9	–	13	69
3	MeO-	40	11	10	21	82
4	MeO ₂ C-	75	2	11	8	96
5		52	5	–	21	78
6	NC-	–	–	55	–	55
7		34	5	8	–	47

^a Total yields of amide **33**, formylamide **35**, amidine **36** and nitrile **37**.

In this reaction, an improved procedure [39] for nitrogen fixation [Ti(OⁱPr)₄ (1 equiv.), Li (4 equiv.) and TMSCl (6 equiv.)] is suitable because an excess amount of Li should accelerate the formation of dimeric compound **50** (see Scheme 23).

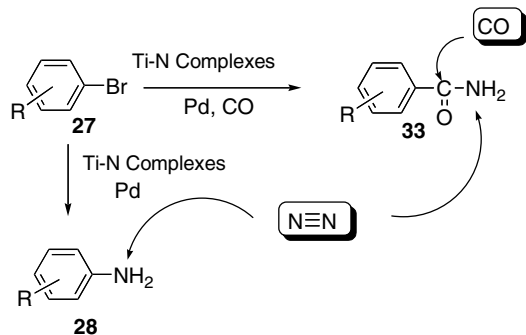
Various allyl halides were used for this reaction, and the desired amides **44** were obtained in moderate yields along with allyl cyanides **49** (see Table 9).

During the search for an appropriate ligand for this reaction, it was found that the use of a bidentate ligand



Scheme 20.

Synthesis of Anilines and Amides from Aryl Halides



Scheme 21.

such as BINAP for this reaction yielded an allylamine derivative. Thus, when allyl chloride **43a** was reacted with **3b** in the presence of Pd(OAc)₂, BINAP, HMPA and K₂CO₃ in toluene at room temperature overnight under argon and then acetyl chloride was added, allylamine derivatives **51a** and **51b** were obtained along with **52** (Scheme 24).

The results indicated that allylamide and allylamine derivatives could be synthesized from the same starting material by the use of different ligands.

6. Synthesis of heterocycles using titanium-catalyzed nitrogenation and reinvestigation of the reaction conditions

This nitrogenation method has been developed for a catalytic reaction based on a titanium complex.

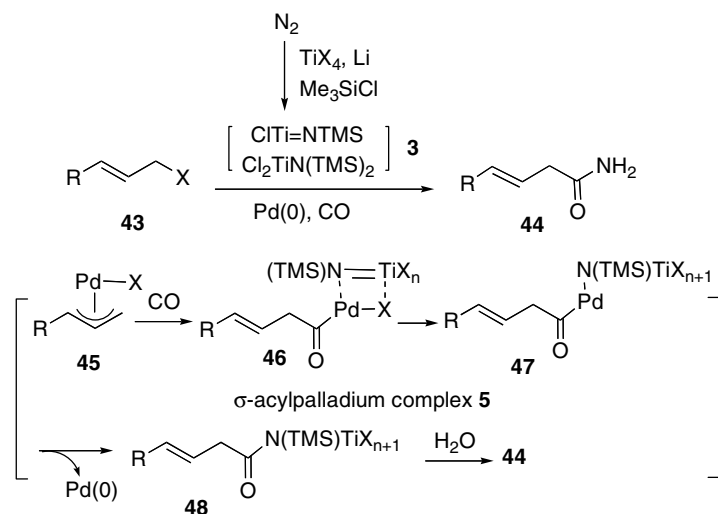
Although the reaction species are not clear, the reaction course is thought to that shown in Scheme 25.

TiX₄ is reduced with Li and converted into TiX₂ **XI**, which would react with N₂ to give **XII**. This would then be converted into titanium-imide complex **VII** by Li and TMSCl, and **VII** would react with TMSCl to give titanium-amide complex **XIII**. In the presence of Li, **XIII** reacts with TMSCl to give N(TMS)₃, and TiX₂ **XI** would be regenerated.

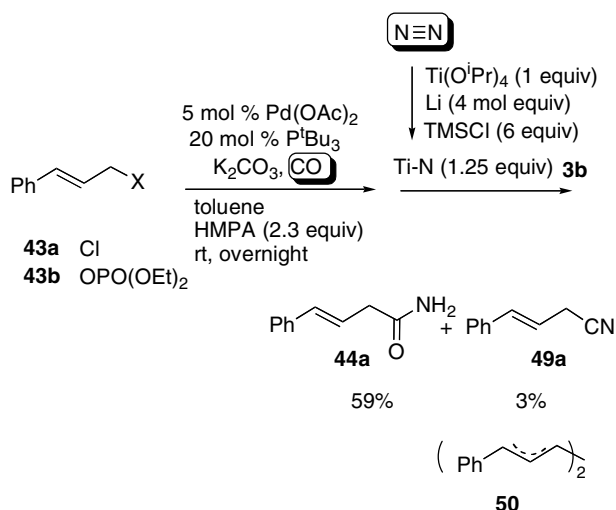
Thus, an experiment was carried out to determine whether a nitrogen-containing compound could be catalytically synthesized based on TiX₄ from molecular nitrogen. Titanium-nitrogen complexes **3a** were synthesized from TiCl₄ (1 equiv.) in the presence of excess amounts of Li (50 mol equiv.) and TMSCl (50 equiv.) under an atmosphere of nitrogen. To this solution was added a THF solution of an excess amount of 1,3-diketone derivative **4b** (10 equiv.), and the solution was refluxed overnight. After the usual workup, enaminone **5** was obtained in 189% yield based on TiCl₄. Subsequently, the syntheses of indole derivatives **8a** and **11** were carried out using a catalytic amount of TiX₄. The reaction procedure was similar to that of the synthesis of **5**, and indole derivatives **8a**, **11c** and **11d** were obtained from **6a**, **8c** and **8d** in 129%, 360% and 335% yields based on TiCl₄, respectively. These results mean that TiCl₄ acts as a catalytic reagent in these reactions (Scheme 26).

We reinvestigated the nitrogenation reaction conditions because excess amounts of Li (10 equiv.) and TMSCl (10 or 16 equiv.) to TiX₄ were used for preparation of titanium-nitrogen complexes **3**. 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 [15,32–36]. Bercaw reported the syntheses of titanium-nitrogen complexes **XIIa** [35], whose structure was confirmed by X-ray crystallography [36]. In 1991, Gambarotta synthesized complex **XIIb** from *trans*-(TMEDA)₂TiCl₂ and (Me₃Si)₂NLi under nitrogen [37]. The existence of these complexes would admit the formation of complex **XII** shown in Scheme 25 (see Fig. 2).

Shiina [15] 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 TiCl₄, N(TMS)₃ was formed from TiCl₄ and TMSCl. This result agrees with the formation of N(TMS)₃ shown in Scheme 25. On the other hand, the synthesis of non-substituted anilines **28** from aryl halides **27** and titanium-nitrogen complexes **3b** and a palladium catalyst [27a] has been described, and disubstituted anilines **31** were produced in some cases (Scheme 16). In this process, titanium-imide complex **VII** acts an important role. Based on these facts, the reaction would proceed as shown in Scheme 25. Thus, the amounts of Li and TMSCl needed for the formation

Our Plan for Synthesis of Allylamide from CO and N₂

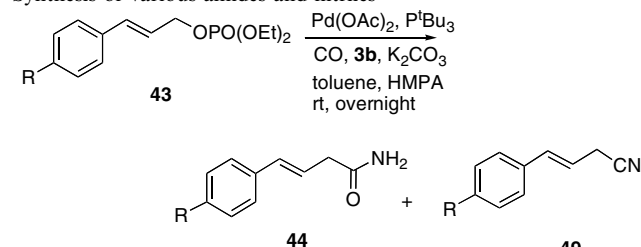
Scheme 22.

Synthesis of Allyl Amide From Allyl chloride, **3b** and CO

Scheme 23.

Table 9

Synthesis of various amides and nitriles



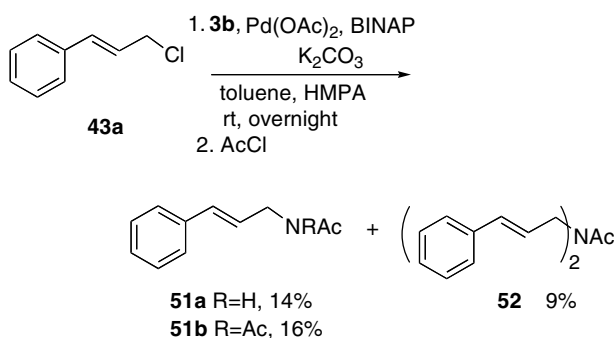
Run	R	Yield (%)	
		44	49
1	H	59	–
2	Me	35	6
3	F	51	3
4	CF ₃	51	–

of each of the titanium–nitrogen complexes **VII**, **XIII** and N(TMS)_3 were calculated (Table 10). Since LiO^iPr is produced when $\text{Ti(O}^i\text{Pr)}_4$ is reduced by Li, a further 3 equiv. of TMSCl would be needed. That is for the formation of complex **VII** from $\text{Ti(O}^i\text{Pr)}_4$, 4 mol equiv. of Li and 4 equiv. of TMSCl would be required, and in the case of TiCl_4 , 4 mol equiv. of Li and 1 equiv. of TMSCl would be required.

Since indole derivative **20a** was synthesized from **3b** and **18a** by the standard nitrogenation conditions in high yield, the required amounts of Li and TMSCl for formation of **3b** were estimated by the yield of **20a**. An experiment was carried out to determine whether indole derivative **20a** can be obtained from keto-alkyne **18a** and N(TMS)_3 as a nitrogenation agent. A THF solution

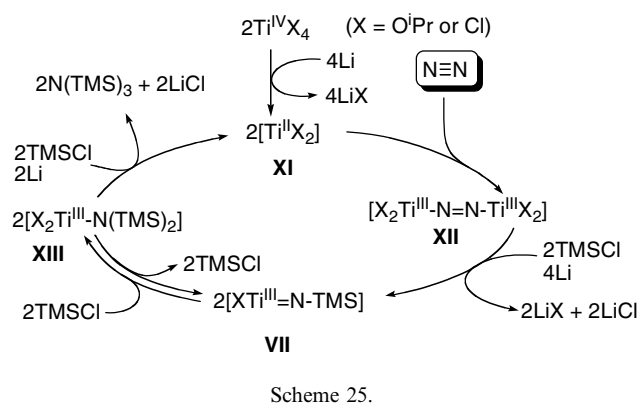
of **18a** and N(TMS)_3 (2 equiv.) was stirred at room temperature for 16 h in the presence of CsF (6 equiv.). After the usual workup, keto-alkyne **18a** was recovered in 94% yield. This means that N(TMS)_3 was not an active nitrogenation species for the synthesis of indole derivative **20a**. A THF solution of titanium–nitrogen complexes **3b** prepared from $\text{Ti(O}^i\text{Pr)}_4$ (1.25 equiv.), Li (10 mol equiv.) and TMSCl (16 equiv.) was added to a THF solution of keto-alkyne **18a** (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 **20a** was obtained in 77% yield based on the substrate **18a** (Table 11, run 1). At first, the amount of Li was changed. When the amount of Li was decreased to 4 mol equiv. and the same amounts of TMSCl (16

Synthesis of Allylamine from 3b.

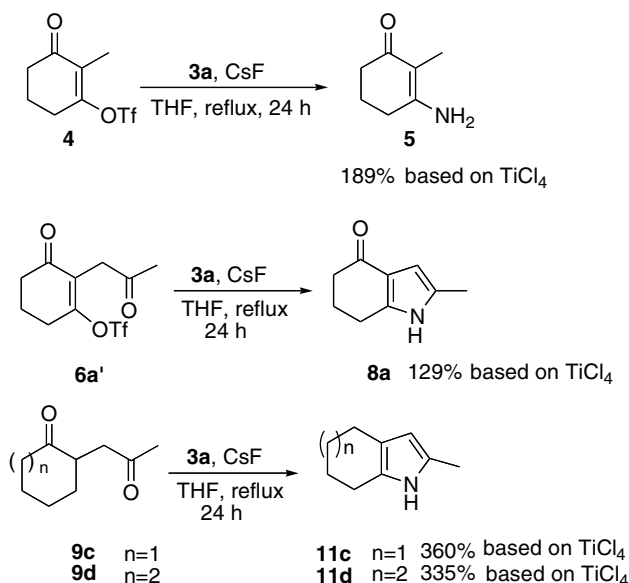


Scheme 24.

Possible Reaction Course



Titanium-Catalyzed Nitrogenation



Scheme 26.

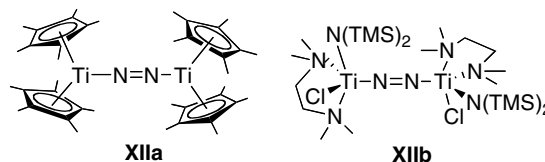
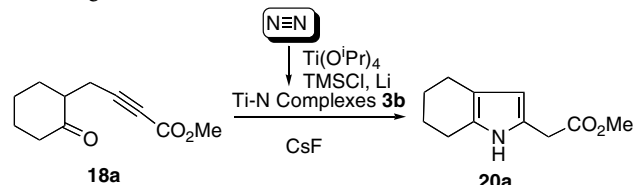


Fig. 2. Titanium–nitrogen complexes.

Table 10
Calculated amounts of Li and TMSCl

Species	Li (mol equiv.)	TMSCl (equiv.)	
		TiCl ₄	Ti(O ⁱ Pr) ₄
XTi=N–TMS VII	4	1	4
XCITi–N(TMS) ₂ XIII	4	2	5
N(TMS) ₃	5	3	6

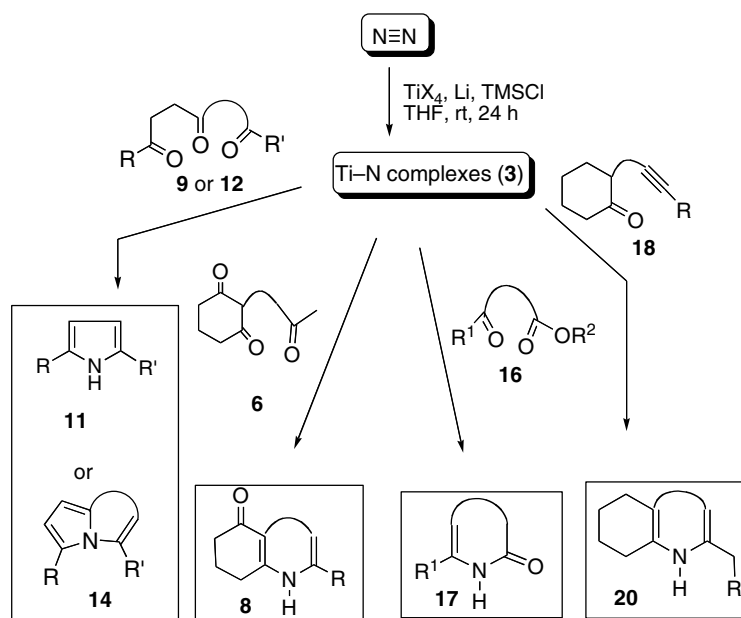
equiv.), Ti(OⁱPr)₄ (1 equiv.), and CsF (6 equiv.) were used for this reaction, the yield of **20a** based on the substrate **18a** was the same (run 2). This means that 4 mol equiv. of Li is sufficient to prepare complex **VII** or **XIII**. Next, the amount of TMSCl required for formation of **3b** was examined. The reaction conditions were slightly modified: CsF was not used [38] and 1.0 equiv. of Ti(OⁱPr)₄ and 1.2 equiv. of the substrate **18a** were used, and the yield was calculated on the basis of Ti(OⁱPr)₄. When 4 mol equiv. of Li and 16 equiv. of TMSCl were used, indole derivative **20a** was obtained in 60% yield (run 3). Then the amounts of TMSCl were changed (runs 4–6). Although the use of 6 equiv. of TMSCl gave the desired compound **20a** in 49% yield (run 5), 4 equiv. of TMSCl gave a trace amount of **20a** (run 6). The use of

Table 11
Reinvestigation of amounts of Li and TMSCl**3b**: XTi=N–TMS, XCITi–N(TMS)₂, N(TMS)₃

Run	Li (equiv.)	TMSCl (equiv.)	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

^a All reactions were carried out using Ti(OⁱPr)₄ (1.0 equiv.) and **18a** (1.2 equiv.), and the yield was calculated on the basis of Ti(OⁱPr)₄.^b Yield was calculated on the basis of a **18a**.

Synthesis of Heterocycles from a Keto-Carbonyl Group



3 equiv. of Li and an excess amount of TMSCl (8 equiv.) gave a moderate yield of the desired compound **20a** (run 7).

These results suggest that 4 mol equivalent of Li and 6 equivalent of TMSCl are required for the synthesis of titanium–nitrogen complexes **3b** from $\text{Ti}(\text{O}^i\text{Pr})_4$, and the real species for this reaction would be **VII** or **XIII** [39].

7. Perspective

Nitrogen fixation is a challenging theme in organic chemistry, and transition metal complexes should play an important role in nitrogen fixation. Initially, we investigated the synthesis of heterocycles from titanium–nitrogen complex **1** reported by Yamamoto. Then we developed novel titanium-catalyzed nitrogenation method using TiX_4 , Li and TMSCl under an atmosphere of nitrogen. Although the structure of titanium–nitrogen complex has not yet been determined, this complex could act as a useful nitrogenation reagent. Various heterocycles could be synthesized using an equimolar amount of complex **3a** or **3b** and keto-carbonyl compounds (Scheme 27).

Titanium–nitrogen complexes **3** can be transmetalated by a palladium catalyst. Thus, a novel method for synthesis of aniline, benzamide, allylamide and allylamine derivatives could be developed. It has already been shown that titanium complexes can be transmetalated with other metals. Thus, various reactions should be developed using **3** and other metals. It is also known

that many transition metals can react with nitrogen to form transition metal–nitrogen complexes. Therefore, the development of nitrogenation methods using various transition metals is expected, and it is also expected that nitrogen or air will be directly used in synthetic organic chemistry instead of NH_3 in the near future.

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