

Miwako Mori

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

Nitrogen fixation is a very attractive process. We succeeded in nitrogen fixation using a TiCl_4 - or $\text{Ti}(\text{O-}i\text{-Pr})_4$ -Li-TMSCl system. Nitrogen fixation proceeds at room temperature under 1 atmosphere pressure of nitrogen to give a mixture of titanium nitride complex **12**, titanium nitrogen complex **13**, and $\text{N}(\text{TMS})_4$. Using the titanium nitrogen complexes **1**, various heterocycles were synthesized from the corresponding ketocarboxyl compounds. Nitrogen in air could be fixed using this method. The total syntheses of lycopodine and monomolin I were achieved from nitrogen in air as the nitrogen source. On the other hand, transmetalation of the nitrogen moiety of titanium nitrogen complexes **1** to a palladium complex was realized, and the non-substituted anilines could be synthesized from ArX and N_2 in the presence of the palladium catalyst. Furthermore, amide could be synthesized from ArX , CO, and N_2 using the palladium catalyst.

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Introduction.

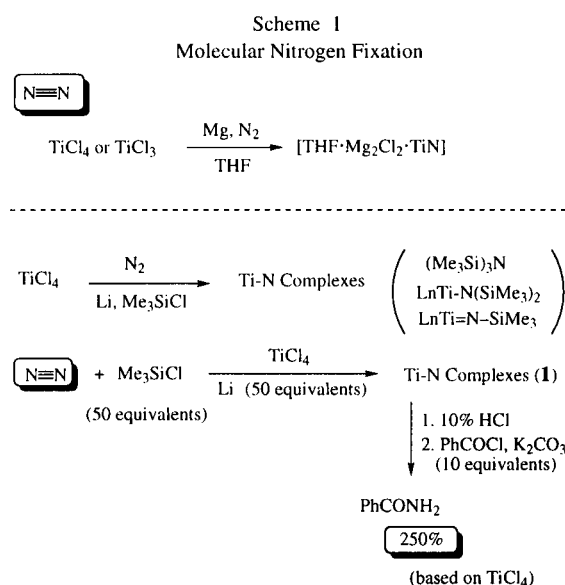
Molecular nitrogen fixation is a very interesting process [1]. Yamamoto succeeded in nitrogen fixation using transition metals such as titanium and cobalt [2]. We have succeeded in nitrogen fixation using a TiX_4 -Li-TMSCl system [3]. To a THF solution of chlorotrimethylsilane (TMSCl) in the presence of Li was added TiCl_4 or $\text{Ti}(\text{O-}i\text{-Pr})_4$ at -78° , and the solution was stirred at room temperature under nitrogen (1 atmosphere) for 24 hours to give a THF solution of titanium nitrogen complexes **1**. This reaction proceeds catalytically in regard to TiCl_4 (1 equivalent) if excess amounts of Li (50 equivalents) and TMSCl (50 equivalents) are used. As a result, we obtained 250% yield of benzamide (PhCONH_2) based on TiCl_4 after hydrolysis of the solution of **1** and then treatment of the aqueous solution with benzoyl chloride (PhCOCl) and potassium carbonate (K_2CO_3).

Using the titanium nitrogen complexes **1**, we could synthesize many heterocycles [4]. For example, from 1,4-diketones **2**, the pyrrole derivatives **3** were synthesized in good yields based on 1,4-diketones **2**. 1,3-Diketones **4** having the ketocarboxyl group in a tether were treated with **1** and gave indoles **5** ($n = 0$) and quinolines **6** ($n = 1$). Since the titanium nitrogen complexes **1** are the equivalent of NH_3 , three substituents can be introduced on nitrogen. Thus, indolizidine and quinolizidine derivatives **7** were synthesized in good yields from triketones **6**.

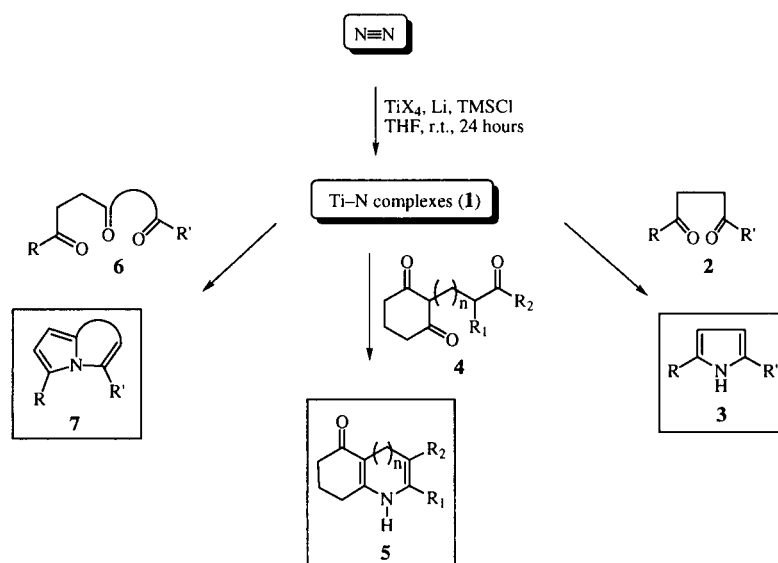
Synthesis of Indole Derivatives.

We planned the synthesis of indole derivatives **9** from ketoalkynes **8** having an electron-withdrawing group on the alkyne. When a THF solution of **8a** and **1** (1.3 equivalents), which was prepared from TiCl_4 , Li, TMSCl and N_2 , was refluxed for several hours, indole derivative **9a** was obtained in 90% yield. When $\text{Ti}(\text{O-}i\text{-Pr})_4$ was used as the titanium complex, the reaction proceeded smoothly at room temperature and the desired indole derivative **9a** was obtained in 82% yield. The reaction was further extended for the synthesis of 2-benzylindole derivatives **11** from ketoalkynes **10** having an aromatic ring on the alkyne. The results are shown in Table 1. Various indole derivatives **11** were obtained in good to moderate yields from the corresponding ketoalkynes **10**. In this reaction, the ketoalkyne having an electron-withdrawing group on the aromatic ring gave good results (runs 3-5), but the *p*-nitro group did not give the desired compound [5].

The reaction mechanism for the formation of titanium nitrogen complexes **1** is not clear. Recently, Ganbarotta reported the synthesis of titanium nitrogen complex **15** from *trans*-(TMEDA) $_2\text{TiCl}_2$ and molecular nitrogen [6]. The structure of **15** was determined by X-ray crystallography. From this result and our considerations, we propose the following reaction mechanism. TiCl_4 is reduced with Li to give TiCl_2 , which reacts with nitrogen in the presence of Li and TMSCl to give titanium nitride complex



Scheme 2
Synthesis of Heterocycles



Scheme 3
Synthesis of Indole Derivatives

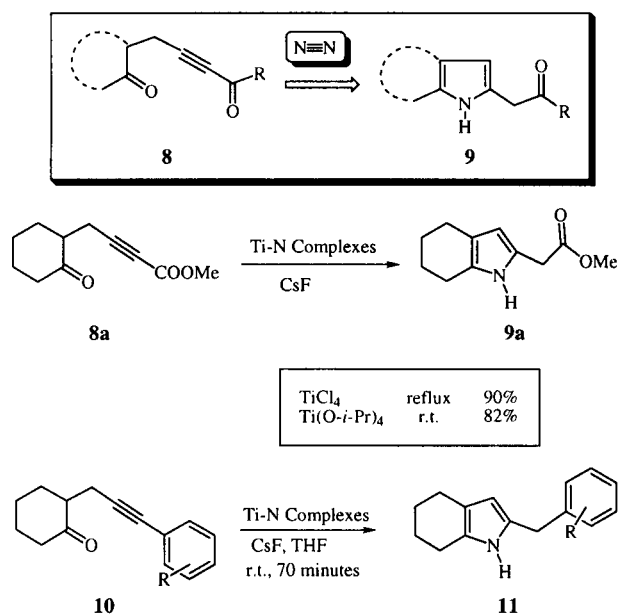
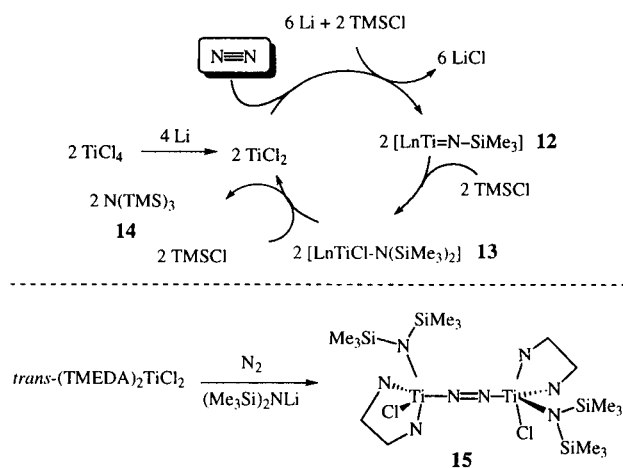


Table 1

Run	R	10	Conditions	Yield (%) of 11
1	H	10a	reflux, 20 hours	35
2	<i>p</i> -CH ₃	10b	reflux, 20 hours	32
3	<i>p</i> -COOMe	10c	reflux, 20 hours	42
4	<i>p</i> -CN	10d	reflux, 5 hours	45
5	<i>p</i> -CF ₃	10e	reflux, 20 hours	49
6	<i>p</i> -NO ₂	10f	reflux, 12 hours	-
7	<i>o</i> -COOMe	10g	40°, 20 hours	35

12. This reacts with TMSCl to give titanium nitrogen complex 13, which further reacts with TMSCl to give N(TMS)₃ and TiCl₂. Thus, the catalytic cycle is established.

Scheme 4
Reaction Course



Atmospheric Nitrogen Fixation.

In air, 80% of the gas is nitrogen. The other gases are oxygen and carbon dioxide. In order to fix nitrogen in air, oxygen and water must be removed. It has been generally accepted that early transition metals are not so sensitive to oxygen but are very sensitive to water. Thus, dry air

passed through a calcium chloride tube was used for the fixation of nitrogen in air. To examine whether nitrogen in *air* can be directly fixed or not, we tried to synthesize benzamide. When a THF solution of TiCl_4 and TMSCl in the presence of Li was stirred under *dry air* passed through a calcium chloride tube at room temperature overnight, the color of the THF solution changed to the same color as that of titanium nitrogen complexes **1** obtained from nitrogen gas. The solution was hydrolyzed with aqueous 10% HCl and then made basic with K_2CO_3 . To this solution was added a benzene solution of benzoyl chloride, and the solution was stirred overnight to give benzamide in 88% yield. When $\text{Ti}(\text{O}-i\text{-Pr})_4$ was used for this reaction, benzamide was obtained in 80% yield. Thus, we succeeded in *atmospheric nitrogen fixation* by a very simple procedure.

Scheme 5
Atmospheric Nitrogen Fixation

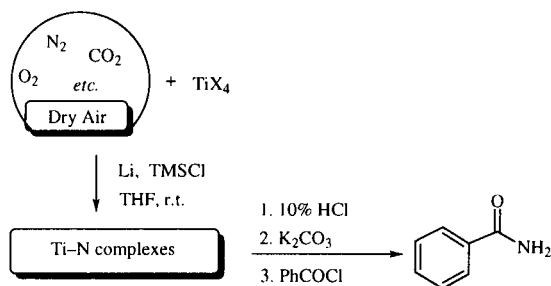


Table 2

Run	TiX_4	Yield of PhCONH_2	
		N_2 Gas	Dry Air
1	TiCl_4	90%	88%
2	$\text{Ti}(\text{O}-i\text{-Pr})_4$	91%	80%

Subsequently, we planned the synthesis of lactams from nitrogen in air. If a ketocarboxylic acid derivative **16** reacts with titanium nitrogen complexes **1** prepared from *air*, lactams **17** would be synthesized. In this reaction, titanium nitrogen complexes **1** would react with the carboxylic acid moiety to give amide, which would react with the ketocarbonyl group. To a THF solution of mixed anhydride, prepared from ketocarboxylic acid and diethyl chlorophosphate in the presence of Et_3N , was added a THF solution of titanium nitrogen complexes **1** prepared from *air*, and the solution was refluxed overnight in the presence of cesium fluoride. Hydrolysis of the reaction mixture gave quinolone derivative **17a** in 60% yield. Using **1** prepared from the nitrogen gas, the same result was obtained. Similar treatment of **16b** with **1** prepared from *air* gave lactam **17b** in 50% yield. In this case, **17b** was obtained in 51% yield from **16b** and **1** prepared from the nitrogen gas. These results indicate that the synthesis of lactams was realized using *air* as the nitrogen source.

Scheme 6
Construction of Lactams

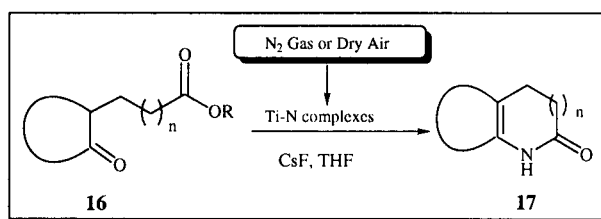


Table 3

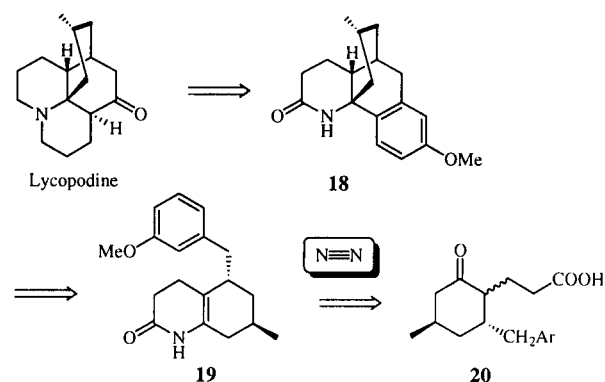
Run	Substrate	Product	Yields (%)	
			Dry Air	N_2
1	16a	17a	60	58
2	16b	17b	50	51

E = $\text{CO}_2-t\text{-Bu}$
R = $\text{PO}(\text{OEt})_2$

Total Synthesis of Natural Products Using *Air* as the Nitrogen Source.

Since lactams could be synthesized from *air* as the nitrogen source, we tried to synthesize the natural product lycopodine using our method. Stork already reported the synthesis of lycopodine in 1968, and he obtained lycopodine from tetracyclic lactam **18**, which was obtained from quinolone derivative **19** [7]. If **19** can be synthesized from ketocarboxylic acid **20**, we can synthesize lycopodine.

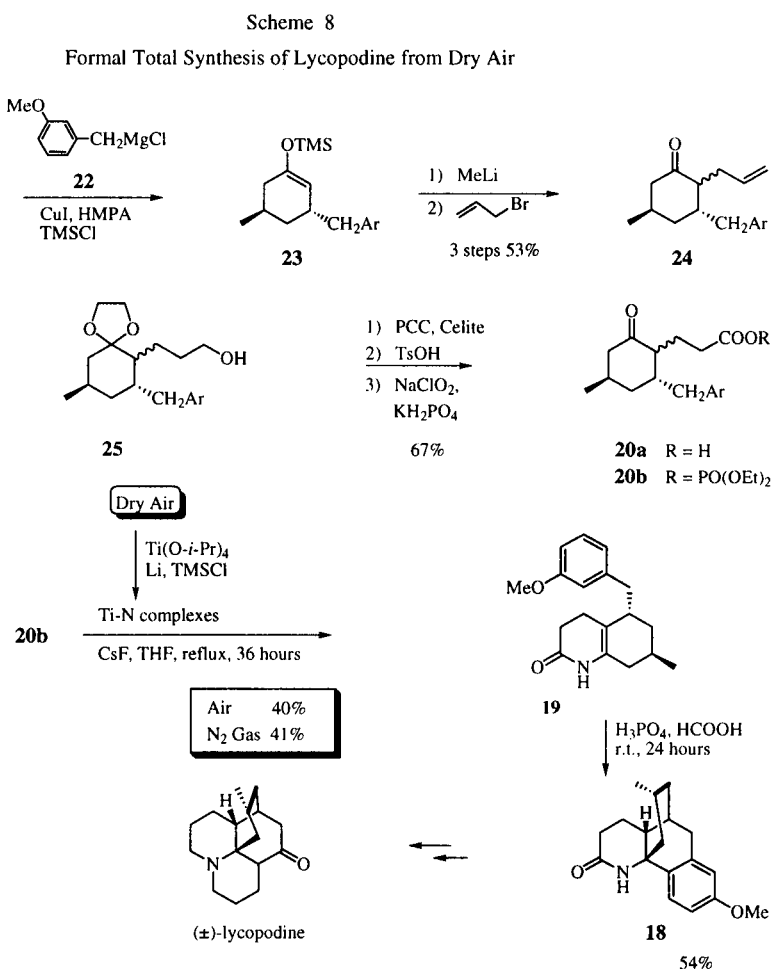
Scheme 7
Total Synthesis of Lycopodine Using Dry Air as the Nitrogen Source

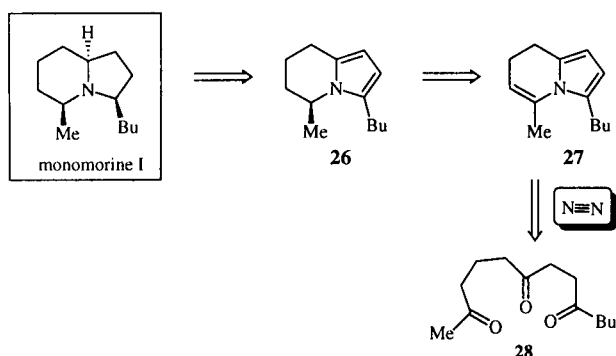


The starting ketocarboxylic acid **20a** was synthesized from 5-methylcyclohexenone **21**. Reaction of **21** with 3-methoxybenzyl magnesium chloride **22** in the presence of CuI followed by treatment with TMSCl gave silyl enol ether **23**, which was treated with methyl lithium and then allyl bromide to afford **24**. Ketalization of **24** followed by hydroboration provided alcohol **25**, which was oxidized with pyridinium chlorochromate (PCC), and then deprotection and further oxidation gave ketocarboxylic acid **20a**. Treatment of **20a** with ClPO(OEt)₂ in the presence of Et₃N afforded mixed anhydride **20b**. To a THF solution of the crude product was added the THF solution of titanium nitrogen complexes **1**, prepared from *dry air*, and the whole solution was refluxed for 36 hours to give the desired quinolone derivative **19** in 40% yield. When nitrogen gas was used for the synthesis of **1**, **19** was obtained in 41% yield. Treatment of **19** with acid according to Stork's procedure afforded tetracyclic compound **18**, which was already converted into lycopodine [7]. Thus, the formal total synthesis of lycopodine was achieved using *air* as the nitrogen source [8].

Next, we tried to synthesize monomoline I, which has an indolizidine skeleton, using our nitrogen fixation method. The retrosynthetic analysis of monomoline I is shown in Scheme 9. Monomoline I would be synthesized from indolizidine **26**, which would be obtained from indolizine **27**. Hydrogenation of **27** would first afford **26** and further hydrogenation would proceed stereoselectively from the backside of the methyl group. If triketone **28** is treated with titanium nitrogen complexes **1**, indolizine **27** will be synthesized.

Ozonolysis of cyclopentene derivative **29** followed by treatment with Me₂S gave **28**, which reacted with **1** prepared from *dry air* to give indolizine derivative **27** in 22% yield. Using nitrogen gas as the nitrogen source, **27** was obtained in 30% yield. Although the yield was low, we could obtain an important intermediate **27** for the synthesis of monomoline I using *air* as the nitrogen source. Hydrogenation of **27** with Rh on Al₂O₃ in EtOH gave monomoline I in 32% yield along with indolizidine 195B in 4% yield. The spectral data of these compounds agree with those reported in the literature [9]. Thus, the total

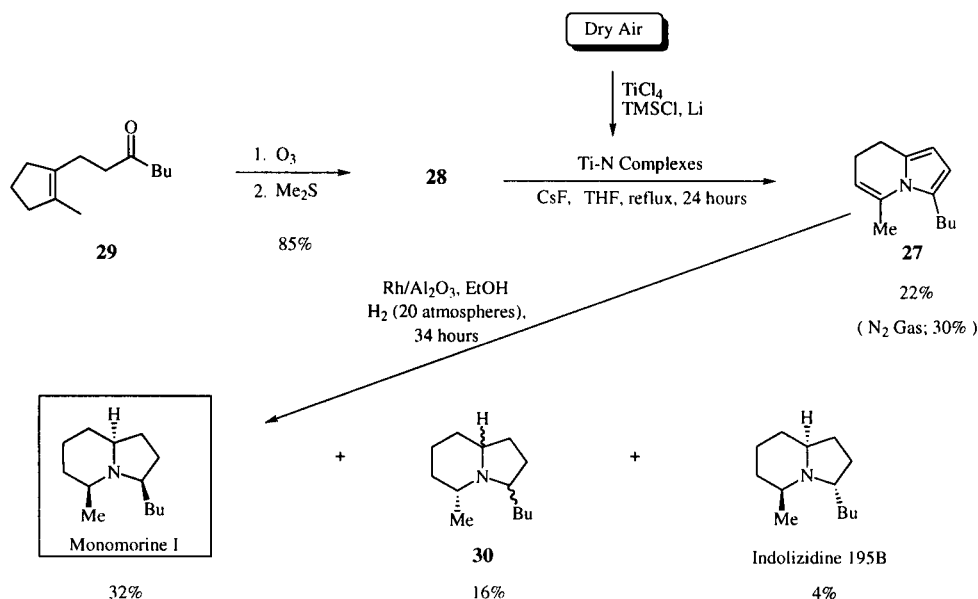


Scheme 9
Retrosynthesis of Monomoline I

synthesis of monomoline I was achieved in two steps from triketone **27** using *air* as the nitrogen source [10].

nitrogen complexes **1** prepared from molecular nitrogen and a TiCl_4 - or $\text{Ti}(\text{O}-i\text{-Pr})_4\text{-Li-TMSCl}$ system. If titanium nitrogen complexes **1** are tranetalated with ArPdX **33** formed from **31** and $\text{Pd}(0)$, arylpalladium nitrogen complex **34** would be formed, and this should be followed by reductive elimination to give nonsubstituted aniline derivatives **32**.

When a toluene solution of titanium nitrogen complexes **1** (2.0 equivalents), which was prepared from $\text{Ti}(\text{O}-i\text{-Pr})_4$ (2.0 equivalents), Li (20 equivalents), and TMSCl (20 equivalents) in THF under an atmosphere of nitrogen at room temperature for 8 hours, was added to a THF solution of tris(dibenzylideneacetone)dipalladium(O)-chloroform adduct ($\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$, 2.5 mole %), tri-*o*-tolylphosphine ($\text{P}(\text{o-tolyl})$, 10 mole %), and sodium *tert*-butoxide (2.8 equivalents), and the solution was refluxed overnight, 4-aminobiphenyl **32a** was obtained in 32%

Scheme 10
Synthesis of Monomoline I and Indolizidine 195B

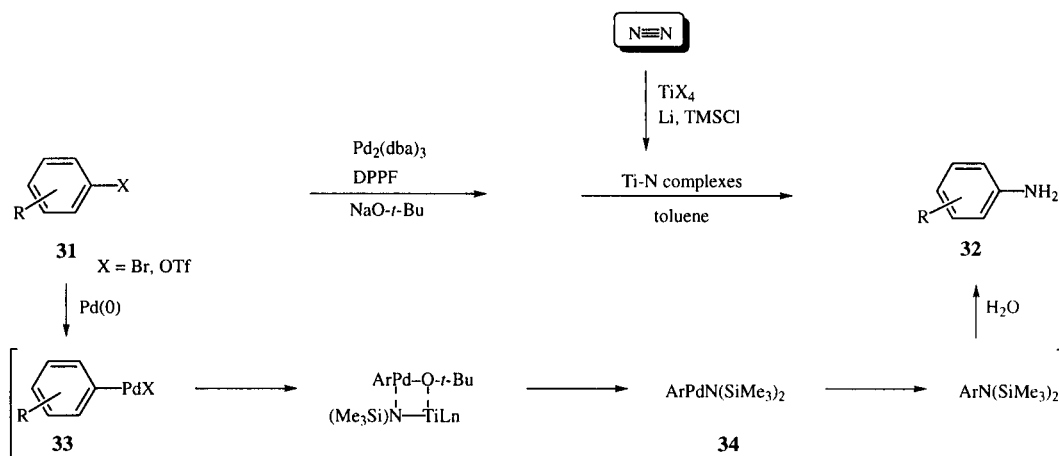
Synthesis of Nonsubstituted Anilines from ArX and N_2 .

Since Migita [11] succeeded in synthesizing disubstituted aniline derivatives from arylpalladium complex and dialkylstannane, a method for synthesizing mono- and disubstituted aniline derivatives from aryl halides using a palladium catalyst has been established by the ingenious studies of Buchwald and Hartwig [12]. However, synthesis of nonsubstituted aniline derivatives from an arylpalladium complex was not reported because we must use NH_3 for that purpose. These results have stimulated us to synthesize nonsubstituted aniline derivatives **32** by a one-step reaction from arylpalladium complex **33** and titanium

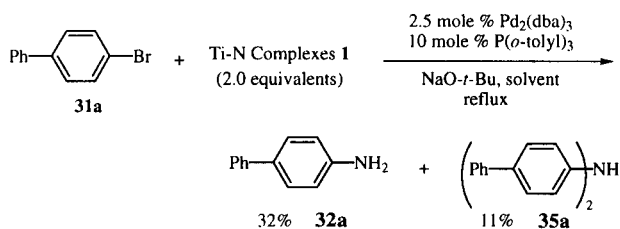
yield along with secondary aniline **35a** in 11% yield. The result indicates that nonsubstituted aniline can be synthesized from aryl halide and molecular nitrogen by a one-step reaction using palladium-catalyzed amination. Sodium *tert*-butoxide was required in this reaction.

Subsequently, aryl triflate **36a** was used for this reaction under the same reaction conditions. As a result, a fair amount of phenol **37a** was produced along with the desired aniline derivative **32a**. It was found that the slow addition of the substrate was important for preventing the formation of phenol (Table 4, run 2), and the use of $\text{Pd}_2(\text{dba})_3$ and 1,1'-bis(diphenylphosphino)ferrocene

Scheme 11
Synthesis of Nonsubstituted Anilines from ArX and N₂



Scheme 12
Synthesis of Nonsubstituted Aniline from **1** and ArX



(DPPF) gave good results (run 5). The lower reaction temperature raised the yield of **32a** (run 6). Finally, when a large amount of NaO-*t*-Bu was used for this reaction (run 9), **32a** was produced in 73% yield.

We reinvestigated whether the slow addition of the substrate was effective or not for the reaction of aryl bromide **31a** with **1**. Slow addition was found to be quite effective, and the desired aniline **32a** was obtained in 77% yield. Various aryl bromides **31** and aryl triflate **36** were examined, and the results are shown in Scheme 14. These results indicate that titanium nitrogen complexes **1** can be used for the synthesis of nonsubstituted anilines **32**.

To determine the species of the reaction intermediate, N(TMS)₃ or HN(TMS)₂ was used instead of titanium nitrogen complexes **1** for this reaction, but no nitrogen containing products were obtained. This indicates that the active species would be titanium nitride complex **12** and/or titanium nitrogen complex **13**, not N(TMS)₃, and that transmetalation of the nitrogen moiety from titanium to palladium is an important process for this reaction [13].

Synthesis of Amide from ArX, CO, and N₂.

On the basis of these results, we planned the synthesis of amide from aryl halide, carbon monoxide, and nitrogen. Our plan is shown in Scheme 15. If acylpalladium complex **38**, formed from aryl halide **31**, Pd(0) and carbon monoxide, could transmetalate with titanium nitrogen complexes **1**, amide **39** would be formed.

When aryl halide **31e** was reacted with titanium nitrogen complexes **1** in the presence of Pd₂(dba)₃ and DPPF in DMF at 90° overnight, the desired amide **39e** was obtained in 75% yield. In this reaction, the carbonyl part of amide **39** was derived from carbon monoxide, and amide nitrogen came from nitrogen gas.

These reactions are summarized in Scheme 16. If the reaction of aryl halides **31** and titanium nitrogen complexes **1** is carried out in the presence of a palladium catalyst in toluene under argon gas, we obtain nonsubstituted anilines **32**. When the same reaction is carried out in DMF under carbon monoxide, the desired amide **39** is formed.

Molecular nitrogen fixation is very interesting and now useful for synthetic organic chemistry. The reaction procedure for nitrogen fixation is very simple, and the reaction proceeds smoothly at room temperature under 1 atmosphere pressure of nitrogen. Using titanium nitrogen complexes **1**, we synthesized various heterocycles, such as pyrroles, indoles, quinolines, indolizines, pyrrolizidines and lactams. In a usual case, the reaction proceeds by the use of a stoichiometric amount of titanium nitrogen complexes **1**. On the other hand, the nitrogen moiety on the titanium nitrogen complex could be transmetalated into transition metals such as palladium and nickel. Thus, we synthesized various nonsubstituted anilines and amides from the corresponding aryl halides. In the future, it is expected that various novel reactions will be developed

Scheme 13
Synthesis of Nonsubstituted Anilines from **1** and ArOTf

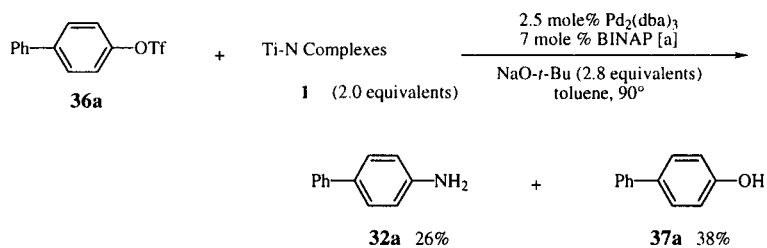
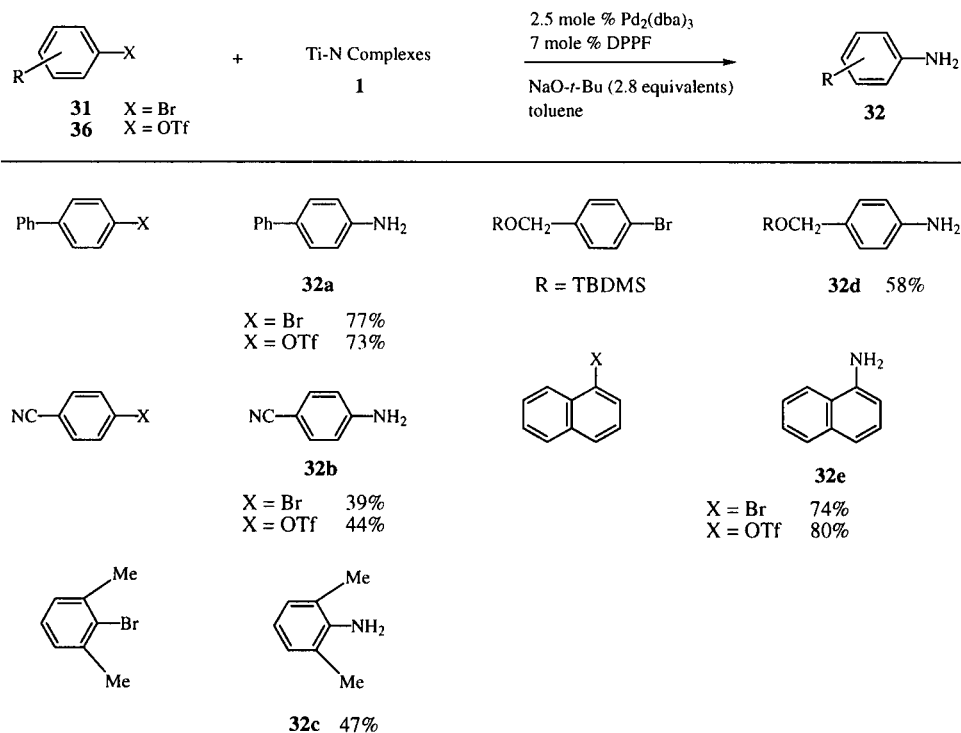


Table 4
Palladium-Catalyzed Amination of **36a** under Various Conditions

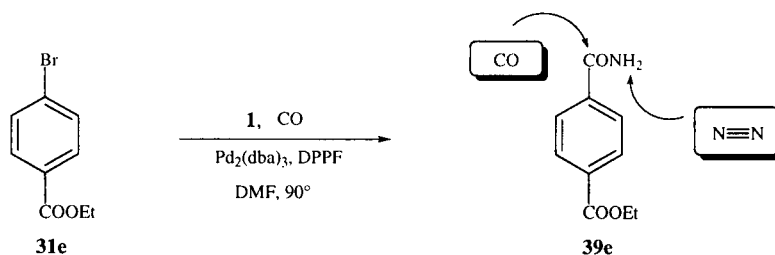
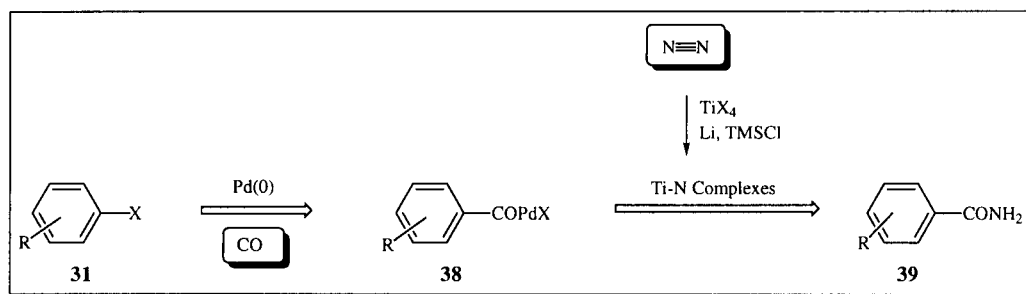
Run	Catalyst	Ligand	Temperature °C	Time (hours)	Yields (%)	
					32a	37
1	Pd ₂ (dba) ₃	(S)-BINAP	90	4	26	38
2	Pd ₂ (dba) ₃	(S)-BINAP	90	4	21	8
3	Pd(OAc) ₂	(S)-BINAP	90	4	31	14
4	Pd(OAc) ₂	DPPF	90	4	41	3
5	Pd ₂ (dba) ₃	DPPF	90	4	45	8
6	Pd ₂ (dba) ₃	DPPF	70	4	53	10
7	Pd ₂ (dba) ₃	DPPF	50	23	46	4
8	Pd ₂ (dba) ₃	P(<i>o</i> -tolyl) ₃	90	4	–	<14
9	Pd ₂ (dba) ₃	DPPF	70	2	73	9

[a] BINAP: 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl.

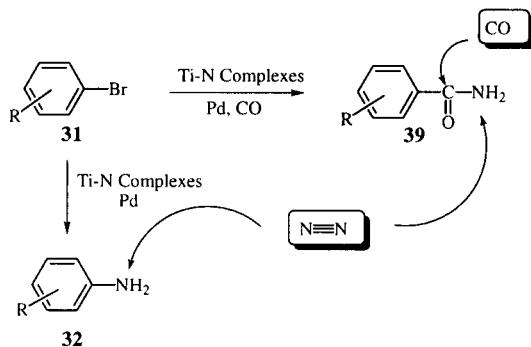
Scheme 14
Synthesis of Various Anilines from Aryl Halide and N₂



Scheme 15
Our Plan for the Synthesis of Amide from ArX, CO, and N₂



Scheme 16
Synthesis of Anilines and Amides



using **1** and transition metals. Unfortunately, the structure of titanium nitrogen complexes **1** has not yet been determined. However, recent studies indicate that the reactive species are titanium nitride complex **12** and/or titanium nitrogen complex **13**. Further studies are required to clarify the reaction mechanism.

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