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SYNTHESIS OF NITROGEN HETEROCYCLES UTILIZING MOLECULAR NITROGEN AS A NITROGEN SOURCE AND ATTEMPT TO USE AIR INSTEAD OF NITROGEN GAS

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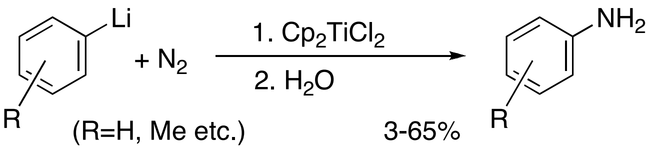
Abstract – Nitrogen fixation using transition metals is a challenging subject. Using a titanium-nitrogen complex, discovered by Yamamoto in 1967, and titanium isocyanate complex, molecular nitrogen could be incorporated into organic compounds to afford various heterocyclic compounds. Furthermore, novel titanium-catalyzed nitrogenation procedure was developed. That is, a THF solution of $TiCl_4$ or $Ti(O^iPr)_4$, and an excess amount of Li and TMSCl was stirred under nitrogen (1 atm) at room temperature overnight and to this solution was added phthalic anhydride. The whole solution was refluxed overnight to afford a phthalimide in over 100 % yield. Using the stoichiometric conditions of the novel nitrogenation, various indole, pyrrole, pyrrolizine, indolizine derivatives and lactams were obtained in good to moderate yields after usual workup. Although the structure of the titanium-nitrogen complex has not been determined yet, the complex is thought to be a mixture of $N(TMS)_3$, $TiX_2N(TMS)_2$ and XTi=NTMS. Nitrogen in air could be directly fixed using this method, and the natural products, such as monomoline I, lycopodine and pumiliotoxin C, could be synthesized from nitrogen in air as a nitrogen source.

CONTENTS

1. INTRODUCTION

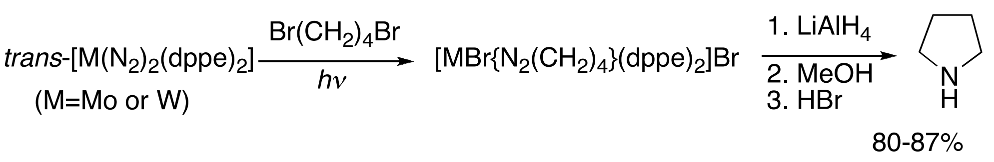
Since Vol'pin and Shur discovered that molecular nitrogen could be fixed by transition metals[1] and reducing agents under mild conditions, various systems of nitrogen fixation have been reported.[2] In 1967, Yamamoto reported the synthesis of a cobalt-nitrogen complex[3] and then a titanium-nitrogen 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 reported the synthesis of aniline from Cp_2TiCl_2 and phenyl lithium under high pressure of nitrogen (eq. 1).[7] Later, van Tamelen succeeded in obtaining isopropyl amine and benzonitrile from diethylketone and benzoyl chloride, respectively using Cp_2TiCl_2 and Mg under nitrogen (eq. 2).[8] In 1977, Chatt synthesized pyrrolidine and isopropyl amine from 1,4-dibromobutane and acetone, respectively, using molybdenum or a tungsten-nitrogen complex (eqs. 3 and 4).[9] Hidai recently reported the synthesis of pyrrole from a tungsten nitrogen-complex (eq. 5).[10] Yamamoto reported the synthesis of an interesting titanium-nitrogen complex (**1**) from $TiCl_4$ or $TiCl_3$ using Mg as a reducing agent (eq. 6).[4] In this reaction, the nitrogen-nitrogen triple bond was cleaved by a reducing agent to give a titanium-nitrogen complex (**1**), which reacted with benzoyl chloride to give benzoyl-titanium complex (**3**).[11] The result is very attractive for the synthesis of nitrogen heterocycles from molecular nitrogen because one nitrogen in N_2 can be used for the synthesis of heterocycles. Later, Sobota reported that the reaction of **1** with CO_2 gave a titanium-isocyanate complex (**2**) (eq. 7).[12]



(1)

$$Cp_2TiCl_2 + Mg + N_2 \xrightarrow[\text{2. } H_2O]{\text{1. } Et_2CO} Et_2CHNH_2 + (Et_2CH)_2NH \qquad (2)$$

25-50%

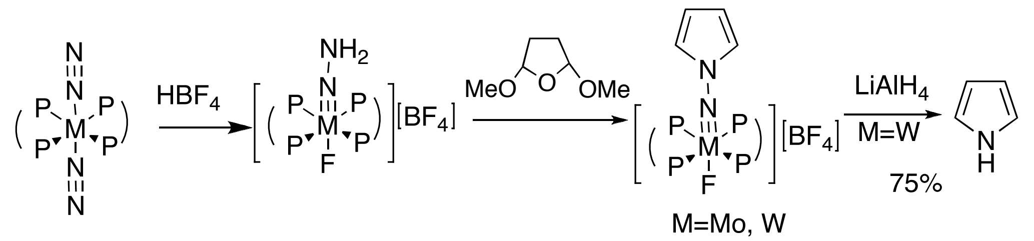


(3)

$$cis\text{-}[W(N_2)_2(PMe_2Ph)_4] \xrightarrow[\text{MeOH}]{\text{HBr}} [WBr_2(NNH_2)(PMe_2Ph)_3] \qquad (4)$$

$$\xrightarrow{Me_2CO} [WBr_2(=N\text{-}N=CMe_2)(PMe_2Ph)_3] \xrightarrow[\text{2. MeOH; 3. HBr}]{\text{1. LiAlH}_4} {}^{i}PrNH_2$$

94%

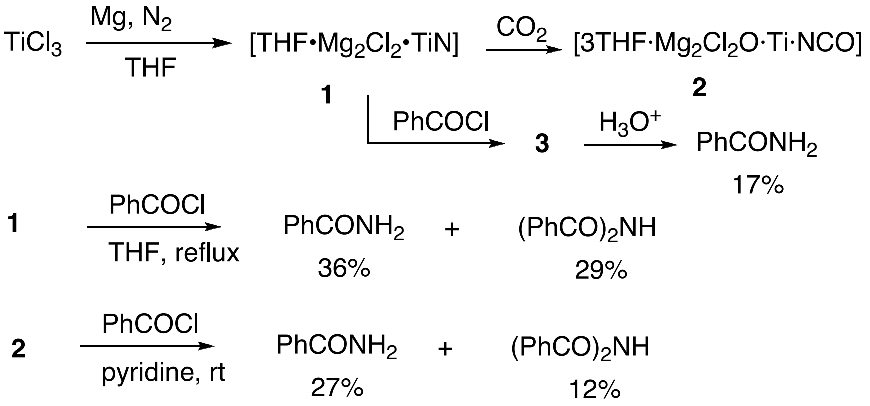


(5)

$$TiCl_4 \text{ or } TiCl_3 \xrightarrow[\text{THF}]{Mg,\ N_2} \underset{\mathbf{1}}{[THF\cdot Mg_2Cl_2\cdot TiN]} \xrightarrow{PhCOCl} \underset{\mathbf{3}}{[TiNCl(PhCO)_{1.5}]} \qquad (6)$$

$$[THF\cdot Mg_2Cl_2\cdot TiN] \xrightarrow{CO_2} \underset{\mathbf{2}}{[THF\cdot Mg_2Cl_2O\cdot TiNCO]} \qquad (7)$$

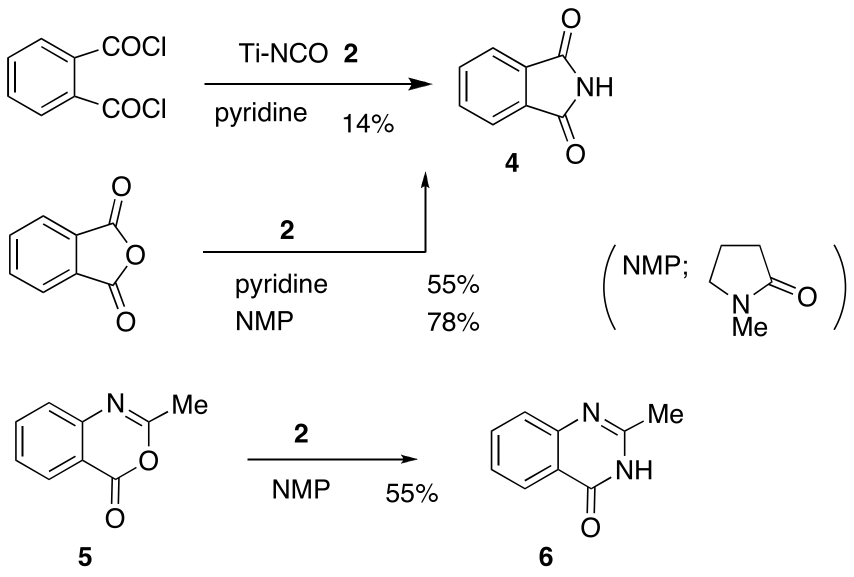
These results are very attractive since organometallic complexes are used for the incorporation of molecular nitrogen into organic compounds. Yamamoto's report indicated that molecular nitrogen could be fixed using $TiCl_3$ or $TiCl_4$ using Mg as a reducing agent under mild conditions to produce titanium-nitrogen complex (**1**), and the reaction of **1** with benzoyl chloride gave benzoyl-titanium complex **3**. However, in benzoyl-titanium complex (**3**), whether carbon-nitrogen bond is formed or not is unclear. Thus, complex (**3**) was prepared from **1** and benzoyl chloride according to the Yamamoto's procedure,[4] and was hydrolyzed. As a result, benzamide was obtained in 17% yield. It means that nitrogen could be incorporated into benzoyl chloride and carbon-nitrogen bond is formed in benzamide. When a THF solution of **1** and benzoyl chloride was refluxed overnight, the yield of benzamide was increased to 36% along with benzimide in 29% yield.[12] Sobota reported that titanium-nitrogen complex (**1**) reacted with CO_2 to give titanium-isocyanete complex (**2**) (eq. 7),[13] which was thought to have the same reactivity with that of benzoyl-titanium complex (**3**). Thus, titanium-isocyanate complex (**2**) was synthesized from **1** and CO_2, and a THF solution of **2** and benzoyl chloride was stirred in pyridine at room temperature overnight. As the result, benzamide was obtained in 27% yield along with benzimide in 12% yield (Scheme 1).[12]



Scheme 1. Reaction of Titanium Nitrogen Complex with PhCOCl

Since isocyanate complex (**2**) is more stable compared with that of titanium-nitrogen complex (**1**), synthesis of nitrogen containing compounds was examined using this complex **2**. When phthaloyl chloride was reacted with **2** in pyridine, phthalimide (**4**) was obtained in 14% yield. Use of phthalic anhydride instead of phthaloyl chloride improved the yield of **4** to 55%. As a solvent, NMP (N-methyl pyrrolidone) gave a good result and desired phthalimide (**4**) was obtained in 78% yield. It was interesting that benzoxazinone (**5**), which is thought to be a kind of a mixed anhydride, was treated in a similar manner to give quinazolinone (**6**) in 55% yield.[12]

On the basis of these results, synthesis of heterocycles using titanium isocyanate complex (**2**) was investigated and novel nitrogenation method was developed. Furthermore, we found that dry air can be used as a nitrogen source for the synthesis of heterocycles.[14]



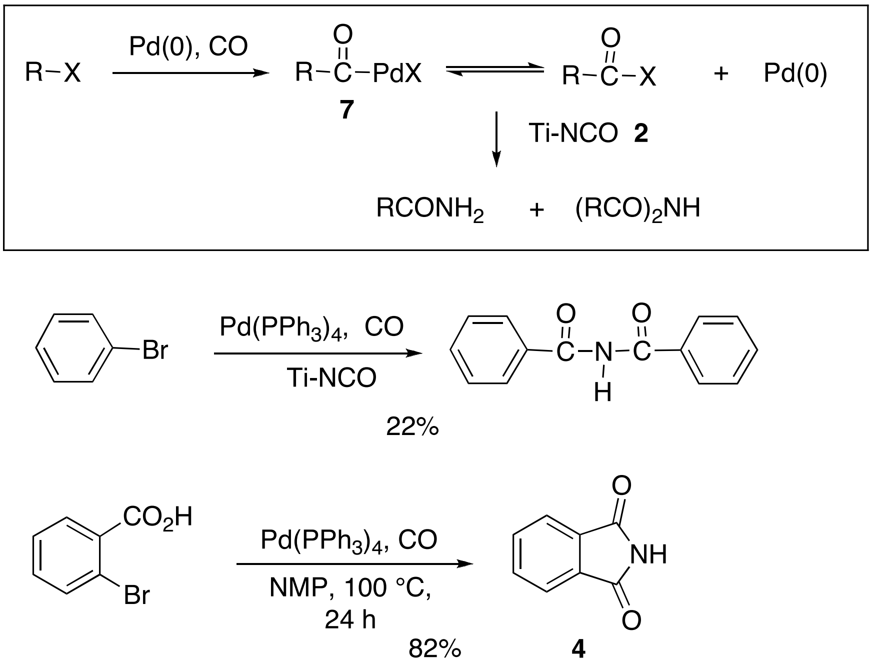
Scheme 2. Reaction of Acid Anhydride with **2**

2. SYNTHESIS OF NITROGEN HETEROCYCLES USING TITANIUM ISOCYANATE COMPLEX AND PALLADIUM COMPLEX

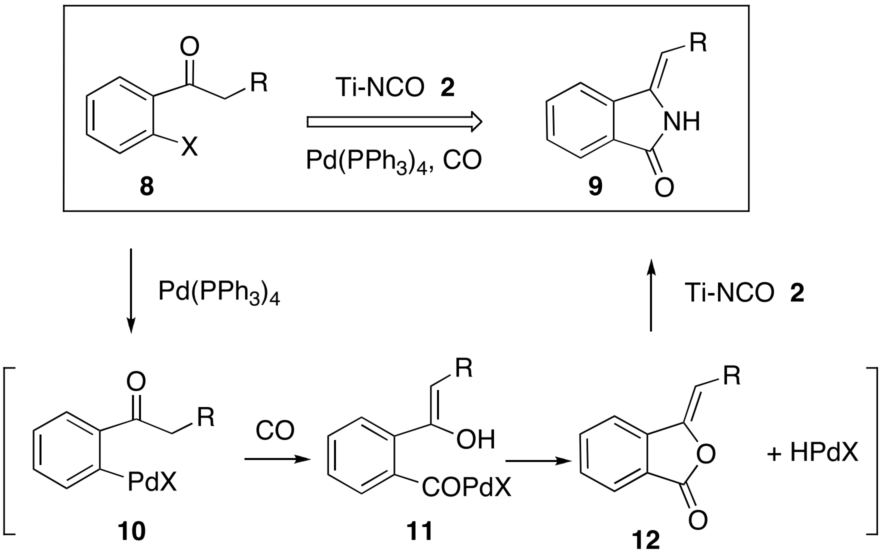
2-1. Synthesis of Heterocycles Using Palladium-Catalyzed Carbonylation and Titanium-Promoted Nitrogenation

It was well known that an oxidative addition of an aryl halide to Pd(0) afforded aryl palladium complex, which was converted into acyl palladium complex (**7**) under carbon monoxide.[15] If acyl palladium complex (**7**) is in a state of equilibrium with acid chloride and Pd(0), titanium-isocyanate complex (**2**) may react with acyl palladium complex (**7**) to give amide or imide (Scheme 3). The problem on this idea is whether titanium-isocyanate complex (**2**) and $Pd(PPh_3)_4$, which are added in the same reaction vessel, can act for each role. When a NMP solution of bromobenzene, $Pd(PPh_3)_4$, titanium-isocyanate complex (**2**), and K_2CO_3 was stirred upon heating at 100 °C for 24 h under carbon monoxide (1 atm), benzimide was obtained in 22% yield. It means that carbon monoxide and nitrogen could be incorporated into aryl halide to give benzimide in one-pot reaction, although the yield was moderate. When 2-bromobenzoic acid was treated in a similar manner, phthalimide (**4**) was obtained in 82% yield.[16]

On the basis of these results, the synthesis of lactam (**9**) from aryl halide (**8**) having a keto-carbonyl group at the 2-position was planned (Scheme 4). If aryl halide (**8**) is reacted with Pd(0) under carbon monoxide, acylpalladium complex (**11**) would be formed via arylpalladium complex (**10**). Since the keto-carbonyl group is in a state of equilibrium with an enol form, the enol part would react with acylpalladium complex to produce enol lactone (**12**). If the enol lactone (**12**) can react with titanium-isocyanate complex (**2**), isoindolinone (**9**) would be produced.

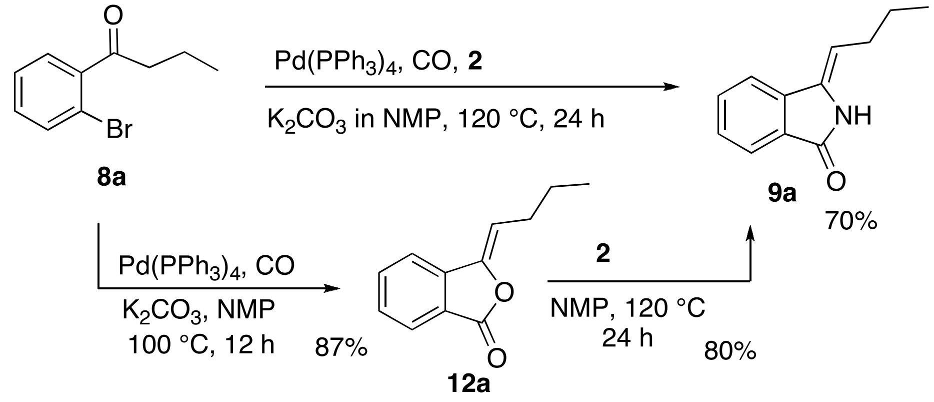


Scheme 3. Reaction of Aryl Halide with **2** under CO in the Presence of $Pd(PPh_3)_4$



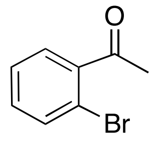
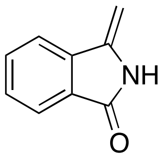
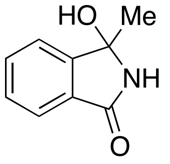
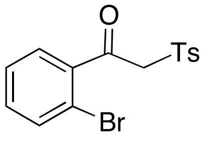
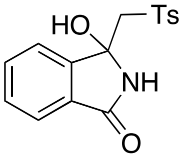
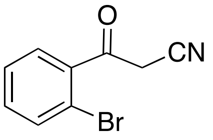
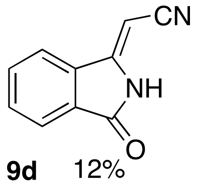
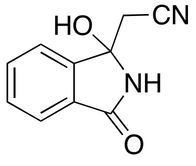
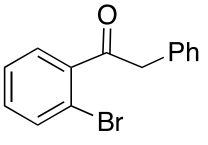
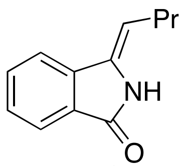
Scheme 4. Plan for Synthesis of Isoindolinone

The idea was realized when *o*-bromobutylophenone (**8a**) was reacted with $Pd(PPh_3)_4$, titanium-isocyanate complex (**2**) and K_2CO_3 in NMP under carbon monoxide at 120 °C for 24 h. As the result, isoindolinone (**9a**) was obtained in 70% yield. To clarify this reaction course, the reaction was carried out in stepwise. When compound (**8a**) was reacted with $Pd(PPh_3)_4$ in NMP at 100 °C for 12 h under carbon monoxide, enol lactone (**12a**) was obtained in 87% yield.[17] Then, compound (**12a**) was reacted with **2** in NMP at 120 °C for 24 h to give isoindolinone (**9a**) in 80% yield.



Scheme 5. Synthesis of Isoindolinone Using $Pd(PPh_3)_4$ and **2** under CO

Table 1. Synthesis of Indoline Derivatives[a]

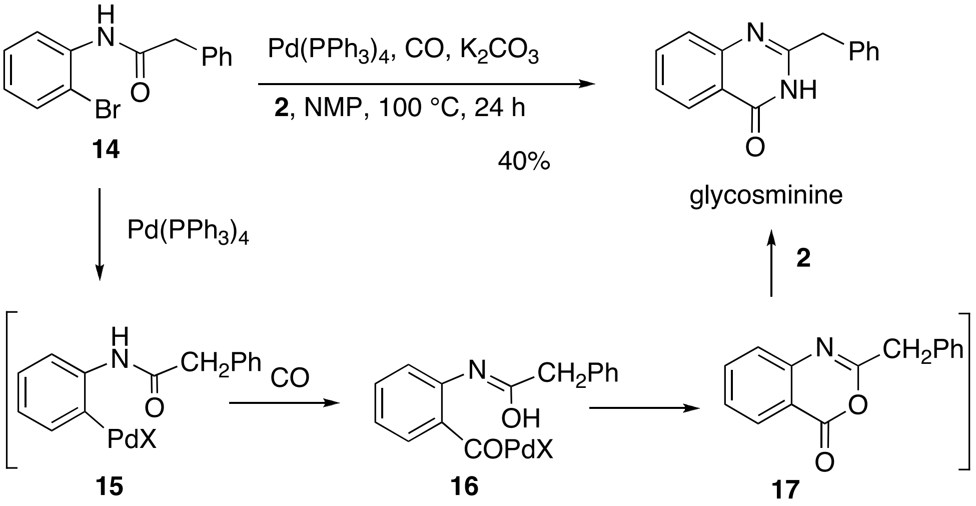
entry	substrate	conditions	products	
1	 **8b**	120 °C, 24 h	 **9b** 55%	 **13b** 20%
2	 **8c**	70 °C, 40 min.		 **13c** 47%
3	 **8d**	80 °C, 1 h	 **9d** 12%	 **13d** 53%
4	 **8e**	120 °C, 24 h	 **9e** 77%	

[a]All reactions were carried out using $Pd(PPh_3)_4$ (5 mol %), **2** (3 equiv.), and K_2CO_3 (2 mol equiv.) under CO (1 atm) in NMP.

Various isoindolinones could be synthesized using this procedure and the results are shown in Table 1. In some cases, hydroxylated isoindolines (**13**) were produced along with isoindolinones (**9**). Presumably, compound (**13**) would be formed from **9** during the workup. The total yields of isoindolinones (**9**) and

(**13**) were high in each case.

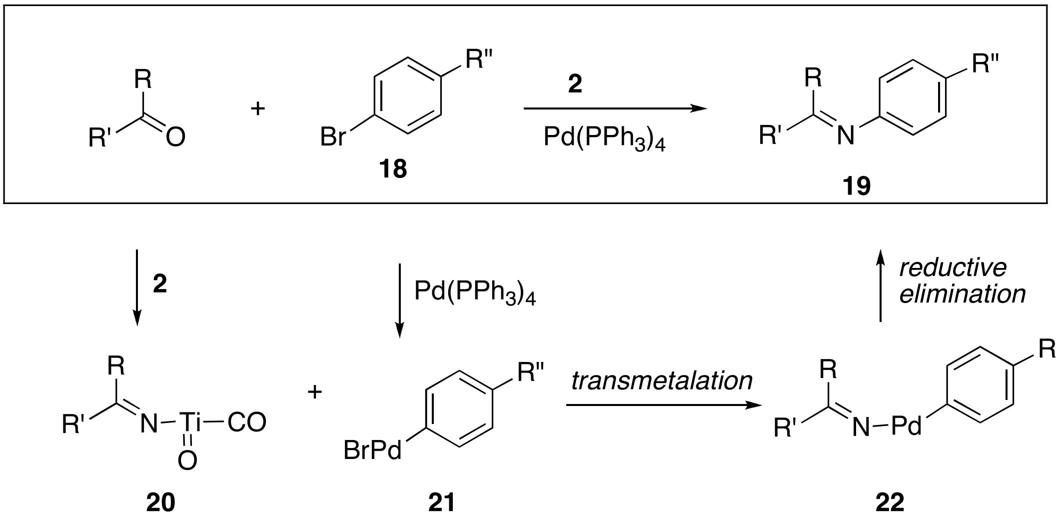
Using this procedure, a natural product, glycosminine, could be synthesized from **14** in a one-pot reaction. A NMP solution of N-acetyl-2-bromoaniline derivative (**14**), $Pd(PPh_3)_4$, **2** and K_2CO_3 was heated under carbon monoxide at 100 °C overnight to afford glycosminine in 40% yield. The reaction course would be same as that of isoindolinone, that is, acylpalladium complex (**16**) would react with an enol part of **16** to afford benzoxazinone (**17**). Then it reacts with **2** to afford glycosminine.[18]



Scheme 6. Synthesis of Glycosminine

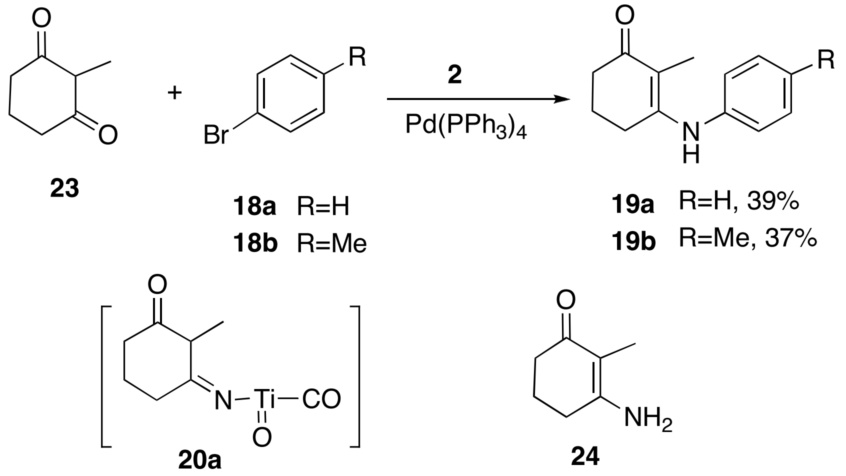
2-2. Synthesis of Heterocycles Using Nitrogenation-Transmetallation Reaction

van Tamelen succeeded in obtaining isopropylamine and diisopropylamine from diethylketone using Cp_2TiCl_2 and Mg under nitrogen (eq. 2).[8]



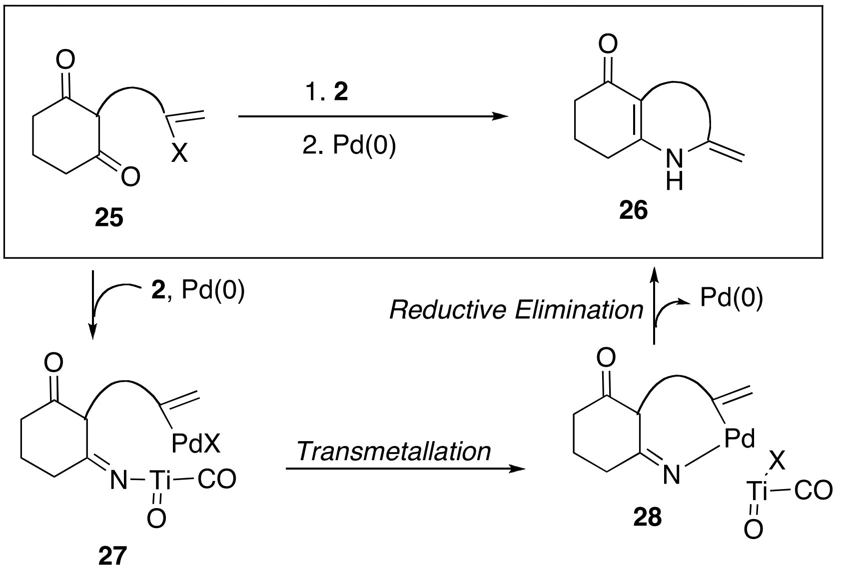
Scheme 7. Plan for Novel C-N-C Bond Formation

If an imino part on titanium-imine complex (**20**) generated from keto-carbonyl compound and **2** is transmetallated to arylpalladium complex (**21**), which was derived from aryl halide (**18**) and Pd(0), and then reductive elimination occurs from resultant palladium complex (**22**), aniline derivative (**19**) would be formed, that is, novel C-N-C bond formation would be developed. When a NMP solution of diketone (**23**), 4-bromobenzene (**18a**), titanium-isocyanate complex (**2**), $Pd(PPh_3)_4$, and K_2CO_3 was heated at 100 °C for 12 h, aniline derivative (**19a**) was obtained in 39% yield along with enaminone (**24**) in 30% yield (Scheme 8). The latter compound (**24**) would be obtained from **20a** by hydrolysis. Similarly, 4-bromotoluene (**18b**) afforded aniline derivative (**19b**) in 37% yield. These results indicated that novel C-N-C bond is formed from ketone (**23**), aryl halide (**18**) and titanium-isocyanate complex **2** using Pd(0), and aniline derivative (**19**) could be obtained.



Scheme 8. Novel C-N-C Bond Formation

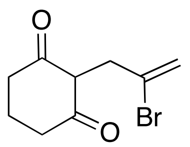
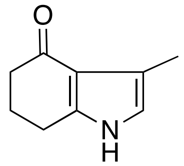
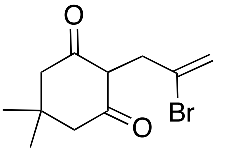
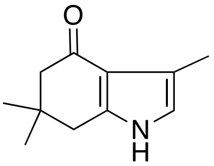
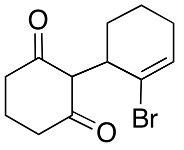
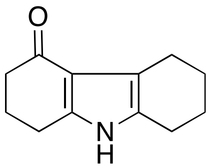
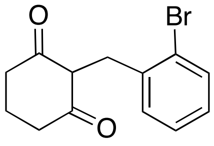
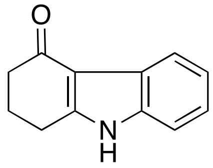
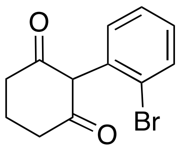
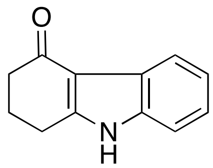
To demonstrate the applicability of this nitrogenation transmetallation process, synthesis of heterocycles by intramolecular reaction was planned as shown in Scheme 9.



Scheme 9. Plan for Synthesis of Heterocycles Using Transmetallation

When a NMP solution of 1,3-diketone (**25a)** having vinyl halide in a tether and **2** was stirred upon heating at 100 °C in the presence of Pd(pph$_3$)$_4$ for 12 h, indole derivative (**26a**) was obtained in 87% yield (Table 2, entry 1). The intermediate should be imino-titanium complex (**27a**), and transmetallation of the imino group on titanium to palladium metal would occur to afford **28a** and then reductive elimination affords desired compound (**26a**).

Table 2. Synthesis of Indole Derivatives[a]

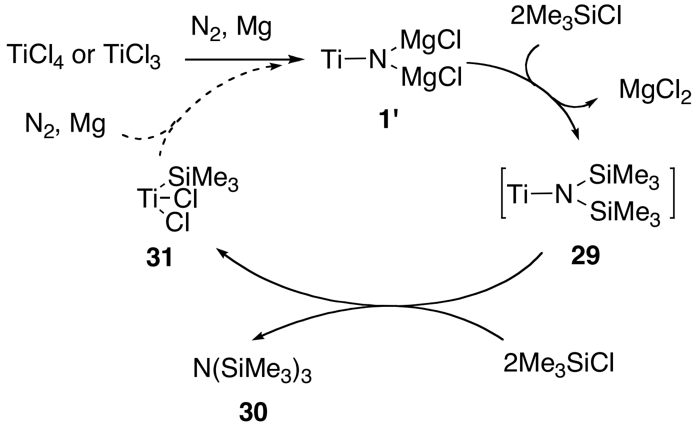
entry	substrate		product		yield (%)
1		**25a**		**26a**	87
2		**25b**		**26b**	73
3		**25c**		**26c**	82
4		**25d**		**26d**	75
5		**25e**		**26e**	85

[a]All reactions were carried out using 3 equiv. of **2** and Pd(PPh$_3$)$_4$ (5 mol %) in NMP at 100 °C for 12 h.

Thus, various indole derivatives (**26**) could be synthesized from 1,3-diketone (**25**) in high yields, respectively, and the novel C-N-C bond formation could be developed (Table 2).[19]

3. DEVELOPMENT TO TITANIUM-CATALYZED NITROGENATION

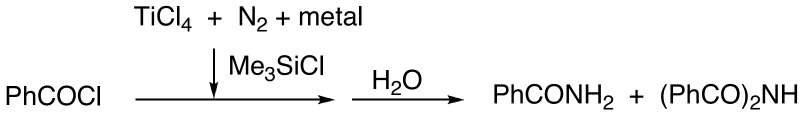
Various heterocycles could be synthesized from molecular nitrogen as a nitrogen source using titanium isocyanate complex (**2**). Although these reactions are unique and interesting, an equimolar amount of titanium-isocyanate complex (**2**) was required. Thus, the next subject is whether this reaction proceed by a catalytic amount of titanium complex. To realize a catalytic reaction, the working hypothesis was shown in Scheme 10. Titanium-nitrogen complex [THF·Mg_2Cl_2·TiN] (**1**) can be represented as **1'**. If TMSCl reacts with **1'**, titanium-trimethylsilylamine complex (**29**) would be formed. σ-Bond metathesis of **29** with TMSCl and then oxidative addition of the TMSCl to the resultant complex would afford **31** and tris(trimethylsilyl)amine (**30**) [$N(TMS)_3$]. Complex (**31**) would be reduced to complex (**1'**) in the presence of excess amount of Mg under nitrogen because complex (**31**) should be the same oxidation state as that of $TiCl_3$.



Scheme 10. Working Hypothesis of Titanium-Catalyzed Nitrogenation

To examine whether this reaction proceeds with a catalytic amount of $TiCl_4$, the reaction was carried out using an equimolar amount of $TiCl_4$ under nitrogen in the presence of an excess amount of reducing agent, TMSCl, and benzoyl chloride. Since benzoyl chloride would react with titanium-nitrogen complex fixed under these reaction conditions to afford benzamide and benzimide, the amount of incorporated nitrogen would be estimated by the total yields of benzamide and benzimide. Initially, a mixture of $TiCl_4$ (1 equiv.), 4 equiv. of Mg, 5 equiv. of TMSCl in THF was stirred at room temperature overnight, and then PhCOCl (10 equiv.) was added. The whole solution was refluxed overnight. After the usual workup, benzamide and benzimide were obtained in 29% yield (Table 3, entry 2). In the absence of TMSCl, the yield is almost same (entry 1). When an excess amount of Mg and TMSCl were used for this reaction, the total yields of amide and imide raised to 56% (entry 4). When Li was used instead of Mg as a reducing agent, the yield is almost same, but the TLC of the reaction mixture was clear compared with that of the use of Mg (entry 5). However, the total yields were almost same as those using Mg and it was not over 100%. The lower and higher reaction temperature did not give the good results (entries 6 and 7). Since it was thought that all of the titanium-nitrogen complexes and $N(TMS)_3$ generated in this reaction could not react with benzoyl chloride under these reaction conditions, the reaction procedure was changed, that is, the reaction mixture was hydrolyzed with 10% HCl to convert titanium-nitrogen complex into NH_4Cl and to the aqueous solution was added an excess amount of benzoyl chloride and K_2CO_3, and the whole solution was stirred overnight. After the usual workup, the yield of benzamide obtained in this reaction was determined based on TiX_4 (entries 8-16). As a result, when Mg was used as a reducing agent, benzamide was obtained in 75% yield (entry 8). On the other hand, when Li was used instead of Mg, benzamide was obtained in 250% yield based on $TiCl_4$ (entry 9). The result indicated that the catalytic cycle in regard to $TiCl_4$ was established.[20]

Table 3. Examination of Novel Incorporation Reaction of Nitrogen Using Titanium Complex



$$PhCOCl \xrightarrow[\ ]{TiCl_4 + N_2 + metal,\ Me_3SiCl} \xrightarrow{H_2O} PhCONH_2 + (PhCO)_2NH$$

entry	metal (equiv.)	Me_3SiCl (equiv.)	Method[a]	temp.	yield (%)[b] of		total yields
					$PhCONH_2$	$(PhCO)_2NH$	
1	Mg (4)	–	A	reflux	27	1	28
2	Mg (4)	5	A	reflux	23	6	29
3	Mg (4)	5	A	rt	13	9	22
4	Mg (50)	50	A	rt	36	20	56
5	Li (50)	50	A	rt	42	17	59
6	Li (50)	50	A	0 °C	21	11	32
7	Li (50)	50	A	reflux	33	6	39
8	Mg (50)	50	B	rt	75	—	75
9	Li (50)	50	B	rt	250	—	250
10	Li (4)	–	B	rt	—	—	—
11	Li (4)	5	B	rt	—	—	—
12	Li (10)	10	B	rt	79	—	79
13	Li (20)	50	B	rt	83	—	83
14	Li (20)	20	B	rt	142	—	142
15	Li (30)	30	B	rt	202	—	202

[a]Method A: A THF solution of $TiCl_4$, Li, TMSCl and PhCOCl (50 equiv.) was stirred. Method B: A THF solution of $TiCl_4$, Li, and TMSCl was stirred, and after hydrolysis of the reaction mixture, PhCOCl (50 equiv.) and K_2CO_3 were added. [b]Yields were calculated based on the amount of $TiCl_4$.

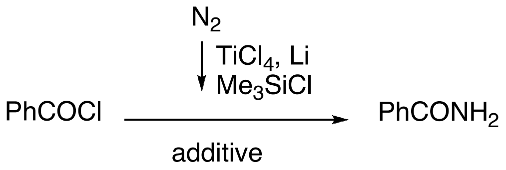
Shiina reported the reductive silylation of molecular nitrogen.[21,22] He obtained tris(trimethylsilyl)amine [$N(TMS)_3$] from various transition metals, TMSCl and Li under nitrogen. When $CrCl_3$ was used as the metal, 5.4 equiv. of $N(TMS)_3$ was produced, but $TiCl_4$ afforded only 0.8 equiv. of $N(TMS)_3$. Shiina's and our result mean that in the case of $TiCl_4$, other titanium-nitrogen complex, such as $ClTi{=}NSiMe_3$ or $Cl_2TiN(TMS)_2$, would be produced under these reaction conditions.

$$Me_3SiCl \xrightarrow[N_2]{MX,\ Li} (Me_3Si)_3N \qquad (8)$$

Since the reaction mechanism was not clear, various amounts of Li and TMSCl were examined to determine the amount of them required for this reaction (entries 10-15). In the absence of TMSCl, benzamide was not obtained (entry 10) and the use of 4 equiv. of Li and 5 equiv. of TMSCl did not afford the product (entry 11). When 10 equiv. of Li and 10 equiv. of TMSCl were used for this reaction, $PhCONH_2$ was obtained in 79% yield (entry 12), and increasing the amount of Li raised the yield of the desired product (entries 12-15).

In order to promote the reaction of benzoyl chloride and the titanium-nitrogen complex formed during the nitrogen fixation, various additives were examined under the stoichiometric reaction conditions modified the conditions of entry 12 [$TiCl_4$ (1.0 equiv.), Li (10 equiv.), TMSCl (10 equiv.) and benzoyl chloride (10 equiv.)]. As the result, addition of CsF improved the total yields of benzamide and benzimide (Table 4). Various titanium complexes and the reducing agents were examined under the same reaction conditions (Table 5). It was interesting that $Ti(O^iPr)_4$ could be used for this reaction (entry 4).[23]

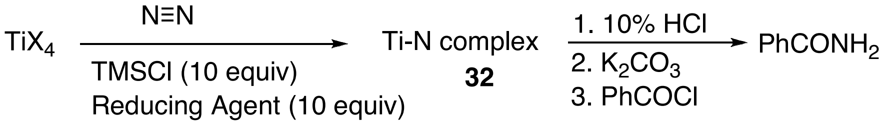
Table 4. Effect of Additive for Nitrogenation



entry	additive	yields (%) of		total yields
		$PhCONH_2$	$(PhCO)_2NH$	
1	—	42	17	59
2	CsF (10)	77	11	88
3	KF (10)	37	17	54
4	KF-HF (10)	39	—	39
5	Me_3SiOTf (0.1)	22	15	37

[a] All reactions were carried out using $TiCl_4$ (1.0 equiv.), Li (10 equiv.), TMSCl (10 equiv.), additive and PhCOCl (10 equiv.) in THF

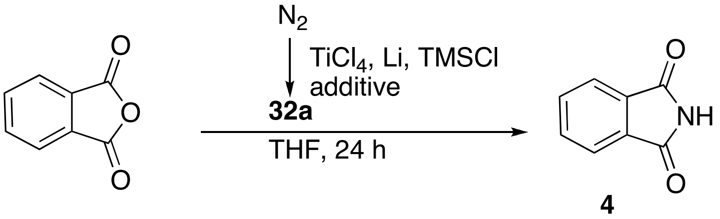
Table 5. Effects of Titanium Complexes and Reducing Agents for Nitrogen Fixation



entry	TiX_4	Ti-N	reducing agent	$PhCONH_2$ (%)
1	$TiCl_4$	**32a**	Li	96
2	Cp_2TiCl_2	**32b**	Li	46
3	$Ti(O^iPr)_4$	**32c**	^{i}PrMgCl	4
4	$Ti(O^iPr)_4$	**32c**	Li	91

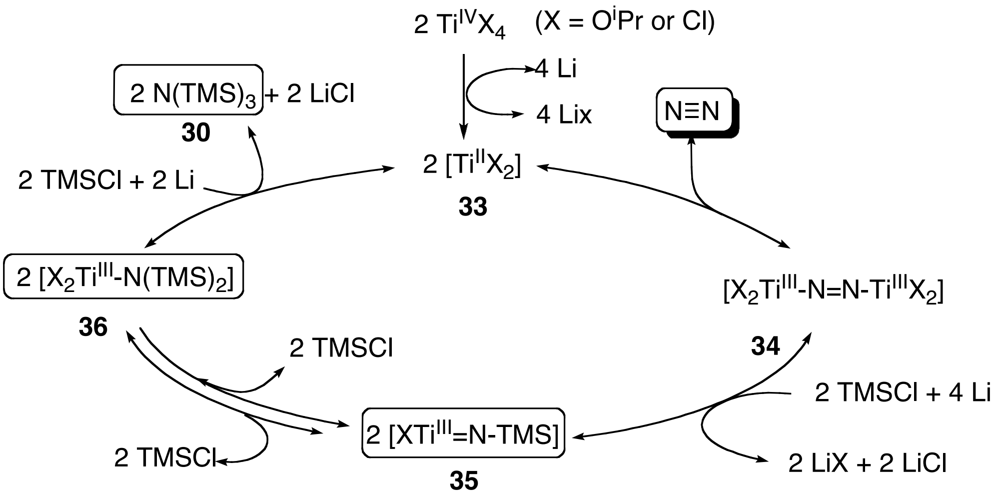
Whether nitrogen of titanium-nitrogen complex (**32**) can be incorporated into phthalic anhydride was examined.[20] To a solution of nitrogenation fixation complex, prepared from $TiCl_4$ (1 equiv.), TMSCl (10 equiv.), and Li (10 equiv.) in THF, was added phthalic anhydride (3 equiv.), and the solution was stirred at room temperature overnight. After hydrolysis, phthalimide (**4**) was obtained in 23% yield (Table 6, entry 1). When the reaction was carried out using 50 equiv. of Li and TMSCl at room temperature, the yield of **4** improved to 51% (entry 2). Interestingly, the yield of phthalimide (**4**) rose up to 204% when the solution was refluxed overnight in the presence of CsF. These results suggest that phthalimide (**4**) could be synthesized from phthalic anhydride using novel titanium-catalyzed nitrogenation.[20]

Table 6. Synthesis of phthalimide Using Novel Nitrogenation Method



entry	Li (equiv.)	additive	temperature	yield (%)
1	10	—	rt	23
2	50	—	rt	51
3	50	CsF	reflux	204

Although the reaction species are not clear, the possible reaction course is considered as shown in Scheme 11.



Scheme 11. Possible Reaction Course for Titanium-Catalyzed Nitrogenation

Titanium complex TiX_4 would be reduced with Li to afford TiX_2 **33**, which would react with N_2 to give **34**. The nitrogen-nitrogen double bond of **34** is cleaved with Li and TMSCl to give titanium-imide complex (**35**), which is reacted with TMSCl to give titanium-amide complex (**36**). In the presence of Li, **36** reacts with TMSCl to give $N(TMS)_3$ (**30**), and TiX_2 (**33**) would be regenerated.

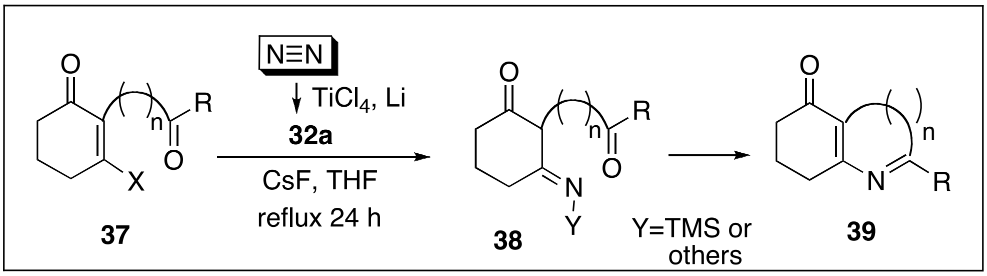
4. SYNTHESIS OF HETEROCYCLES USING NOVEL TITANIUM-PROMOTED NITROGENATION

4-1. Synthesis of Heterocycles from Compounds Having Keto-Carbonyl Group Using Titanium-Nitrogen Complex

4-1-1. Synthesis of Indole, Quinoline and Pyrrole Derivativves from Compounds Having Diketone.

Although various heterocyclic compounds could be synthesized from molecular nitrogen as a nitrogen source using titanium-isocyanate complex (**2**), synthesis of titanium-isocyanate complex (**2**) was not easy, that is, titanium-nitrogen complex **1** was synthesized from $TiCl_4$ and Mg under nitrogen and was isolated. Then isolated **1** was reacted with CO_2 to produce **2**, which was isolated. However, complex (**1**) is not stable and it was occasionally difficult to obtain the reproducibility of the preparation of **2**. Since a solution of titanium-nitrogen complex (**32**)[24] could be easily prepared from $TiCl_4$ or $Ti(O^iPr)_4$, TMSCl, and Li in THF under nitrogen (1 atm) at room temperature, whether nitrogen fixed by new method can be used to synthesize various heterocycles *in situ* was examine.

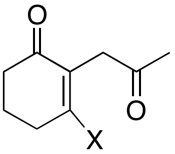
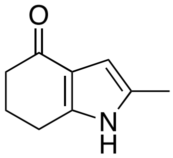
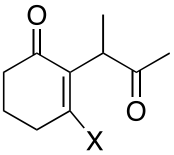
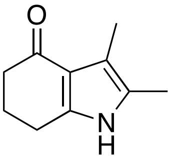
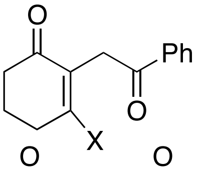
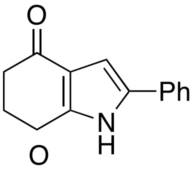
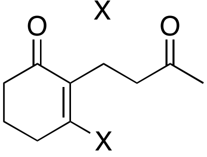
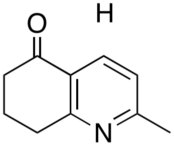
If cyclohexenone (**37**) bearing a keto-carbonyl group in a tether at the 2-position is treated with titanium nitrogen complex (**32a**), nitrogen in **32** would attack the 3-position of cyclohexenone to produce imine (**38**), whose imino group would further react with the carbonyl group in a tether intramolecularly to give cyclized compound (**39**) (Scheme 12).



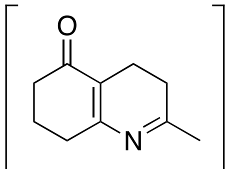
Scheme 12. Plan for Synthesis of Indole and Quinoline Derivatives from Cyclohexadione

When to a THF solution of **32a**, prepared from $TiCl_4$, TMSCl, Li, and CsF under nitrogen using the stoichiometric reaction conditions, was added **37aa** and the whole solution was refluxed overnight, indole derivative (**39a**) was obtained in 51% yield (Table 7, entry 1). Various indole derivatives (**39**) could be synthesized from diketone derivative (**37**) and **32a** prepared *in situ* in high yields by one operation. The hydroxyl group was suitable as a leaving group (entries 2 and 4). Elongation of the methylene group in a tether gave quinoline derivative (**40**) in moderate yield (entry 6). In this reaction, the spot on the TLC of the reaction mixture was different from that of the purified product (**40**). Presumably, tetrahydroquinoline derivative (**39d**) would be formed, and it was converted into dihydroquinoline derivative (**40**) by an air oxidation during the workup. Treatment of triketone (**37db**) in a similar manner afforded **40** in the same yield (entry 7).

Table 7. Synthesis of Indole and quinoline Derivatives from Cyclohexadiones

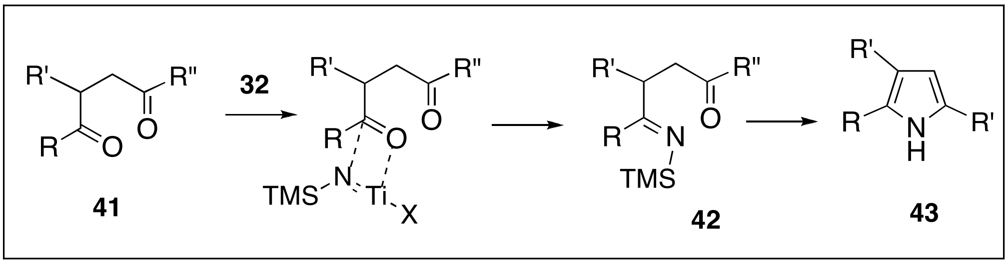
entry	substrate	X		product		yield[a] (%)
1		OTf	**37aa**		**39a**	51
2		OH	**37ab**		**39a**	86
3		OTf	**37ba**		**39b**	46
4		OH	**37bb**		**39b**	86
5		OH	**37cb**		**39c**	57[b]
6		OTf	**37da**		**40**	32
7		OH	**37db**		**40**	32

[a] All reactions were carried out using a THF solution of **32a**, prepared from $TiCl_4$(1.25 equiv.), Li (12.5 equiv.), TMSCl (12.5 equiv.) and CsF (6 equiv.) and to this solution was added **37** (1 equiv.) and the whole solution was refluxed overnight. [b] 2 equiv. of **32a** was used.



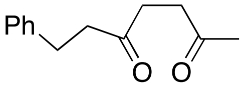
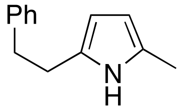
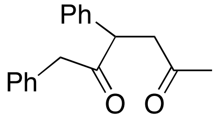
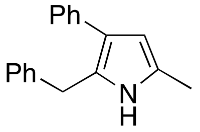
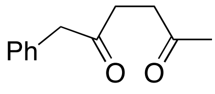
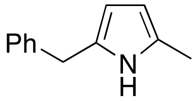
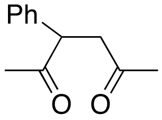
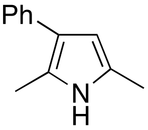
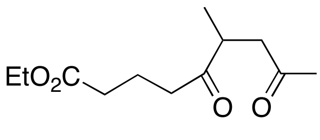
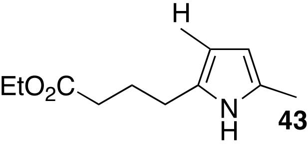
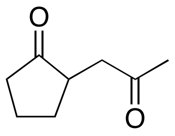
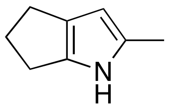
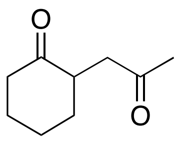
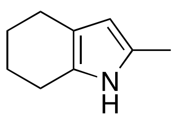
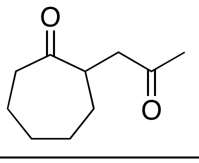
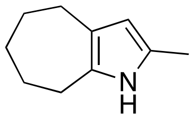
39d

The reaction procedure for the synthesis of indole **39** and quinoline derivatives **40** is very simple and the reproducibility was easily obtained, that is, to a THF solution containing Li (12 equiv.), TMSCl (12 equiv,) and CsF (6 equiv.) was added $TiCl_4$ (1.25 equiv.) under nitrogen (1 atm) and the solution was stirred under nitrogen overnight. The colorless solution was changed to black. To this solution was added substrate (**37**) (1 equiv.) and the whole solution was refluxed overnight under argon. After the usual workup, desired compound (**39**) or (**40**) was obtained.[25]



Scheme 13. Plan for Synthesis of Pyrrole, Pyrrolizine and Indolizine Derivatives

Table 8. Synthesis of pyrrole derivatives (**43**) from 1,4-diketone (**41**) using **32a**

run	substrate		product		yield (%)[a]
1		**41a**		**43a**	25
2		**41b**		**43b**	39
3		**41c**		**43c**	54
4		**41d**		**43d**	64
5		**41e**		**43e**	60
6		**41f**		**43f**	23
7		**41g**		**43g**	41
8		**41h**		**43h**	41

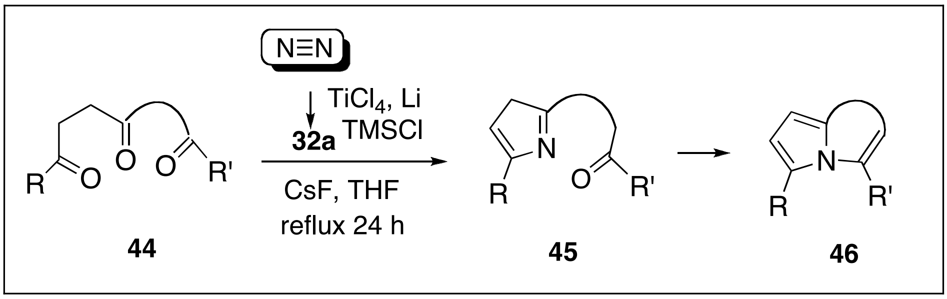
[a] All reactions were carried out upon heating in THF for 24 h.

Since it is thought that titanium-nitrogen complex (**32a**) can react with the carbonyl group to form imine, the imino group of **42**, generated from 1,4-diketone (**41**) and **32a**, would further react with the keto-carbonyl group intramolecularly to form pyrrole derivative (**43**) (Scheme 13).

Various 1,4-diketones (**41**) were treated with **32a** prepared from $TiCl_4$, Li, TMSCl and CsF under nitrogen in THF to give pyrrole derivatives (**43**) in good yields (Table 8).[25] These results indicated that titanium-nitrogen complex **32a** could react with two keto-carbonyl groups intramolecularly to give pyrrole derivatives.

4-1-2. Synthesis of Pyrrolizine and Indolizine Derivatives from Compounds Having Triketone.

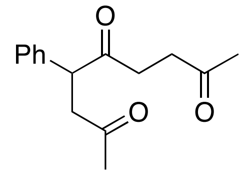
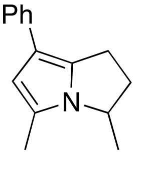
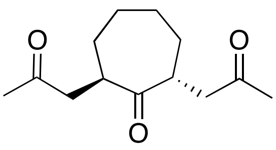
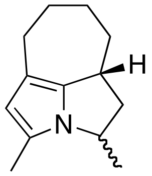
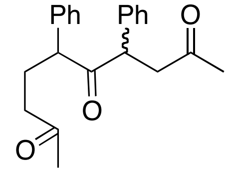
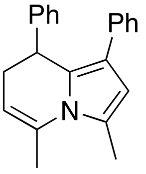
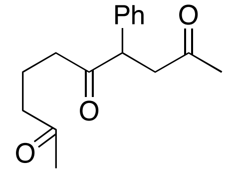
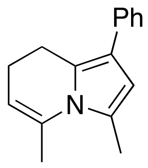
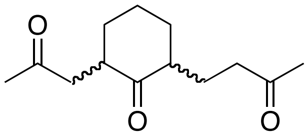
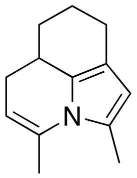
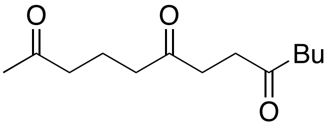
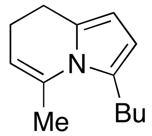
Next try is the reaction of triketone (**44**) with titanium-nitrogen complex (**32a**). If this reaction proceeds, pyrrolizine or indolizine derivative (**46**) would be synthesized from compound (**44**) having tri-ketocarbonyl groups and **32a** in one-pot reaction (Scheme 14).



Scheme 14. Plan for Synthesis of Pyrrolizine and Indolizine Derivatives

Reaction of triketone (**44**) with **32a** prepared in a usual manner gave pyrrolizine derivative (**46a**) in 30% yield (Table 9, entry 1). Although the yield is moderate, it is interesting that pyrrolizine derivative (**46a**) could be synthesized from straight chain compound (**44a**) having triketone and **32a** by a one-pot reaction. Triketone (**44b**) was treated with **32a** in a similar manner to give tricyclic compound (**46b**) as a mixture of two inseparable isomers in 31% yield (entry 2). Triketone (**44c**), whose carbon chain length was elongated, was reacted with **32a** to give indolizine derivative (**46c**) in 29% yield. When 2 equiv. of **32a** was used for this reaction, the yield of **46c** was increased to 41% (run 3). In a similar treatment of **44d**, **44e**, and **44f** with **32a** (2 equiv.), indolizine derivatives **46d**, **46e** and **46f** were obtained in 56%, 30% and 30% yields, respectively (entries 4-6).[25] Various pyrrolizine and indolizine derivatives could be easily synthesized from straight chain compounds **44** having triketone and titanium-nitrogen complex **32** by a one-pot reaction.

Table 9. Synthesis of pyrrolizine and indolizine derivatives

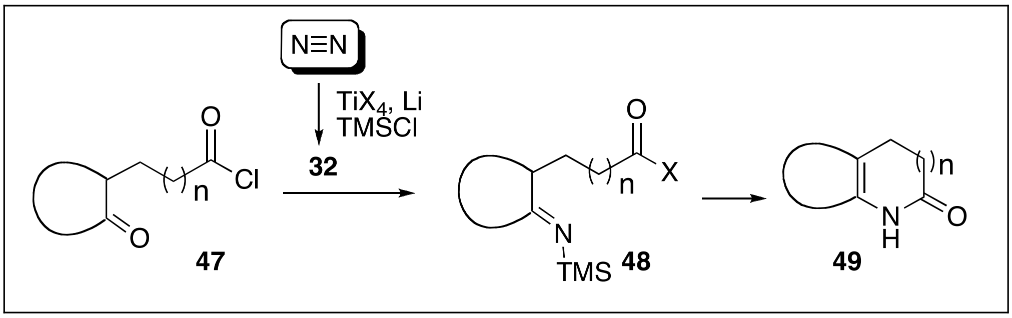
entry	triketone		pyrrolizine or indolizine		yield (%)
1		**44a**		**46a**	30
2		**44b**		**46b**	31
3		**44c**		**46c**	41[b]
4		**44d**		**46d**	56[b]
5		**54e**		**46e**	30[b]
6		**44f**		**46f**	30[b]

[a]Two isomers of the ratio of 3.4:1 (determined by 1H NMR (500 MHz). [b]2 equiv. of **32a** was used.

4-2. Synthesis of Lactams from Compounds Having Keto-Carboxyl Group

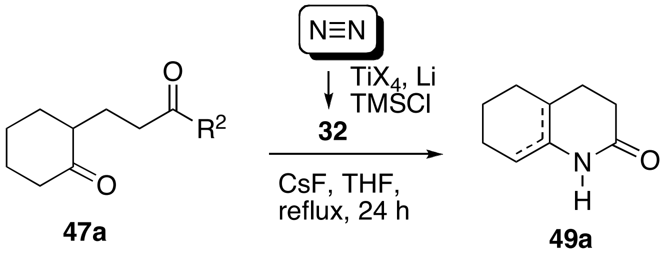
It is thought that if compound **47** having the keto-carbonyl group and the carboxyl group reacts with **32** to produce imine **48** and an imine part of **48** would react with the carboxyl group intramolecularly, lactam (**49**) would be obtained (Scheme 15).

When a THF solution of acid chloride (**47aa**) and **32a**, which was prepared using a $TiCl_4$-Li-TMSCl system under nitrogen, was refluxed in the presence of CsF overnight, lactam (**49a**) was obtained in 28% yield (Table 10, entry 1). Use of titanium-nitrogen complex (**32b**) prepared using a $Ti(O^iPr)_4$-Li-TMSCl system slightly increased the yield of **49a** (entry 2). In this reaction, various carboxylic acid derivatives, such as chloride (**47aa**), mixed anhydrides (**47ab**) (entries 3-5), ester (**47ae**) (entry 7), and even the carboxylic acid (**47ad**) (entry 6), could be used and lactam (**49a**) was produced in good yields (entries 1-7).



Scheme 15. Plan for Synthesis of Lactams

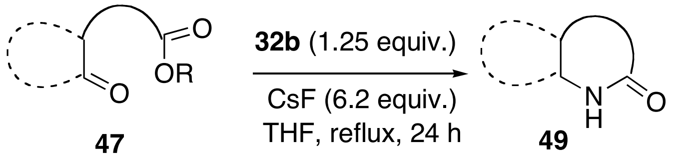
Table 10. Synthesis of Perhydroquinolone Derivatives from Cyclohexanone Having Carboxyl Group

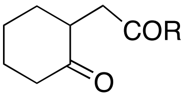
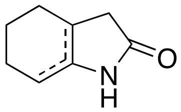
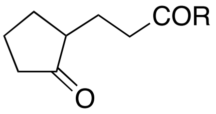
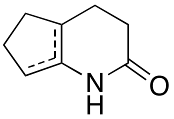
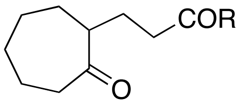
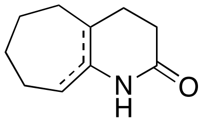
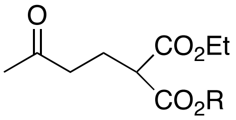
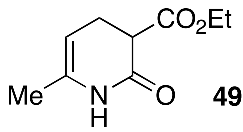
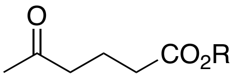
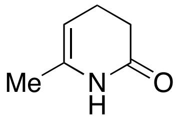
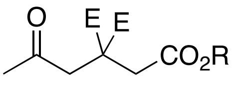
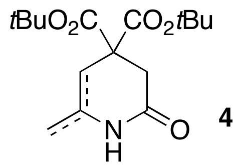


entry	R^2		TiX_4	Ti=NX	yield (%) of **49a**
1	Cl	**47aa**	$TiCl_4$	**32a**	28
2	Cl	**47aa**	$Ti(O^iPr)_4$	**32b**	31
3	OCO_2Et	**47ab**	$Ti(O^iPr)_4$	**32b**	55
4	OCO_2Et	**47ab**	$TiCl_4$	**32a**	25
5	$OP(O)(OEt)_2$	**47ac**	$Ti(O^iPr)_4$	**32b**	58
6	OH	**47ad**	$Ti(O^iPr)_4$	**32b**	53
7	OEt	**47ae**	$Ti(O^iPr)_4$	**32b**	50

Various bicyclic lactams (**49b-d**) were obtained in good yields from corresponding keto-carboxylic acid derivative (**47b-d**) using this method (Table 11, entries 1-5). In a similar manner, piperidone derivatives (**49e-g**) were also obtained in moderate yields from corresponding straight chain compounds (**47e-g**) (entries 6-8).[26] It is interesting that the carboxylic acids **47cd** and **47dd** afforded lactams **49c** and **49d** in moderate yields.

Table 11. Synthesis of lactams from Keto-Carboxylic Acid Derivatives

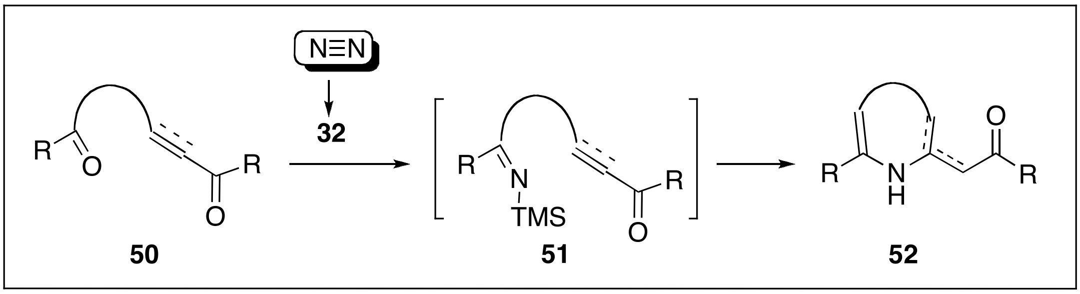


entry	substrate	R		product		yield (%)
1[a]		OEt	**47be**		**49b**	24
2		OH	**47cd**		**49c**	22
3		OPO(OEt)$_2$	**47cc**		**49c**	38
4		OH	**47dd**		**49d**	32
5		OPO(OEt)$_2$	**47dc**		**49d**	42
6		OPO(OEt)$_2$	**47ec**		**49e**	19
7		OPO(OEt)$_2$	**47fc**		**49f**	29
8	 E = CO_2tBu,	OPO(OEt)$_2$	**47gc**		**49g**	51

[a] Reaction time; 1 h.

4-3. Synthesis of Heterocycles from Compounds Having Keto-Alkyne Group

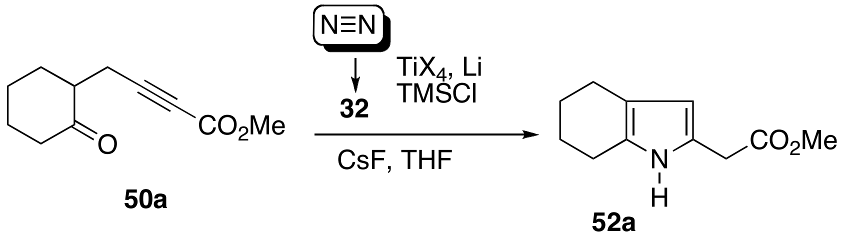
If compound **50** having the keto-carbonyl group and an alkyne part can react with **32**, and the imine part of **51** generated from the keto-carbonyl group can react with an α,β-unsaturated ester moiety intramolecularly by Michael-type addition, cyclic compound (**52**) would be formed after hydrolysis (Scheme 16).



Scheme 16. Plan for Synthesis of Heterocycles from Compounds Having Keto-Alkyne

A solution of keto-alkyne (**50a**) (1 equiv.) and titanium-nitrogen complex (**32a**), which was prepared from $TiCl_4$ (1.2 equiv.), Li (10 equiv.), and TMSCl (10 equiv.) in THF under nitrogen, was refluxed in the presence of CsF (6 equiv.) for 17 h to give indole derivative (**52a**) in 90% yield (Table 12, entry 1). When the reaction was carried out at room temperature for 24 h, desired indole derivative (**52a**) was obtained in 59% yield (entry 2). On the other hand, when titanium-nitrogen complex (**32b**) prepared from $Ti(O^iPr)_4$, Li and TMSCl was used for this reaction, the reaction proceeded at room temperature for only 50 min and **52a** was obtained in 82% yield (entry 3). In the absence of CsF, the yield was slightly decreased (entry 4). The reaction was carried out using $N(TMS)_3$ instead of **32**, no product was formed. It means that the real species for formation of indole derivative (**52a**) is titanium-nitrogen complex, not $N(TMS)_3$.

Table 12. Synthesis of Indole Derivative from Cyclohexanone Derivative Having an Alkyne



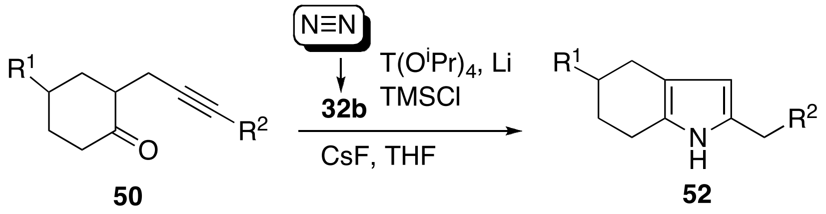
entry	TiX_4		CsF	temp (°C)	time	yield (%) of **52a**	yield (%) of **50a**
1	$TiCl_4$	**32a**	+	reflux	17 h	90	—
2	$TiCl_4$	**32a**	+	rt	24 h	59	30
3	$Ti(O^iPr)_4$	**32b**	+	rt	50 min.	82	—
4	$Ti(O^iPr)_4$	**32b**	—	rt	2 h	77	—
5[a]	—	—	+	rt	16 h	0	94

[a] $N(TMS)_3$ was used instead of **32**.

Indole derivative (**50b**) having an acetoxy group on a cyclohexane ring was also synthesized from keto-alkyne **(52b)** (Table 13, entry 1). The effect of a substituent on alkyne was examined. In the case of keto-alkyne (**50c**) having a nitrile group on the alkyne, the yield of **52c** was also high (entry 2), and

50d or **50e** bearing the amide or keto-carbonyl group on the alkyne gave desired indole derivative (**52d**) or (**52e**) in moderate yield (entries 3 and 4). The keto-alkyne (**50f**) having the methyl group on the alkyne gave desired indole derivative (**52f**) in only 3% yield, but the phenyl group on the alkyne gave desired compound (**52g**) in 35% yield (entry 6). The yield of **52h** having trifluoromethyl group on an aromatic ring is higher than that of **52i** having the methyl group (entries 7 and 8). These results indicate that the electron-withdrawing group on the alkyne gave a good result. Presumably, theses groups would accelerate the addition of an imine part of **51** to an alkyne part.

Table 13. Synthesis of indole derivatives

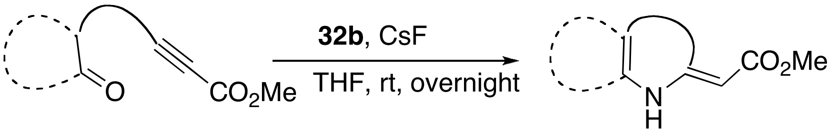


entry	substrate	R^1	R^2	temp.	time (h)	yield^a (%) of 52	yield^a (%) of 50
1	**50b**	OAc	CO_2Me	rt	50 (min)	62	—
2	**50c**	H	CN	rt	12	92	—
3	**50d**	H	$CONEt_2$	rt	24	45	—
4	**50e**	H	$COCH_3$	rt	1.5	35	—
5	**50f**	H	Me	reflux	20^b	3^d	45
6	**50g**	H	Ph	reflux	20^c	35^e	21
7	**50h**	H	$C_6H_4{}^pCH_3$	reflux	20	32	31
8	**50i**	H	$C_6H_4{}^pCF_3$	reflux	20	49	14

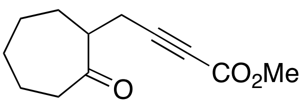
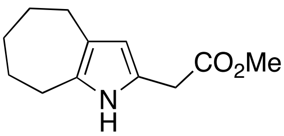
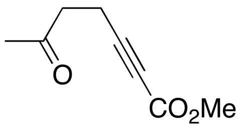
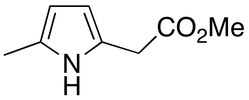
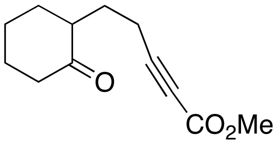
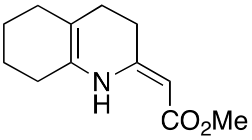
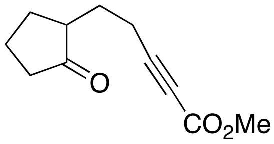
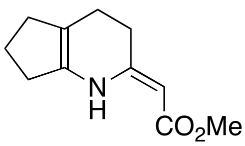
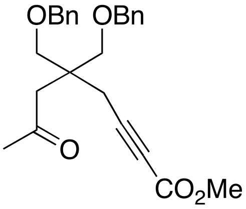
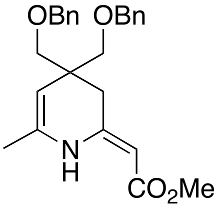
[a] **32b** was prepared from Ti(O^{i}Pr)$_4$ (1 equiv.), Li (10 equiv.), and TMSCl (10 equiv.). All reactions were carried out using **50** (1 equiv.), CsF (6 equiv.), and **32b** (1.25 equiv.). [b] The solution was stirred at rt for 2 h and then refluxed. [c] The solution was stirred at rt for 70 min and then refluxed.

Various keto-alkynes (**53**) having an ester group on the alkyne were reacted with titanium-nitrogen complex (**32b**), prepared using Ti(O^{i}Pr)$_4$-Li-TMS system under nitrogen, in THF at room temperature (Table 14). As the results, the desired heterocyclic compounds such as pyrrole derivatives (**54a**) and (**54b**) (entries 1 and 2), quinoline derivative (**54c**) (entry 3), and piperidine derivatives (**54d**) and (**54e**) (entries 4 and 5) were obtained from corresponding keto-alkynes (**53**) in good to moderate yields.[27]

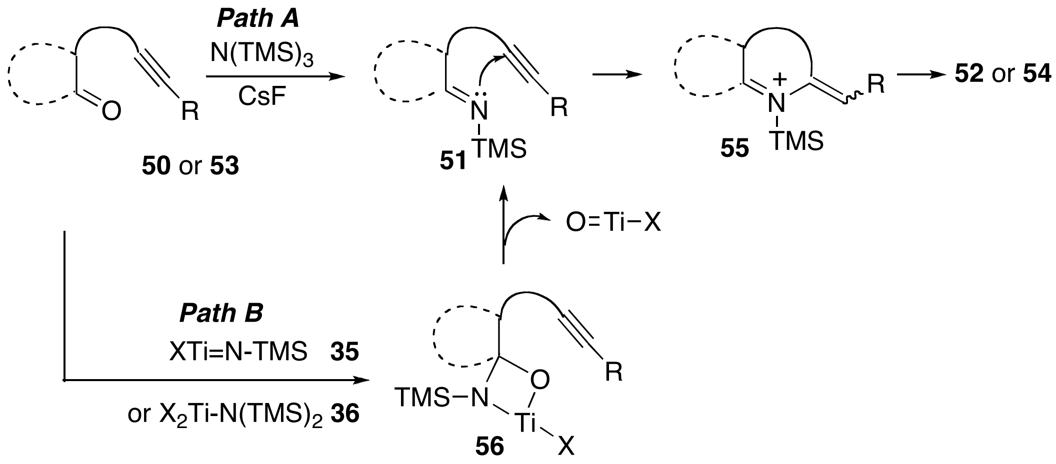
Table 14. Synthesis of Heterocycles from Keto-Alkyne



53 **54**

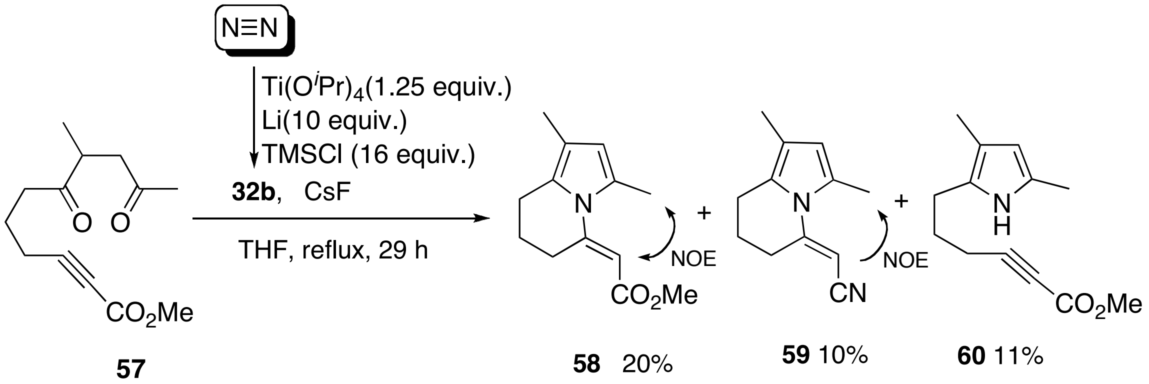
entry	substrate		product		yield (%)
1		**53a**		**54a**	72
2		**53b**		**54b**	39
3		**53c**		**54c**	66
4		**53d**		**54d**	34
5		**53e**		**54e**	63

The possible reaction course for the formation of heterocyclic compound (**52**) or (**54**) from keto-alkynes (**50**) or (**53**) is shown in Scheme 17. Two possible pathways should be considered. If the reaction of keto-alkyne (**50**) or (**53**) with $N(TMS)_3$ proceeds in the presence of CsF, imine (**51**) would be formed. Then Michael addition of nitrogen of imine would afford **55**, which would isomerize to give **52** or **54** (path A). However, when **50** 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 complex (**32b**) is not an active species. Thus, the active species in this reaction would be titanium-imide complex [XTi=N(TMS)] (**35**) or titanium-amide complex $[X_2Ti\text{-}N(TMS)_2]$ (**36**), and the complex reacts with the carbonyl carbon to give imine (**51**) via **56** by σ-bond metathesis.[28,29] Then the Michael addition of nitrogen gives **55**. 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.[30]



Scheme 17. Possible Reaction Course

Subsequently, the reaction of 1,4-diketo-alkyne (**57**) with **32b** was examined and indolizidines (**58**) and (**59**) were obtained in 20% and 10% yields, respectively, along with pyrrole derivative (**60**) in 11% yield. The structures of them were determined by NOE experiments. The ester group of indolizine (**58**) would be converted into the nitrile group by titanium nitrogen complex (**32**) to give indolizine (**59**).[31]

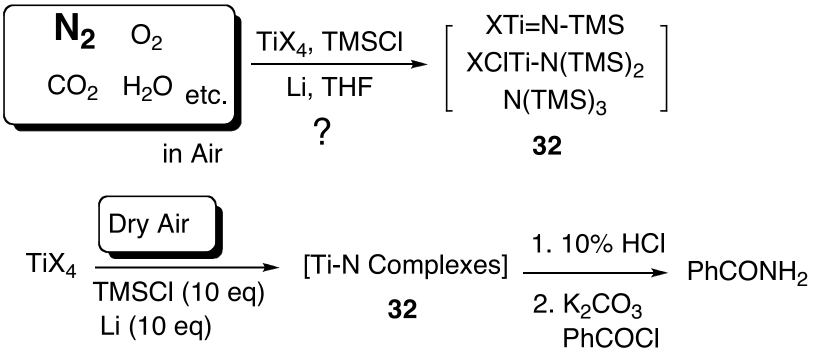


Scheme 18. Synthesis of indolizidine Derivative

5. NITROGEN FIXATION USING DRY AIR

5-1. Examination to Utilize Dry Air as a Nitrogen Source

It is well known that nitrogenase catalyzes the reduction of atmospheric nitrogen to NH_3. Nitrogen accounts for 80% of the gases in air, the other gases being oxygen and carbon dioxide. If nitrogen in air can be fixed directly using our nitrogenation method, the results is interesting. Since early transition metals are not so sensitive to oxygen but are very sensitive to water, whether *dry air* could be used for nitrogenation was examined.



Scheme 19. Fixation of Nitrogen in Dry Air

Initially, it was examined whether titanium-nitrogen complex (**32**) is generated from *dry air*, TiX_4, Li and TMSCl. To confirm the fixation of nitrogen in air, preparation of benzamide from benzoyl chloride and **32** generated from *dry air* was tried. 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, benzoyl chloride and K_2CO_3 were added to this aqueous solution. It was very pleased to find that benzamide could be isolated in 89% yield, although the use of nitrogen gas in a similar manner gave benzamide in 96% yield (Table 15, entry 1). The result obtained using a $Ti(O^iPr)_4$-Li-TMSCl system under *dry air* was the same as that obtained using a $TiCl_4$-Li-TMSCl system (entry 2). It had already been shown that this nitrogen fixation reaction proceeded catalytically based on $TiCl_4$.[20]

Table 15. Utilization of Nitrogen from Dry Air

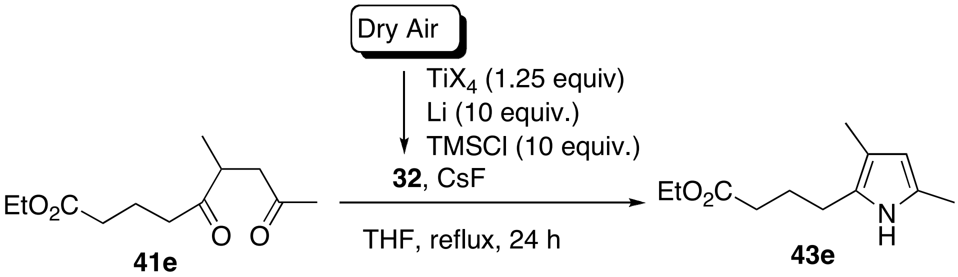
entry	TiX_4	TMSCl, Li (equiv)	time (h)	yield (%)^a of $PhCONH_2$	
				32 from air	**32** fromN_2 gas
1	$TiCl_4$	10	24	89	96
2	$Ti(O^iPr)_4$	10	24	80	91
3	$Ti(O^iPr)_4$	50	48	356	496

^{a} Based on TiX_4.

Thus, an experiment was carried out to determine whether the nitrogen fixation reaction using *dry air* proceeds catalytically. Titanium-nitrogen complex (**32b**) was synthesized from $Ti(O^iPr)_4$ (1 equiv), excess amounts of Li (50 mol equiv) and TMSCl (50 equiv) under dry air for 2 days. After the solution had been hydrolyzed and then benzoyl chloride (50 equiv.) and K_2CO_3 were added. The solution was stirred at room temperature overnight to give benzamide in 356% yield based on an amount of $Ti(O^iPr)_4$ (entry 3). The results indicated that nitrogen in air could be directly fixed from *dry air*.[32]

Subsequently, whether the heterocycle could be synthesized from *dry air* as a nitrogen source was examined. To a THF solution of 1,4-diketone (**41e**) and CsF was added a THF solution of **32a** prepared from $TiCl_4$, Li, and TMSCl under *dry air,* and the whole solution was refluxed overnight. After the usual workup, pyrrole derivative (**43e**) was obtained in 37% yield based on 1,4-diketone (**41e**) (Table 16, entry 1). When $Ti(O^iPr)_4$ was used instead of $TiCl_4$, **43e** was obtained in 38% yield (entry 2). Although these yields were lower compared with those used N_2 gas, dry air could be used directly as a nitrogen source.

Table 16. Synthesis of Pyrrole Derivatives from Dry Air as a Nitrogen Source.

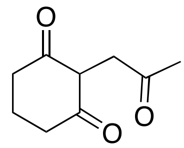
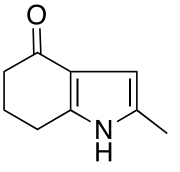
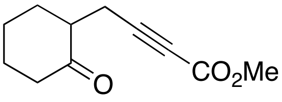
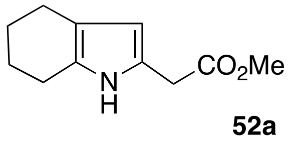
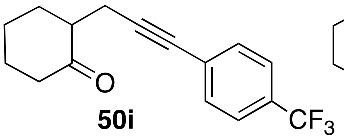
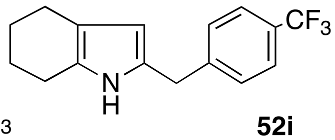
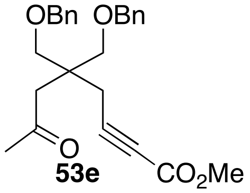
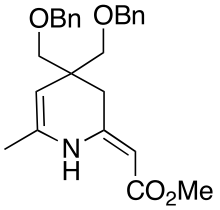
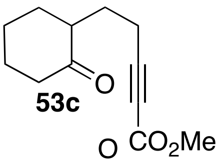
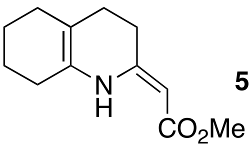
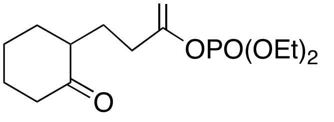
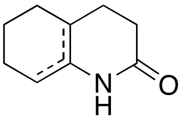
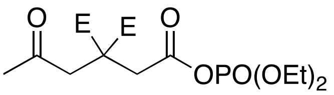
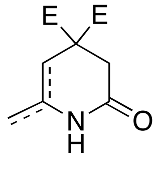


		yield (%)	
entry	TiX_4	air	N_2
1	$TiCl_4$	37	60
2	$Ti(O^iPr)_4$	38 [a]	46

[a] **41e** was recovered in 35% yield.

Various heterocycles were synthesized using titanium-nitrogen complex (**32**) prepared from *dry air*, TiX_4, Li, and TMSCl, and in each case, desired heterocycles could be synthesized in good yields (Table 17). The yield obtained from *dry air* was slightly lower than that obtained using nitrogen gas.[26] These results indicate that *dry air* could be used for the synthesis of various nitrogen heterocycles as the nitrogen source instead of nitrogen gas.

Table 17. Nitrogen Fixation Using Dry Air.

entry	substrate	product	TiX_4	yield (%)[a]	
1	 **37ab**	 **39b**	$TiCl_4$	Air	56%
			$TiCl_4$	N_2	86%
2	 **50a**	 **52a**	$Ti(O^iPr)_4$	Air	72%
			$Ti(O^iPr)_4$	N_2	82%
3	 **50i**	 **52i**	$Ti(O^iPr)_4$	Air[b]	34%
			$Ti(O^iPr)_4$	N_2	49%
4	 **53e**	 **54e**	$Ti(O^iPr)_4$	Air	61%
			$Ti(O^iPr)_4$	N_2	63%
5	 **53c**	 **54c**	$Ti(O^iPr)_4$	Air	54%
			$Ti(O^iPr)_4$	N_2	66%
6	 **47ac**	 **49a**	$Ti(O^iPr)_4$	Air	60%
			$Ti(O^iPr)_4$	N_2	58%
7	 **47gc** E=CO_2tBu	 **49h**	$Ti(O^iPr)_4$	Air	50%
			$Ti(O^iPr)_4$	N_2	51%

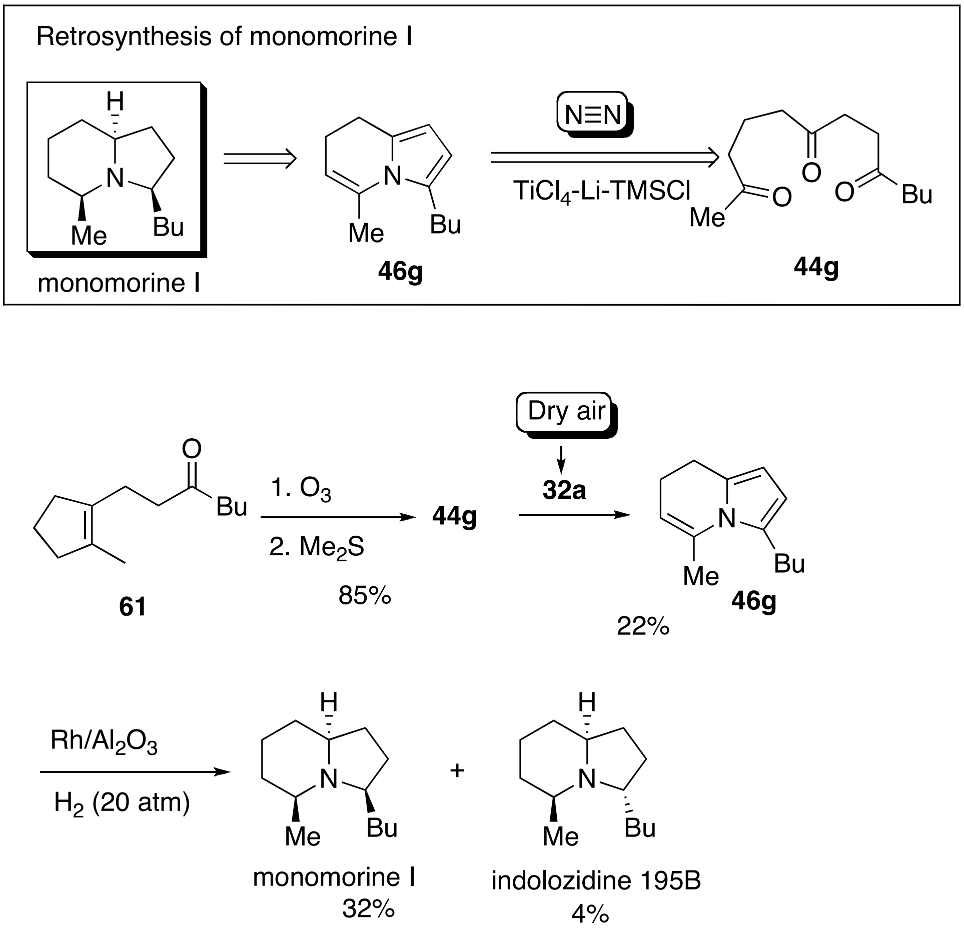
[a] **32** was prepared by reaction of TiX_4 (1.25 equiv.), Li (12.5 mol equiv.) and TMSCl (12.5 equiv.) in THF under dry air or nitrogen gas at room temperature for 24 h. All reactions were carried out using **32** in the presence of CsF (6 equiv) in THF upon heating for 24 h. Yields are based on the substrate.

[b] Reaction was carried out at room temperature for 24 h.

5-2. Synthesis of Natural Products from Dry Air as a Nitrogen Source

5-2-1. Synthesis of Monomoline I

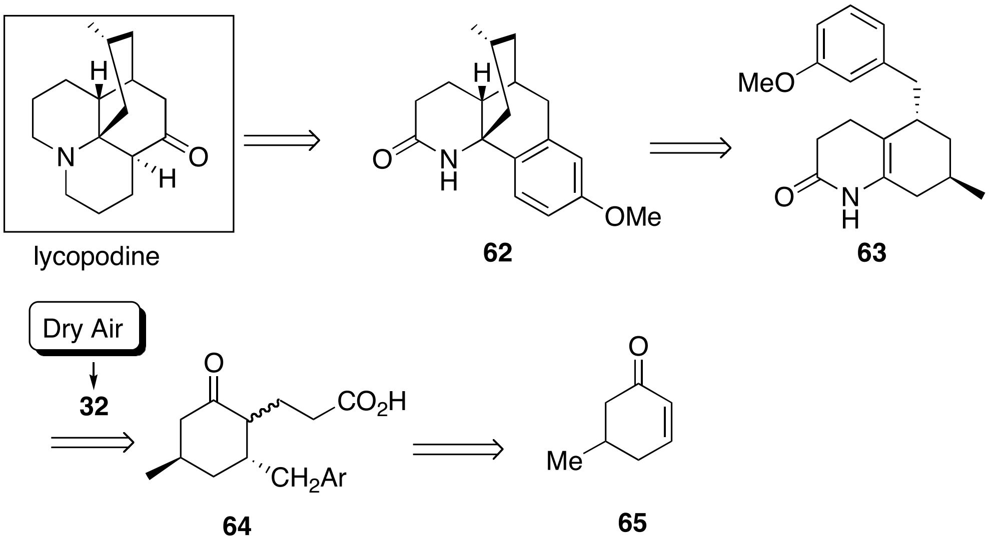
Since various heterocycles could be prepared from dry air as a nitrogen source, synthesis of the natural products using this complex (**32**) was examined. At first, the synthesis of the natural product, monomorine I[33] from indolizine derivative (**46**) was planned. The retro synthetic analysis of monomoline I using this method is shown in Scheme 20. Monomorine I would be obtained by hydrogenation of indolizine (**46g**) because hydrogen on the catalyst would approach from the backside of the substituents. Indolizine (**46g**) would be obtained from triketone (**44g**) using the present nitrogenation. Ozonolysis of **61**[34] followed by treatment with Me_2S gave triketone (**44g**) in 85% yield. A THF solution of triketone (**44g**) and titanium nitrogen complex (**32a**) (2 equiv), prepared from $TiCl_4$, Li and TMSCl under *dry air*, was refluxed for 24 h. After the usual workup, desired indolizine derivative (**46g**) was obtained in 22% yield. In this reaction, same compound (**46g**) was obtained in 30% yield from nitrogen gas as the nitrogen source. Hydrogenation of **46g** with Rh on alumina (20 atm) afforded monomorine I as a main product in 32% yield along with indolizidine 195B in 4% yield.[35] Thus, a short-step synthesis of monomorine I and indolizidine 195B was achieved using titanium-nitrogen complex (**32a**) prepared from dry air as a nitrogen source.[36]



Scheme 20. Short Total Synthesis of Monomoline I Using Dry Air as the Nitrogen Source

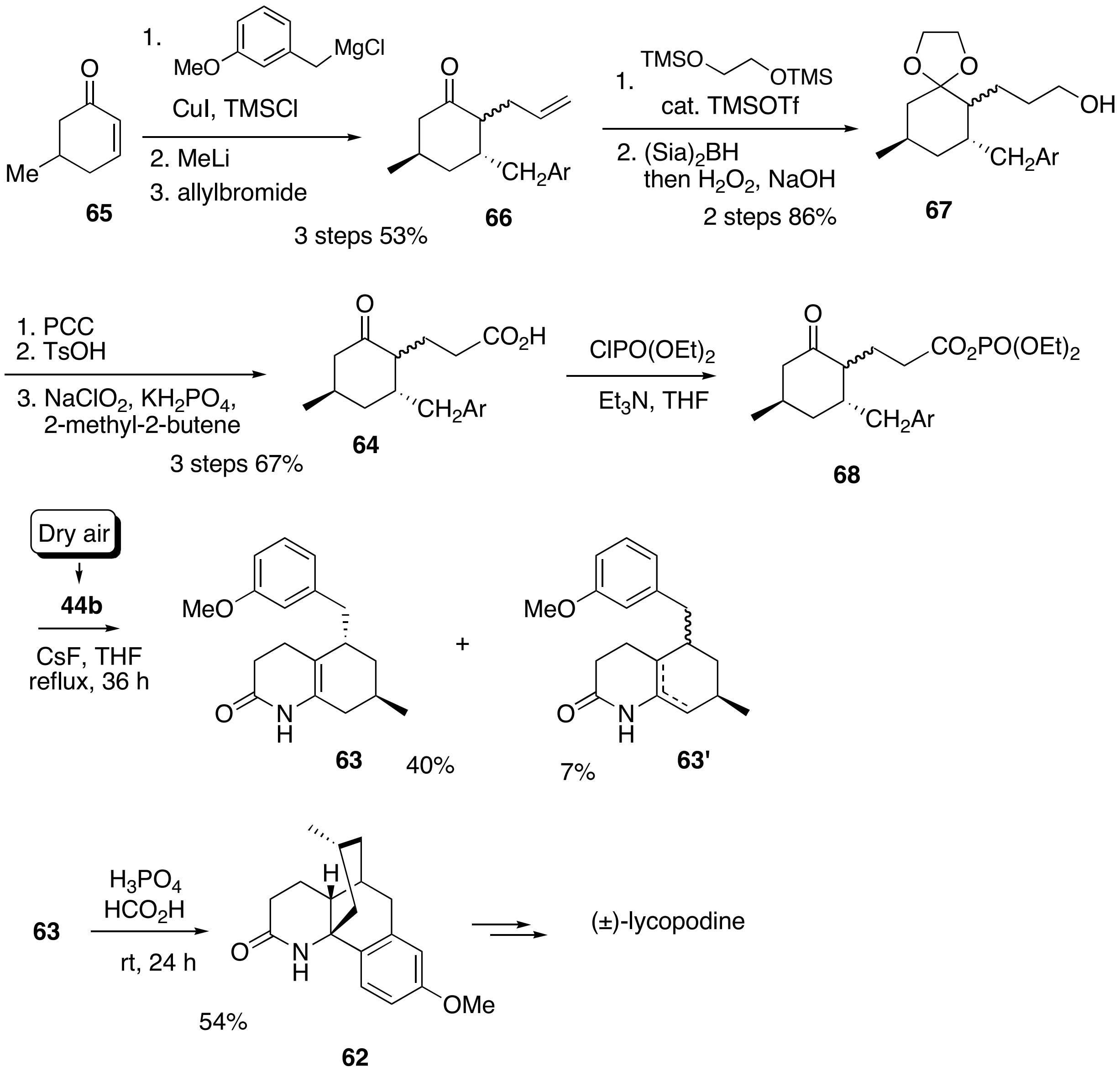
5-2-2. Formal Total Synthesis of Lycopodine

Since quinolone derivative (**49a**) could be synthesized from **47ac** and *dry air* as a nitrogen source, the synthesis of lycopodine[37] was planed. The retrosynthetic analysis was shown in Scheme 21. The total synthesis of (±)-lycopodine was achieved by Stork and co-workers[38] from tetracyclic compound (**62**), which was obtained from lactam (**63**). The key compound (**63**) should be synthesized from carboxylic acid (**64**) using *dry air* as the nitrogen source. Carboxylic acid (**64**) would be synthesized from cyclohexenone (**65**).



Scheme 21. Retrosynthetic Analysis of Lycopodine

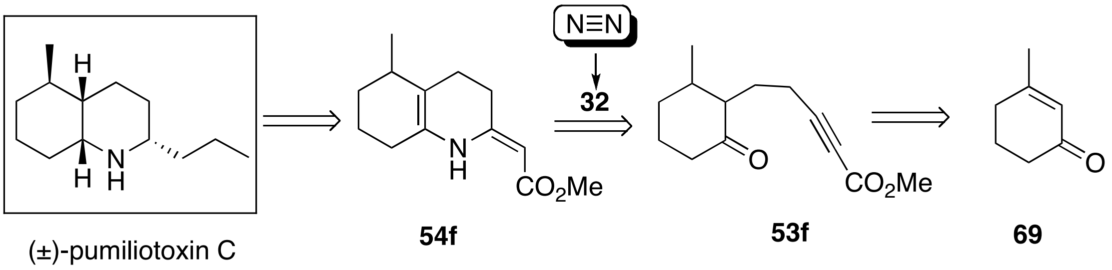
Ketalization of **66**, which was easily prepared from 5-methyl-2-cyclohexenone (**65**),[39] followed by hydroboration gave alcohol (**67**) in high yield. Conversion of the hydroxyl group of **67** into the carboxyl group with the usual method afforded **64**, which was treated with diethyl phosphorochloridate to give **68**. When a THF solution of (**68**) and titanium-nitrogen complex (**32a**), prepared from Ti(O^{i}Pr)$_4$, Li, and TMSCl under *dry air*, was refluxed for 36 h, lactam (**63**) was isolated in 40% yield along with the stereoisomers (**63'**) in 7% yield. When the reaction was carried out using nitrogen gas, **63** was obtained in 39% yield. It means that dry air could be used as the nitrogen source instead of nitrogen gas. The melting point of **63** was in complete agreement with that reported in the literature.[38] Compound (**63**) was treated with H_3PO_4 in HCOOH according to the Stork's procedure[38] to afford tetracyclic compound (**62**) . Thus, a formal total synthesis of (±)-lycopodine could be achieved using titanium-nitrogen complex (**32**) prepared from *dry air*.[26]



Scheme 22. Formal Total Synthesis of (±)-Lycopodine.

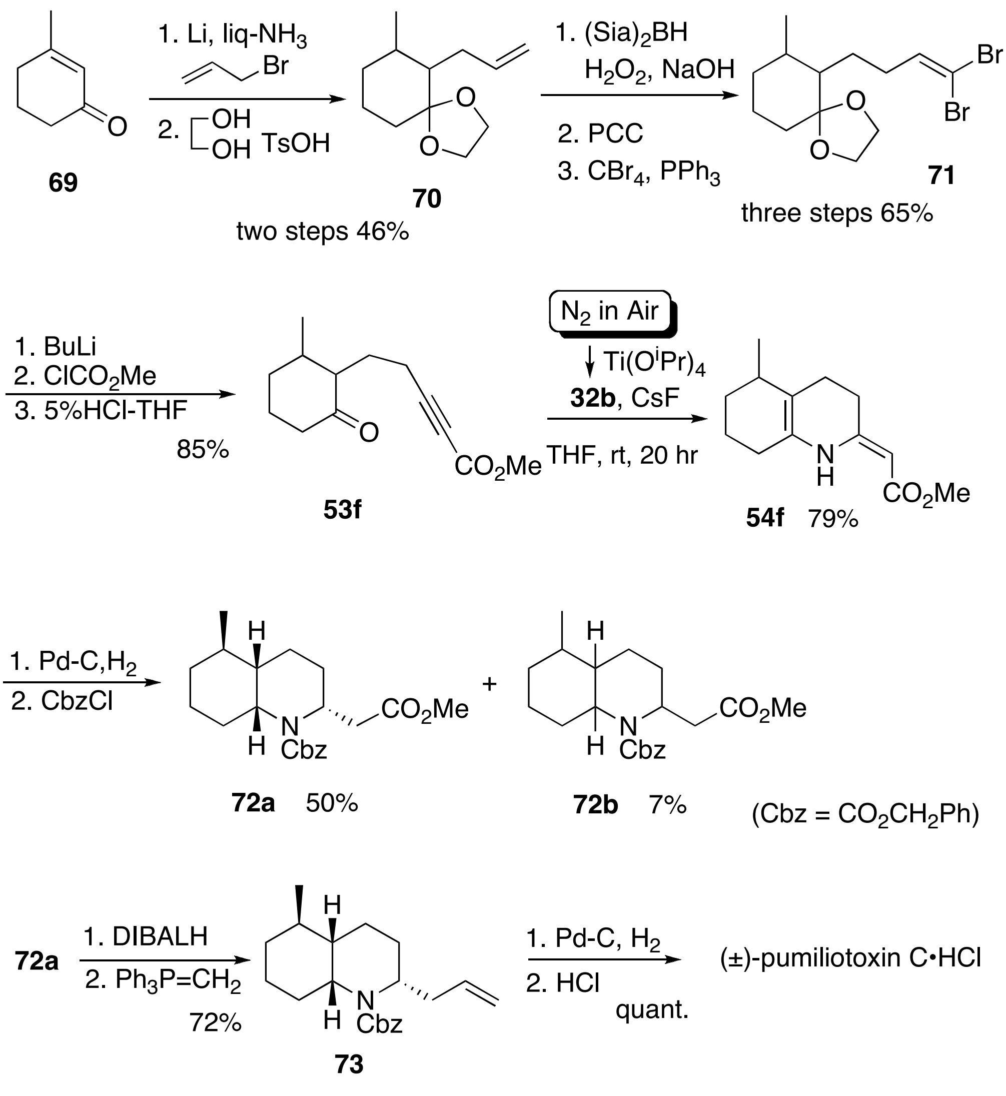
5-2-3. Synthesis of Pumiliotoxine C

Perhydroquinoline derivatives **54c** could be synthesized from the compound (**53c**) having the keto-alkyne part and **32** prepared from air as the nitrogen source. Thus, the total synthesis of (±)-pumiliotoxine C was planned. Pumiliotoxin C was isolated[40] from skin extracts of the Panamanian poisonous frog *Dendrobates pumilio*[41] as the first member of one major class of dendrobatid alkaloids and has a *cis*-decahydroquinoline skeleton. The retrosynthetic analysis of pumiliotoxin C using air as the nitrogen gas is shown in Scheme 23. Pumiliotoxin C would be synthesized from quinoline derivatives (**54f**), which should be able to be synthesized from keto-alkyne (**53f**) and air using the present method. From commercially available 3-methylcyclohexenone (**69**), keto-alkyne (**53f**) would be synthesized.



Scheme 23. Retrosynthetic Analysis of Pumiliotoxin C

Allylation of 3-methylcyclohexenone (**69**)[42] followed by ketalization afforded compound (**70**). Hydroboration followed by oxidation with PCC and then treatment with CBr_4 and PPh_3 gave **71**.

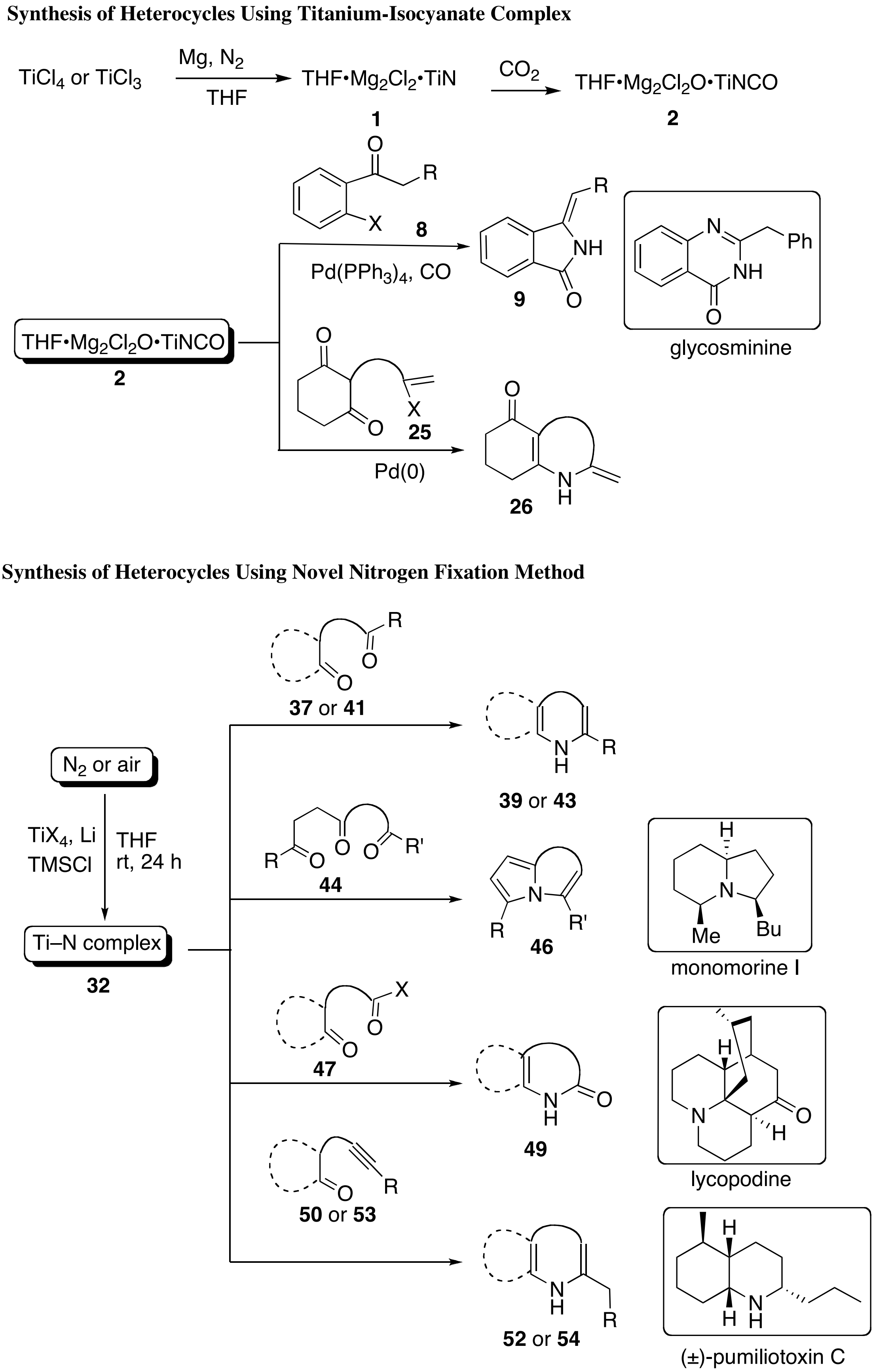


Scheme 24. Total Synthesis of Pumiliotoxine C

Treatment of **71** with BuLi gave lithium acetylide, which was reacted with methyl chloroformate followed by deketalization to give keto-alkyne (**53f**). Synthesis of quinoline (**54f**) was successfully achieved by the reaction of keto-alkyne (**53f**) with titanium-nitrogen complex (**32b**) prepared from air in high yield. Hydrogenation of compound (**54f**) was carried out using 5 mol % of palladium on charcoal (STD-type) and then protection of the secondary amine with carbobenzyloxy chloride afforded **72a** and **72b** in 57% yields in a ratio of 7 to 1. The major isomer (**72a**) was treated with DIBAL-H followed by the reaction with a Wittig reagent to give compound (**73**). Hydrogenation of (**73**) with 5% palladium on charcoal followed by treatment with $Et_2O{\cdot}HCl$ afforded pumiliotoxine C hydrochloride, whose spectral data agreed with those reported in the literature. Thus the total synthesis of pumiliotoxin C was achieved using air as a nitrogen source.[43]

6. Conclusion

Nitrogen fixation and utilization of the fixed nitrogen are a challenging theme in synthetic organic chemistry, and transition metal complexes should play an important role in nitrogen fixation. Titanium-nitrogen complex (**1**) reported by Yamamoto is very interesting because one atom pressure of nitrogen could be fixed by $TiCl_4$ or $TiCl_3$ and Mg at room temperature, and nitrogen-nitrogen triple bond was cleaved under these reaction conditions. Sobota reported that that titanium-nitrogen complex (**1**) easily reacted with CO_2 to produce titanium-isocyanate complex **2**. Since complex (**2**) is more stable and handling of **2** is easier compared with that of **1**, various heterocyclic compounds could be synthesized using titanium-isocyanate complex (**2**) and palladium catalyst. To develop to the catalytic reaction in regard to the titanium complex, an excess amount of Li and TMSCl were added to the THF solution of $TiCl_4$ or $Ti(O^iPr)_4$ solution under nitrogen. As the result, the novel titanium-catalyzed nitrogenation method could be developed. Since this procedure was very simple and it was not required to isolate titanium-nitrogen complex (**32**), the stoichiometric reaction conditions were confirmed by modification of the catalytic reaction conditions, that is, a THF solution of $TiCl_4$ or $Ti(O^iPr)_4$ (1 equiv.) was stirred in the presence of Li (10 equiv.) and TMSCl (10 equiv.) under nitrogen at room temperature overnight to afford a solution of titanium nitrogen complex (**32**). To this THF solution of **32** were added a THF solution of the substrate and CsF, and the solution was stirred an appropriate temperature under argon. After the usual work up, various heterocyclic compounds could be synthesized. Furthermore, nitrogen in air instead of nitrogen gas could be fixed directly using this method. As the results, various heterocyclic compounds could be synthesized from air as the nitrogen source, and the several natural products, such as monomoline I, lycopodine and pumiliotoxine C, could be synthesized from dry air as the nitrogen source. These results indicated that titanium-nitrogen complex (**32**) prepared from air could be used as a nitrogen source in synthetic organic chemistry.



Synthesis of Heterocycles Using Titanium-Isocyanate Complex

Synthesis of Heterocycles Using Novel Nitrogen Fixation Method

Scheme 25. Summary for Titanium-Promoted and -Catalyzed Nitrogenation

Furthermore, we have already reported that non-substituted aniline derivatives or benzolactams could be synthesized by use of palladium-catalyzed coupling reaction and palladium catalyzed-carbonylation in the presence of an aryl halide and **32**.[44] Presumably, nitrogen-containing compounds such as amino acid and nucleic acid will be synthesized from air as a nitrogen source. It is also known that many transition metals can react with nitrogen to form transition metal-nitrogen complexes, which should be used as a nitrogenation agent in the future. As the results, nitrogen gas or air will be directly used as a nitrogen source in synthetic organic chemistry in the future.

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