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Formation of azatitanacyclopentanes from ene-imines and a Ti(O-*i*-Pr)$_4$/2*i*-PrMgX reagent and their synthetic reactions

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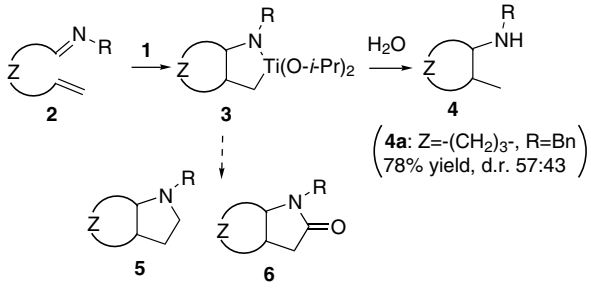
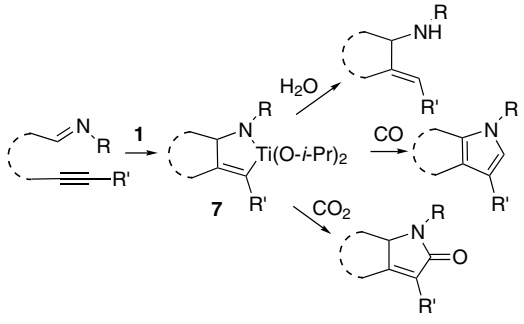
Abstract—ω-Vinylimines reacted with a Ti(O-*i*-Pr)$_4$/2*i*-PrMgX reagent to generate the corresponding azatitanacyclopentanes in quantitative yield, which in turn reacted with H_2O, I_2 and O_2 to give 2-methyl-, 2-iodomethyl-, 2-hydroxymethyl-1-aminocyclic compounds, respectively. The azatitanacyclopentanes thus generated reacted with formaldehyde to afford the corresponding 2,3-annulated pyrrolidines in good yield.

Recently, the formation of the azatitanacyclopentane **3a** [R = Bn, Z = –(CH$_2$)$_3$–] from ene-imine **2a** and a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2*i*-PrMgX (**1**)[1] has been reported, which provided the corresponding amine **4a** in good yield after hydrolysis (Scheme 1).[2] Utilization of the reaction, however, has not been explored.[3] We thought that further investigation of the reaction of this type and utilization of the resulting titanacycle **3** by treatment with electrophiles other than H^+ might provide new methods for preparation of cyclic amino compounds such as **5** and **6** in addition to **4** (Scheme 1) because it has been also reported that the azatitanacyclopentenes **7** derived inter- and intra-molecularly from alkynes and imines by the reaction with **1** reacted with CO and CO_2 to provide pyrroles and 1,5-dihydro-2*H*-pyrrol-2-ones, respectively (Scheme 2).[2,4] Herein we report a highly stereoselective formation of azatitanacycles **3** and we found their reaction with formaldehyde produced the 2,3-annulated pyrrolidines **5** in good yield, although **3** could not react with CO and CO_2.



Scheme 1.

First, we carried out the reactions of various ene-imines **2b–h** with the reagent **1** and the following hydrolysis to confirm the efficiency and stereoselectivity of the cyclization (Table 1). Thus, ene-imine **2** was treated with **1** (1.3 equiv) in ether at −40 °C for 3 h and the mixture was quenched by addition of H_2O.[5] As can be seen from Table 1 summarizing the results, the corresponding cyclized products **4** were formed in moderate to excellent yields. *N*-Phenyl derivative **2c** as well as *N*-benzyl compounds **2b** and **2d** were good substrates. Five- and six-membered carbocyclic compounds **4e–g** as well as



Scheme 2.

Keywords: Low valent titanium; Azatitanacyclopentane; Cyclization; Ene-imine.
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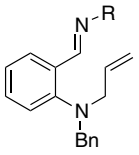
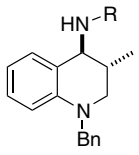
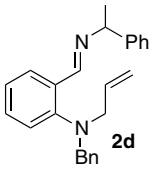
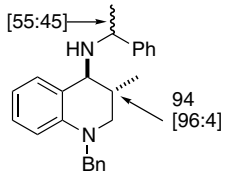
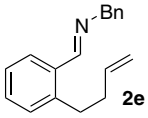
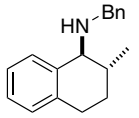
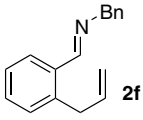
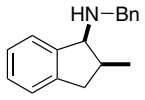
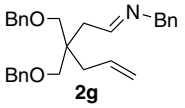
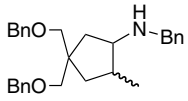
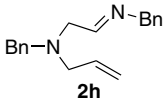
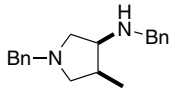
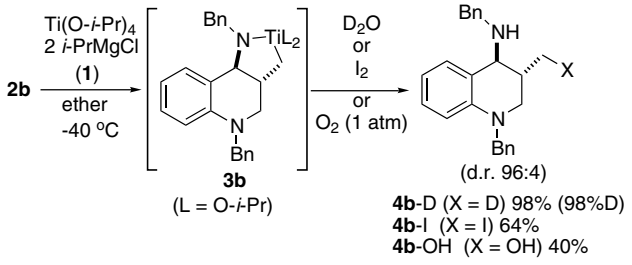
Table 1.

Entry	2	4	Yield (%) [dr]
			
1	**2b** (R = Bn)		**4b** 98 [96:4]
2	**2c** (R = Ph)		**4c** 93 [94:6]
3			
4			94 [93:7]
5			94 [96:4]
6			74 [61:39]
7			41 [88:12]

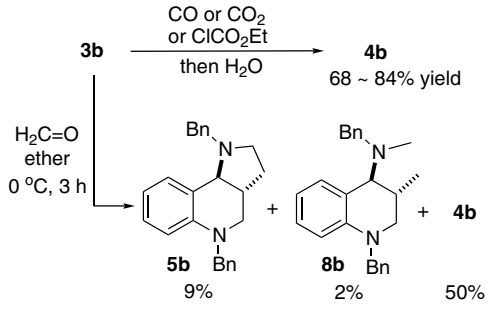
N-heterocycles such as pyrrolidine **4h** and tetrahydroquinolines **4b–d** could be synthesized. High diastereoselectivity was observed in the reaction starting from appropriate substrates such as **2b–f** and **2h** (entries 1–5 and 7).[6] However, the stereoselectivity for the formation of cyclopentane derivative **4g** was low similar to that for **4a**. Attempts for asymmetric induction by introducing a chiral center into the *N*-substituent also failed (entry 3).

As illustrated in Scheme 3, addition of D_2O instead of H_2O to the reaction mixture derived from **1** and **2b** provided **4b**-D with nearly complete deuterium incorporation. The result indicates the quantitative generation of azatitanacyclopentane intermediate **3b**. Similarly, azatitanacyclopentane **3b** could readily react with I_2 and O_2 (1 atm) at the carbon of the titanium α to provide the corresponding **4b**-I and **4b**-OH, respectively.[7]

Based on these results showing quantitative formation of azatitanacyclopentanes **3**, we next carried out the reaction of the complex **3** with one-carbon electrophiles, expecting their bicyclization to annulated pyrrolidine derivatives **5** or **6** (Scheme 2). Thus, **3b** was treated with excess amount of CO (1 atm), CO_2 (1 atm), or $ClCO_2Et$ under various reaction conditions but, unfortunately, no tricyclic compound(s) was produced. However, we found that addition of an ethereal solution of formaldehyde to **3b** afforded pyrrolidine **5b** (9%) with *N*-methylated compound **8b** (2%) and **4b** (50%) (Scheme 4, entry 1



Scheme 3.



Scheme 4.

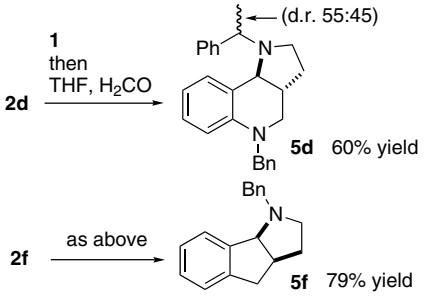
Table 2.[a]

Entry	Conditions	Additive	Yield (%)		
			5b	**8b**	**4b**
1	0 °C, 3 h	—	9	2	50
2	rt, 2 days	—	40	28	14
3	rt, 2 days	THF[b]	70	5	6
4	rt, 2 days	Pyridine[c]	50	8	13
5[d]	rt, 2 days	—	17	5	<2

[a] **3b** was prepared in situ from **2b** (1.0 mmol) and **1** (1.3 mmol) in ether (6 mL).
[b] 6 mL was added.
[c] 1.3 mL was added.
[d] The reaction of **2b** with **1** was carried out in THF instead of ether.

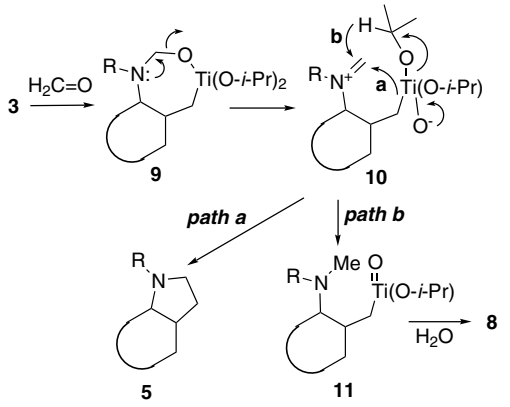
in Table 2). As revealed from Table 2 which summarizes the results of a search for the appropriate reaction conditions for selective production of **5b**, increasing temperature and elongation of the reaction time increased the total yield of **5b** and **8b** (entry 2). We found that addition of THF or pyridine prior to addition of formaldehyde improved the yield and selectivity of **5b** (entries 3 and 4).[5] Thus, **5b** was obtained in 70% isolated yield (entry 3). Use of THF instead of ether for generation of **3b** from **2b** and **1**, however, resulted in low conversion of **2b** (entry 5). Unfortunately, the titanacycle **3** did not react at all with other carbonyl compounds such as benzaldehyde and pentanal, and hydrolysis of the reaction mixture afforded **4b**.

Scheme 5 shows other results of this one-pot synthesis of the 2,3-annulated pyrrolidines **5**. Thus, treatment of the azatitanacyclic intermediates derived from **2d** and **2f** with formaldehyde after addition of THF produced *N*-heterocycle- and carbocycle-annulated pyrrolidines **5d** and **5f** in 60% and 79% isolated yield, respectively.[5]

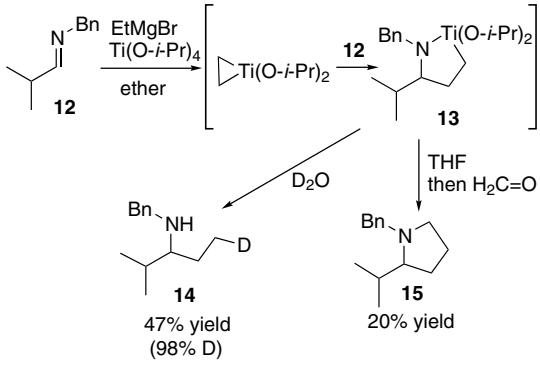


Scheme 5.

Scheme 6 illustrates our proposed mechanism to explain the production of **5** and **8** from **3** and formaldehyde.[8] Thus, the reaction of **3** with formaldehyde may afford iminium salt **10** through compound **9**. Pyrrolidine **5** can be formed from **10** by nucleophilic addition of carbanion at the titanium α (path a). Production of *N*-methylated **8** can be explained by assuming that the iminium moiety in **10** would be reduced by transfer of a hydride from the β-position to the Ti-atom (path b) to provide **11**. Additives such as THF and pyridine may act as a Lewis base and coordinate to the Ti-atom to increase the nucleophilicity of carbanion at the titanium α and the reaction via path a could be relatively accelerated.



Scheme 6.



Scheme 7.

In addition to these results, we demonstrate the possibility of extension of this pyrrolidine synthesis to the reaction of azatitanacyclopentanes generated *intermolecularly* from imines and Grignard reagents (Scheme 7). It has been reported that the reaction of an alkyl Grignard reagent having a β-hydride with esters, amides and nitriles in the presence of titanium compounds proceeds via the corresponding titanacyclopropanes to give cyclopropanols and cyclopropylamines.[9,10] On this basis, we carried out the reaction of EtMgBr with imine **12** in the presence of Ti(O-*i*-Pr)$_4$. The titanacyclic intermediate **13**, the formation of which was confirmed by deuteriolysis providing **14** (47%), was treated with formaldehyde after addition of THF. As expected, the reaction afforded the pyrrolidine **15** in one-pot from **12**, albeit in low yield.

In summary, we have demonstrated that a divalent titanium reagent **1** effectively cyclizes ene-imines **2** to the azatitanacycles **3** in a highly stereoselective manner, which readily reacted with H^+, I_2, O_2 and formaldehyde to give the corresponding 2-methyl-, 2-iodomethyl-, 2-hydroxymethyl-cycloalkylamines and 2,3-annulated pyrrolidines, respectively.

Acknowledgements

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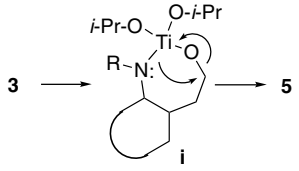
4. For the reactions of imines with (η^2-alkyne)Ti(O-*i*-Pr)$_2$ complexes, see: Gao, Y.; Harada, K.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 5913; Gao, Y.; Shirai, M.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 7787; Gao, Y.; Shirai, M.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 6849; For the reaction of alkynes with (η^2-imine)Ti(O-*i*-Pr)$_2$ complexes, see: Gao, Y.; Yoshida, Y.; Sato, F. *Synlett* **1997**, 1353; Fukuhara, K.; Okamoto, S.; Sato, F. *Org. Lett.* **2003**, *5*, 2145; Quntar, A. A. A. A.; Dembitsky, V. M.; Srebnik, M. *Org. Lett.* **2003**, *5*, 357.
5. *Preparation of* **4**: To a solution of **2** (1.0 mmol) and Ti(O-*i*-Pr)$_4$ (1.3 mmol) in ether (6 mL) was added *i*-PrMgCl (2.74 mL, 0.95 M in ether, 2.6 mmol) at −40 °C and the mixture was stirred for 2 h at this temperature. Hydrolysis, deuteriolysis and iodolysis were carried out by addition of H_2O (excess), D_2O (excess) or I_2 (1.5 mmol) to the reaction mixture, respectively. **4** (X = OH) was obtained by treatment of the reaction mixture with O_2 gas (1 atm, balloon). ^{1}H NMR data ($CDCl_3$), **4b** (270 MHz): δ 7.20–7.39 (m, 10H), 7.07 (d, J = 7.3 Hz, 1H), 7.03 (t, J = 8.1 Hz, 1H), 6.60 (t, J = 7.3 Hz, 1H), 6.53 (d, J = 8.1 Hz, 1H), 4.51 (s, 2H), 3.86 and 3.92 (2d, J = 13.2 and 13.2 Hz, each 1H), 3.86 (dd, J = 3.5, 11.3 Hz, 1H), 3.43 (d, J = 3.0 Hz, 1H), 2.99 (ddd, J = 1.1, 3.0, 11.3 Hz, 1H), 2.12–2.22 (m, 1H), 0.95 (d, J = 7.3 Hz, 3H). **4f**: (500 MHz): δ 7.42 (d, J = 7.5 Hz, 2H), 7.35–7.36 (m, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.0 Hz, 1H), 7.16 (m, 3H), 4.13 (d, J = 6.0 Hz), 3.87 and 3.92 (2d, J = 13.0 and 13.0 Hz, each 1H), 2.92 (dd, J = 7.0, 15.5 Hz, 1H), 2.64–2.74 (m, J = 6.5 Hz, 1H), 2.60 (dd, J = 4.0, 15.5 Hz, 1H), 1.51, (br s, 1H), 0.97 (d, J = 6.5 Hz, 3H). *Preparation of* **5**: To a solution of **3** generated in situ from **2** (1.0 mmol) and **1** (1.3 mmol) in ether (6 mL) as mentioned above were added THF (6 mL) and then a solution of formaldehyde (ca. 15 mmol) in ether (5 mL) at −40 °C. The resulting mixture was stirred for 2 days at room temperature. After addition of water, usual work-up and the following column chromatography on silica gel provided **5**. ^{1}H NMR data ($CDCl_3$), **5b** (600 MHz): δ 7.53 (d, J = 7.3 Hz, 2H), 7.14–7.42 (m, 9H), 7.04 (t, J = 7.0 Hz 1H), 6.67 (t, J = 7.0 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 4.55 (s, 2H), 4.53 (d, 1H, J = 13.5 Hz), 3.53 (d, J = 13.5 Hz), 3.46–3.49 (m, 1H), 3.38 (d, J = 10.8 Hz, 1H), 3.34–3.37 (m, 1H), 3.29 (dd, J = 10.2, 12.0 Hz, 1H) 2.68 (dd, J = 2.4, 11.4 Hz, 1H), 2.17–2.25 (m, 1H), 1.94–1.99 (m, 1H), 1.54–1.61 (m, 1H). **8b** (270 MHz): δ 7.10–7.27 (m, 11H), 6.96 (t, J = 7.0 Hz, 1H), 6.56 (t, J = 7.3 Hz, 1H), 6.46 (d, J = 8.1 Hz, 1H), 4.36 and 4.48 (2d, J = 16.7 and 16.7 Hz, each 1H), 3.59 and 3.65 (2d, J = 13.5 and 13.5 Hz, each 1H), 3.53 (dd, J = 3.8,11.6 Hz, 1H), 3.30 (d, J = 4.6 Hz, 1H), 2.95 (dd, J = 4.3, 11.3 Hz, 1H), 2.26–2.38 (m, 1H), 2.12 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H). **5f** (500 MHz): δ 7.12–7.38 (m, 9H), 4.20 (d, J = 8.0 Hz, 1H), 4.11 (d, J = 13.0 Hz, 1H), 3.49 (d, J = 13.0 Hz, 1H), 3.13, (dd, J = 9.0, 16.5 Hz, 1H), 3.01–3.09 (m, 1H), 2.86 (ddd, J = 3.5, 6.5, 9.5 Hz, 1H), 2.80 (dd, J = 3.5, 16.5 Hz, 1H), 2.48 (dt, J = 6.5, 9.0 Hz, 1H), 2.06–2.14 (m, 1H), 1.57 (ddt, J = 8.5, 12.5, 6.5 Hz, 1H).
6. Stereochemistry was determined by NOE–DIF experiments.
7. Deuteriolysis and iodolysis of azatitanacyclopentenes derived from alkyne, imine and **1**, see: Ref. 4 Deuteriolysis and iodolysis of azazirconacyclopentanes and –pentenes, see: Ref. 3g,h and Makabe, M.; Sato, Y.; Mori, M. *Synthesis* **2004**, 1369.
8. Alternatively, the formation of **5** from **3** and formaldehyde can be explained by considering the reaction pathway through the intermediate **i** shown below.



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