

Titanium-mediated [4 + 1] assembly of 1,3-dienes and nitriles: formation of 3-cyclopentenyl amines and cyclopentenones

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In the presence of $\text{Ti}(\text{O}^i\text{Pr})_4$ and $^i\text{PrMgCl}$, dienes couple with nitriles to afford the title products in good yields.

Transition metal-mediated reactions that allow the construction of five-membered carbocycles are of significant synthetic interest.¹ Whereas the reactions involving [2 + 2 + 1] or [3 + 2] strategies have attracted much attention,^{1,2} those involving [4 + 1] strategies are much less common.³ Of those reactions, very few have used conjugated dienes as four-carbon components.^{3a,d-f}

Among conjugated diene complexes, those of Group 4 transition metals ($M = \text{Ti, Zr, Hf}$) are well documented (Fig. 1). In particular, diene-zirconocenes and related compounds have been extensively studied,⁴ and the metallacyclopentene form (Δ^3 -zirconacyclopentene **III** in Fig. 1) has been considered to reasonably fit the structure of *s-cis* diene complexes. Therefore, insertion reactions into the zirconium–carbon bond in **III** ($\text{ML}_n = \text{ZrCp}_2$) have been carried out, but only open-chain products were obtained after hydrolysis.⁵ Furthermore, there have been reports of the synthetic uses of diisopropoxy titanacyclopentene complexes of type **III**. Two recent papers have reported some reactions of **III** ($\text{ML}_n = \text{Ti}(\text{O}^i\text{Pr})_2$), through the insertion of aldehydes, ketones, esters and nitriles.⁶ The open-chain products were also formed in these reactions. By using 1,3-dienes, the titanium-mediated de Meijere synthesis of tertiary cyclopropylamines from amides⁷ was extended to 2-alkenyl substituted derivatives.⁸ To our knowledge, no conversion of metallacyclopentenones ($M = \text{Zr, Ti}$) of type **III** (derived from 1,3-dienes) to 5-membered carbocycles is known.

In this paper we report the first example of a titanium-mediated reaction that allows the formation of 5-membered carbocyclic derivatives from 1,3-dienes and a one-carbon component.

As part of our work on the titanium-mediated synthesis of cyclopropylamines from nitriles,⁹ we studied the feasibility of preparing cyclopropylamines bearing a 2-alkenyl moiety. In keeping with this aim we applied a ligand exchange procedure with the initial titanacyclopentane complex **A** and isoprene (Scheme 1).¹⁰ When $^i\text{PrMgCl}$ was added to a solution of benzyl

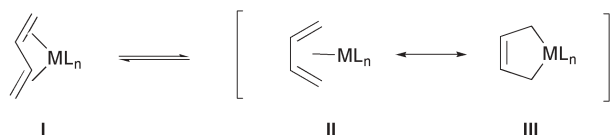
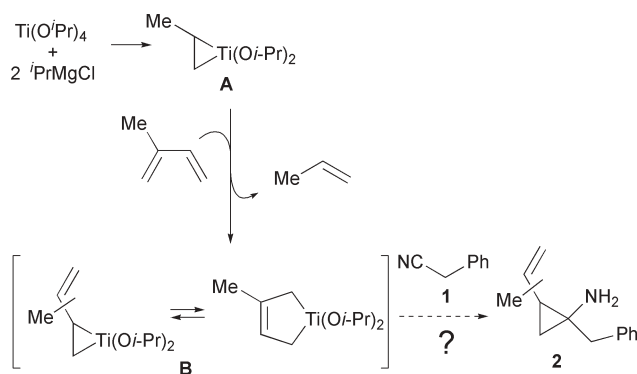


Fig. 1 Conjugated diene forms **I**, **II** and **III**.

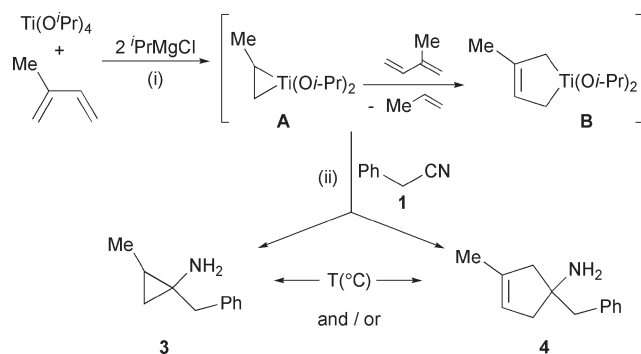
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Scheme 1

cyanide (**1**), isoprene and $\text{Ti}(\text{O}^i\text{Pr})_4$, followed by $\text{BF}_3 \cdot \text{OEt}_2$, only cyclopropylamine **3** was obtained (Scheme 2). No trace of the vinylcyclopropylamine **2** was observed. Obviously, the insertion of the nitrile into **A** occurred before the formation of **B**.¹¹ We then considered preforming the titanacyclopentene intermediate **B** before adding the nitrile (Scheme 2). Thus, $\text{Ti}(\text{O}^i\text{Pr})_4$ and isoprene (2 equiv.) were dissolved in ether, the solution cooled to -78°C and $^i\text{PrMgCl}$ (2 equiv.) added dropwise. The temperature was allowed to slowly increase to room temperature within *ca.* 2–3 h, and during this period a nitrile was added (step ii). The reaction was completed by the addition of $\text{BF}_3 \cdot \text{OEt}_2$ at room temperature.

We noticed that the course of the reaction strongly depended on the temperature at which the latter addition occurred. When adding the nitrile **1** at -60°C , only **3** (derived from the complex **A**) was formed. When adding **1** at higher temperatures, within the range of -50 to -30°C , mixtures of the cyclopropylamine **3** and the unexpected cyclopentenyl amine **4** were formed (**3** : **4** = 95 : 5, 45 : 55 and 20 : 80 for -50 , -40 and -30°C respectively).



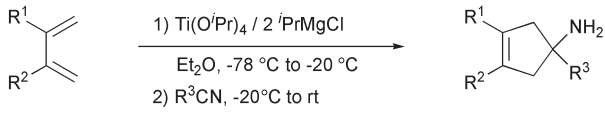
Scheme 2

Interestingly, increasing the addition temperature to $-20\text{ }^{\circ}\text{C}$ led to the exclusive formation of **4**. Addition of **1** at higher temperatures ($0\text{ }^{\circ}\text{C}$ to rt) decreased the yield of **4**. The exclusive formation of **4** similarly took place in the absence of an additional Lewis acid, the yield of **4** being the same with or without $\text{BF}_3\cdot\text{OEt}_2$. These results clearly indicate that ligand exchange occurs partially (-50 to $-30\text{ }^{\circ}\text{C}$) or completely ($-20\text{ }^{\circ}\text{C}$) in the reaction conditions. The relative instability of the intermediate complex **B** could explain the decrease of the yield at temperatures higher than $0\text{ }^{\circ}\text{C}$.

The reaction pathway depicted in Scheme 2 opens the way for the assembly of 5-membered carbocyclic rings through titanium-mediated $[4 + 1]$ addition reactions. When applying the optimised conditions below, the reaction of nitriles with 1,3-dienes proceeded smoothly to afford the corresponding 3-cyclopentenyl amines in good yields. Table 1 summarises the results employing different nitriles and dienes, together with $^i\text{PrMgCl}$ and $\text{Ti}(\text{O}^i\text{Pr})_4$. Both aliphatic and aromatic nitriles coupled with isoprene (entries 1–3 and 4, 5 respectively). The reaction even took place with the sterically hindered 1-adamantanecarbonitrile (entry 3) and an α,β -unsaturated nitrile (entry 6). A bromine atom can be present in the substrate and is tolerated by the reaction conditions (entry 5). The use of other 2-substituted and 2,3-substituted dienes was also successful (entries 7–9).¹²

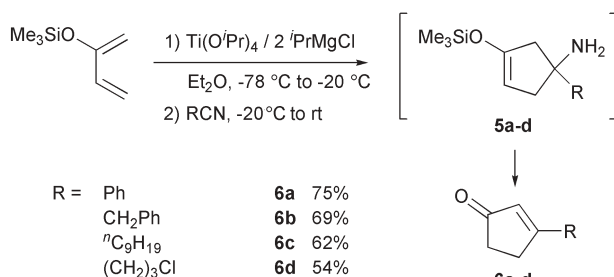
The reaction with nitriles is not limited to the preparation of 3-cyclopentenyl amines. It also offers a new access to 3-substituted 2-cyclopentenones (Scheme 3). With 2-trimethylsilyloxybutadiene the reaction took place using the previously established conditions, leading to the corresponding silyloxycyclopentenyl amines **5a–d**.

Table 1 Preparation of 3-cyclopentenylamines[†]

				
Entry	R ¹	R ²	R ³	Yield (%) ^{a,b}
1	Me	H	CH ₂ Ph	61
2	Me	H	ⁿ C ₉ H ₁₉	84
3	Me	H	1-Adamantyl	79
4	Me	H	Ph	74
5	Me	H	3-BrC ₆ H ₄	66
6	Me	H	CH=CH-Ph	45
7	(CH ₂) ₂ -CH=CMe ₂	H	ⁿ C ₉ H ₁₉	77
8	Ph	H	ⁿ C ₉ H ₁₉	79
9	Me	Me	ⁿ C ₉ H ₁₉	63 ^c

^a All reactions were performed under Ar with 1.1 eq of $\text{Ti}(\text{O}^i\text{Pr})_4$, 2 equiv. of diene and 2.2 equiv. of $^i\text{PrMgBr}$ unless otherwise stated.

^b Isolated yields. ^c Reaction performed with two-fold amount of reagents.



Scheme 3

The spontaneous elimination in the hydrolytic workup conditions afforded the cyclopentenone derivatives **6a–d** in good yields. Both aromatic and aliphatic nitriles were successfully employed for this transformation. Finally, the same procedure could be applied with esters. Thus, the reaction of myrcene with ethyl acetate afforded 3-(4-methyl-3-pentenyl)-1-methyl-3-cyclopenten-1-ol in 59% yield.¹³

In conclusion, we have reported the first example of a titanium-mediated reaction of 1,3-dienes with one-carbon components, leading to cyclopentenone derivatives. The simplicity of the procedure as well as the readily available reagents and starting materials are noteworthy. Further studies on titanium-mediated $[4 + 1]$ assembly reactions are currently underway.

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Notes and references

[†] Representative procedure, preparation of 3-methyl-1-nonyl-3-cyclopentenylamine (entry 2, Table 1): To a solution of $\text{Ti}(\text{O}^i\text{Pr})_4$ (0.33 mL, 1.1 mmol) and isoprene (0.2 mL, 2 mmol) in Et_2O (5 mL) a solution of $^i\text{PrMgCl}$ (1.1 mL, 2 M in Et_2O) was added under argon at $-78\text{ }^{\circ}\text{C}$. The mixture was warmed for ca. 2 h up to $-20\text{ }^{\circ}\text{C}$, during which period the solution became green. At this temperature, decanenitrile (0.19 mL, 1 mmol) was added. After the resulting dark red mixture was allowed to warm to rt and stirred for 1 h, 1 N HCl (ca. 3 mL) and ether (ca. 15 mL) were added. NaOH (10% aq, ca. 10 mL) was added and the mixture was extracted with ether. The combined ether layers were dried (MgSO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel ($\text{Et}_2\text{O} : \text{Et}_3\text{N}$ 98 : 2) to afford 188 mg (84%) of the title product as a colourless oil; IR ν/cm^{-1} 3355, 2924, 1591, 1466; $^1\text{H-NMR}$ (250 MHz; CDCl_3) δ 0.85 (t, $J = 6.8$ Hz, 3H), 1.20–1.35 (m, 18H), 1.70 (s, 3H), 1.97–2.12 (m, 2H), 2.30–2.46 (m, 2H), 5.25 (s, 1H); $^{13}\text{C-NMR}$ (63 MHz; CDCl_3) δ 14.5, 17.3, 23.1, 25.3, 29.7, 30.0, 30.1, 30.7, 32.3, 43.6, 48.6, 52.5, 61.4, 122.7, 138.8; MS (70 eV) m/z 223 (M^+ , 15), 208 (13), 194 (6), 154 (48), 124 (84), 96 (100); Analysis calculated for $\text{C}_{15}\text{H}_{29}\text{N}\cdot\text{HCl}$ (%): C, 69.33; H, 11.64; N, 5.39; found C, 69.14; H, 11.69; N, 5.29.

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