NOVEL SYNTHESIS OF QUINOLINE DERIVATIVES BY ZIRCONIUM-PROMOTED CYCLIZATION

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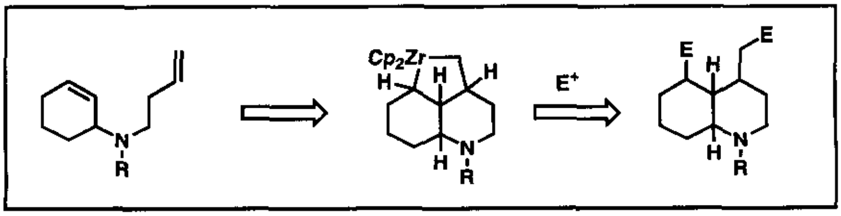
Abstract——Zirconium-promoted cyclization of the diene (**1**) resulted in the perhydroquinoline derivatives (**2a**) and (**3a**) in moderate yields. The intermediary zirconacycles can be converted into the iodinated products (**2c**) and (**3c**) by treatment with iodine, and into the tricyclic ketones (**12**) by treatment with carbon monoxide.

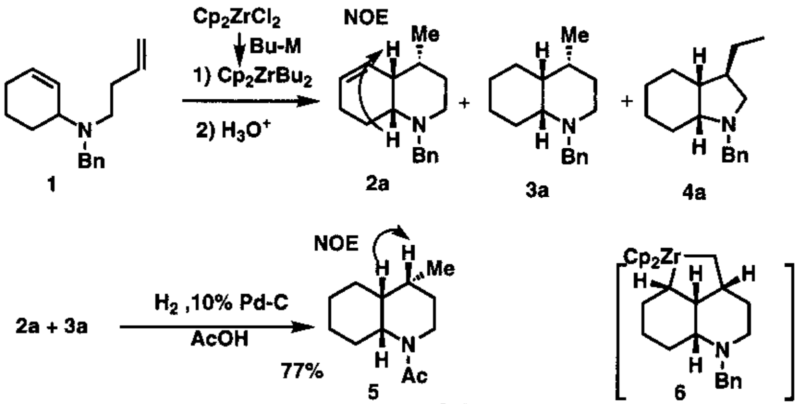
Zirconium promoted cyclization is very useful synthetic method because new carbon-carbon bonds were formed from the multiple bonds. In a previous study, we reported the total synthesis of (-)-dendrobine[1] by means of a zirconocene-promoted intramolecular reductive coupling reaction.[2] This reaction would be further extended for the synthesis of quinoline derivatives as shown in Scheme 1. We now wish to report the application of this method for the synthesis of quinoline derivatives.



Scheme 1

A THF solution of *N*-benzyl-*N*-3-butenyl-2-cyclohexenylamine (**1**) and Cp_2ZrBu_2, obtained from the reaction of BuLi (2.5 eq.) and Cp_2ZrCl_2 (1.3 eq.),[3] afforded the perhydroquinoline derivatives (**2a**) and (**3a**) in 12% and 23% yields, respectively, along with **4a** in 22% yield. (Table 1, run 1). The yields of six membered compounds (**2a** and **3a**) were improved when BuMgBr was used instead of BuLi (runs 2-5). The stereochemistry of the perhydroquinoline derivative was determined as follows. The ring junction protons of **2a** was determined to be *cis* by NOE experiments. A mixture of **2a** and **3a** was hydrogenated with 10% palladium on charcoal in AcOH giving unexpected acetylated compound (**5**) in 77% yield. From the NOE experiment of **5**, the ring junction protons are *cis* and the methyl group was found to be *trans* to the ring junction protons. This means that the stereochemistry of the zirconacycle is determined to be **6**. The stereochemistry of five membered compound (**4a**) could not be determined in this stage.

Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

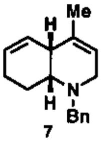


Scheme 2

Table 1 : Zirconocene-promoted cyclization of 1

run	Bu-Metal (eq.)	Cp_2ZrCl_2 (eq.)	reaction time (h)	yield (%)			(2a+3a):4a
				2a	3a	4a	
1	BuLi (2.5)	1.3	5	12	23	22	2:1
2	BuMgBr (2.5)	1.3	5	11	37	20	2.6:1
3	BuMgBr (4.0)	1.0	5	9	42	17	3:1
4	BuMgBr (4.0)	2.0	2	6	45	25	2:1
5	BuMgBr (6.0)	3.0	1	6	45	26	2:1

All reactions were carried out in THF at room temperature
A small amount (4%) of 7 was obtained in each case.



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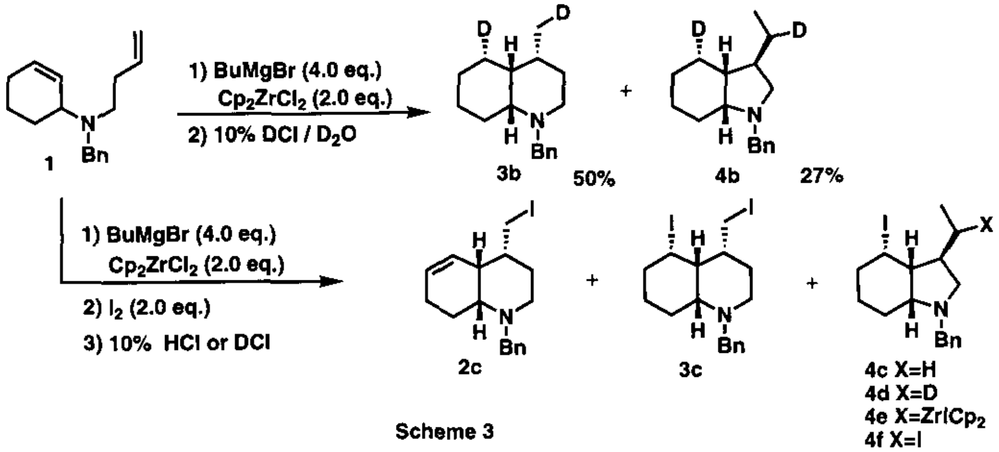
Deuterolysis of the reaction mixture derived from **1** and Cp_2ZrBu_2 under the best conditions for cyclization (Table 1, run 4) with 10% DCl in D_2O afforded **3b** and **4b** in 50% and 27% yields, respectively. Iodination of the reaction mixture with 3 eq. of I_2 gave only the mono-iodinated products (**2c**) and (**4c**) in 47% and 25% yields, respectively (Table 2, run 1). Increasing the amount of I_2 to 6 eq., the di-iodinated product (**3c**) is obtained in 25% yield along with **2c** and **4c**. In this case, the reaction mixture, treated with iodine, was quenched with 10% DCl in D_2O. However, the mono-deuterated product (**4d**) was obtained and the corresponding di-iodinated product (**4f**) was not detected. This means that the carbon-zirconium bond of **4e** was not cleaved by iodine under the conditions used here (run 2). Since the use of the exess amount of I_2 provided the di-iodinated product (**3c**) rather than the mono-iodinated product (**2c**), the same reaction was carried out at the lower temperature to give di-iodinated product (**3c**) as the main product (run 3). It meanes that β-hydride elimination of zirconacycle (**6**) was inhibited at the lower reaction temperature. Using zirconocene prepared from Cp_2ZrCl_2 and BuLi also did not give a good result (run 4).

A possible reaction course is shown in Scheme 4. Reaction of the diene (**1**) with zirconocene forms the zirconacycle (**6**) which reacts with electrophiles to cleave the carbon-zirconium bond producing the species (**8**). It can undergo β-elimination resulting in **2** or insert another eletrophilic moiety giving **3**. On the other hand, the terminal olefin is isomerized by Cp_2Zr[4] to provide **9**, which can undergo the same cyclization process. A strong indication for the intermediacy of **11** was the detection of **4d** when the reaction mixture was quenched by I_2 followed by treatment with 10% DCl in D_2O (Table 2, run 2).

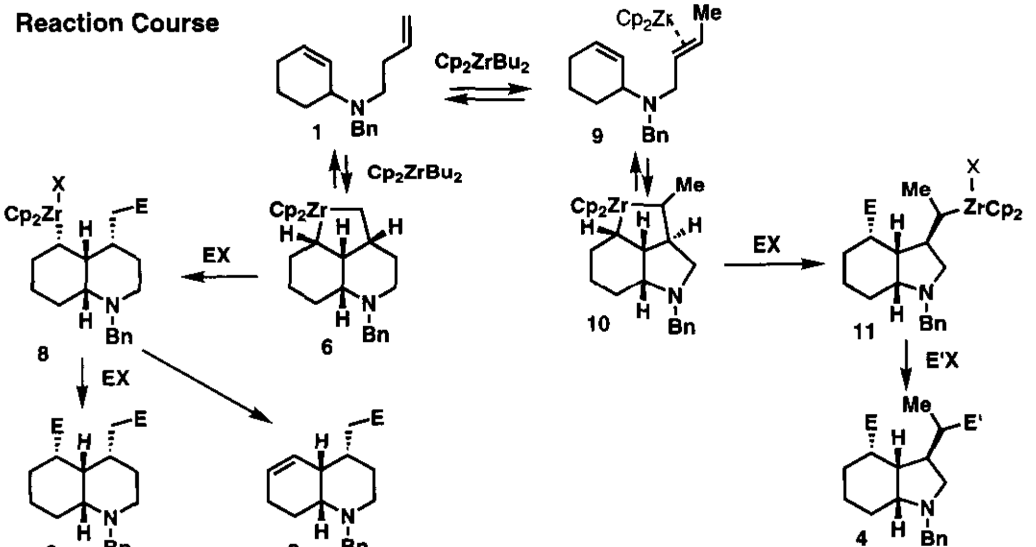


Scheme 3

Table 2: Iodination of the zirconacycles under various conditions

run	Bu-Metal (eq.)	Cp_2ZrCl_2 (eq.)	I_2 (eq)	Temp (°C)	yield (%) 2c	 3c	 4c
1	BuMgBr (4.0)	2.0	3	25	47	0	25
2[a)]	BuMgBr (4.0)	2.0	6	25	14	25	2[b)]
3	BuMgBr (4.0)	2.0	6	-18 ~ -12	<5	33	23
4	BuLi (2.5)	1.3	3	25	10	14	11

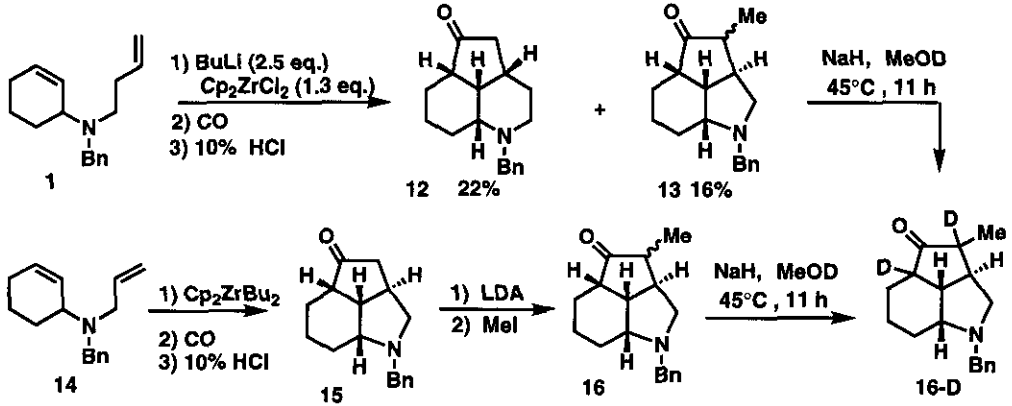
To a THF solution of zirconacycles prepared from Cp_2ZrCl_2 and Bu-Metal in the presence of 1 at -78 °C and gradually warmed to room temperature, was added a THF solution of iodine followed by quenching with 10% HCl.
a) Quenching with 10% DCl b) The product was 4d.



Scheme 4

Subsequently, the insertion of carbon monoxide into the zirconacycle was carried out. A solution of zirconacycle generated from **1**, BuLi (1.3 eq.), and Cp_2ZrCl_2 (2.5 eq.), was stirred under carbon monoxide (1 atm.) at room temperature to afford the tricyclic ketones (**12**) and (**13**) in 22% and 16% yields, respectively. However, we are very surprized to find that none of the carbonylated product was obtained when the zirconacycle, prepared from Cp_2ZrCl_2 (1.3 eq.) and BuMgBr (2.5 eq.), was treated with carbon monoxide.

The stereochemistry of **13** (namely **4a**) was determined as follows: **13** was treated with NaH in MeOD at 45 °C for 11 h to give **16-D**. A tricyclic ketone (**15**),[5] which was prepared from the diene (**14**) and Cp_2ZrBu_2 followed by treatment with carbon monoxide, was treated with LDA and MeI to give compound (**16**). Treatment of compound (**16**) with NaH in MeOD at 45 °C for 11 h gave compound (**16-D**), whose spectral data agreed with those of compound (**16-D**) obtained from the ketone (**13**). Thus, the stereochemical configurations of **10**, **4** and **13** were confirmed: The ring junction protons of the two six and five membered rings are *cis* and those of the five and five membered rings are *trans*.



Scheme 5

The zirconocene-promoted cyclization reaction is a useful synthetic method for the synthesis of perhydroquinoline derivatives. Further studies are in progress.

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