Ring Construction by Zirconium-promoted Reductive Coupling of Nitriles with Alkenes

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Intramolecular reductive coupling of nitrile with alkene units in the presence of zirconocene prepared from $(C_5H_5)_2ZrCl_2$ and BuLi gives cyclic ketones; the intermediary metallacycle prepared from the 2-cyano-*N*-allylaniline derivative is very reactive and provides various quinoline derivatives by treatment with electrophiles and other reagents.

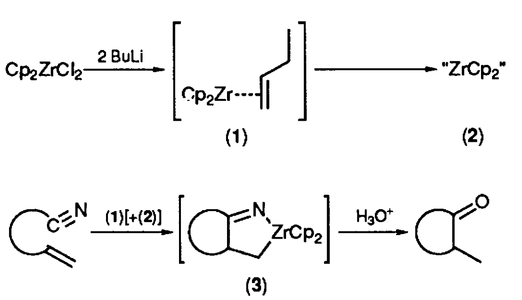
Reductive coupling of two unsaturated molecules by use of a low-valent transition metal is an interesting field in synthetic organic chemistry. A new carbon–carbon bond is formed and the intermediary metallacycle can then be used in further reactions. Zirconocene is quite effective[1] and the reductive coupling of unsaturated molecules such as alkynes, alkenes[2a] and imines[2b] has been reported. We report the intramolecular reductive coupling of nitrile[3] and alkene units *via* the metallacycle, (**3**), by use of low-valent zirconocene as shown in Scheme 1.

To a tetrahydrofuran (THF) solution of zirconocene (**1**) [+(**2**)] (1.2 mol equiv.) prepared from Cp_2ZrCl_2 ($Cp = C_5H_5$) and BuLi[4] was added a solution of nitrile (**4**) in THF at −78 °C. The solution was stirred at 50 °C for 5 h under an argon

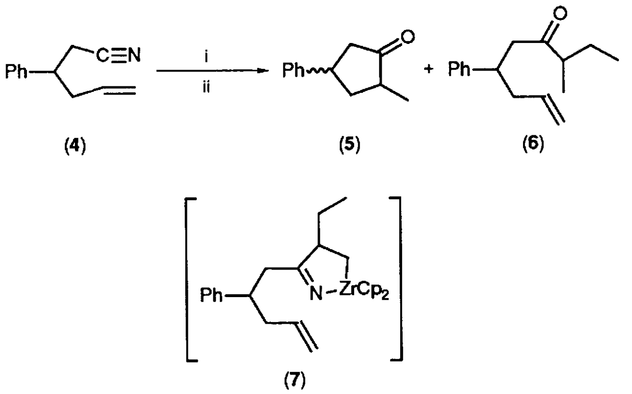
Table 1. Reaction of (**8a**) with (**1**)[+(**2**)] under various conditions.

Run No.	$ZrCp_2$/ mol equiv.	Ligand	T/°C	t/h	Yields (%)[a] (**9a**)	(**9c**)	(**10**)	(**11**)	(SM)
1	1.2	—	50	3	54	—	—	—	31
2	2.2	—	r.t.	13	11	—	18	10	—
3	1.2	PPh_3	50	1.5	60	—	—	—	—
4	2.2	PPh_3	r.t.	14	30	21	9	7	—

[a] Isolated yields: SM = starting material; r.t. = room temperature.

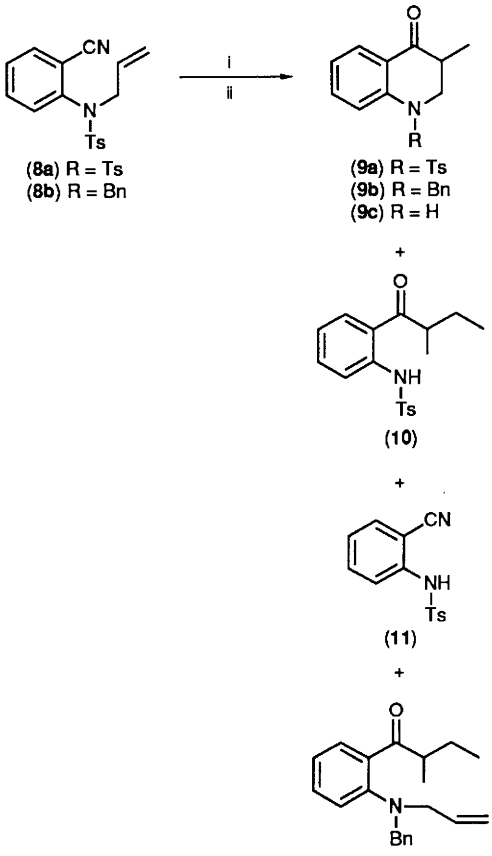


Scheme 1



Scheme 2. i, (**1**)[+(**2**)]; ii, H_3O^+.

atmosphere. Hydrolysis of the reaction mixture with 10% HCl afforded the five-membered cyclic ketone (**5**) in 34% yield together with ketone (**6**) (8% yield). Compound (**6**) is assumed to be derived from the metallacycle (**7**) produced by intermolecular coupling between the nitrile group of (**4**)§ and compound (**1**). The yield of cyclic ketone (**5**) could not be improved because the acidic proton of the nitrile disturbs the reaction under the reaction conditions. Treatment of nitrile (**8a**) with zirconocene (1.2 mol equiv.) in a similar manner, leads to the desired quinoline derivative (**9a**) in 54% yield together with deallylated product (**11**) (See Table 1, Run 1). However, the use of excess of zirconocene (2.2 mol equiv.) afforded a small amount of the desired compound (**9a**) (11%) together with ketone (**10**) (18%) and (**11**) (10%). The yield was slightly improved in the presence of PPh_3 (2.2 mol equiv.) as ligand (Run 3) and the excess of zirconocene co-ordinated to PPh_3 afforded the detosylated product (**9c**) (Run 4). Presumably, electron transfer from zirconocene to the sulphonyl group of (**9a**) occurs to give (**9c**). The reaction of nitrile, (**8b**), with zirconocene at 0 °C for 15.5 h led to the cyclized product (**9b**) in 54% yield together with ketone (**12**) (9%).



Scheme 3. i, (**1**)[+(**2**)]; ii, H_3O^+. Ts = p-$MeC_6H_4SO_2$; Bn = $PhCH_2$.

Zirconacycle (**13**) prepared from (**8a**) and zirconocene (**1**) [+(**2**)] *in situ* was treated with 10% DCl, which afforded (**14**) in 33% yield. By using the reactivity of the zircono–imine bond, reduction with $LiAlH_4$ followed by acetylation was carried out to give 4-acetamidotetrahydroquinoline derivatives (**15**) (R = H) and (**15'**) (R = H) (E:Z = 3:2) in 40% yield; stereochemical assignments were deduced from the NMR spectra.† Reduction of (**13**) with $LiAlD_4$ afforded (**15**) (R = D) and (**15'**) (R = D) in 54% yield. The zircono–imine bond can also be reduced with excess of di-isobutylaluminium

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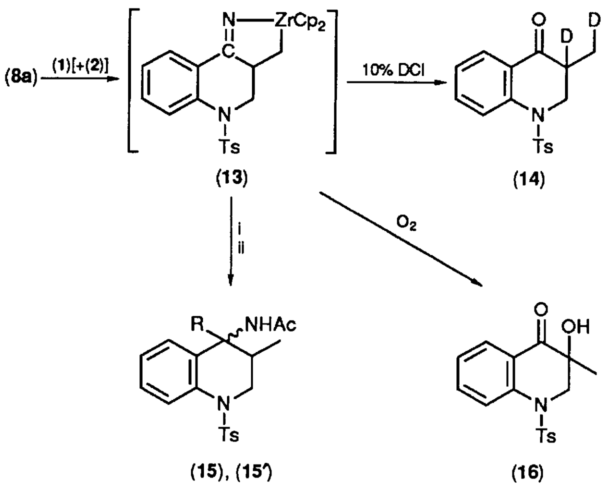
† (**15**) (E): NMR ($CDCl_3$-CD_3OD) δ 0.97 (d, J 7.0 Hz, 3 H), 1.76—2.08 (m, 1 H), 1.96 (s, 3 H), 2.42 (s, 3 H), 3.38 (dd, J 9.6, 14.5 Hz, 1 H), 4.08 (dd, J 4.0, 14.5 Hz, 1 H), 4.88 (d, J 8.7 Hz, 1 H, 4-H), 6.96—7.80 (m, 8 H). (**15'**) (Z): 0.92 (d, J 6.8 Hz, 3 H), 1.52—2.08 (m, 1 H), 1.84 (s, 3 H), 2.40 (s, 3 H), 3.16 (dd, J 11.2, 14.0 Hz, 1 H), 3.98 (dd, J 4.5, 14.0 Hz, 1 H), 5.00 (d, J 5.0 Hz, 1 H, 4-H), 6.96—7.98 (m, 8 H).



Scheme 4. i, Reducing reagents; ii, Ac_2O; Py.

hydride (DIBAL) followed by acetylation to give the same compounds (**15**) (R = H) and (**15′**) (R = H) (27%, *E*:*Z* = 2:1). A THF solution of metallacycle (**13**) was stirred under O_2 at room temperature for 45 h and provided the hydroxylated compound (**16**) (33%).‡ The results indicate that the zirconium–carbon bond of metallacycle (**3**) can be functionalised by treatment with electrophiles and the zircono–imine bond can be used in further reactions.§

This is the first example[5] of zirconium-promoted intramolecular reductive coupling of an aromatic nitrile with an internal alkene. Various quinoline derivatives can be obtained by use of the carbon–zirconium bond and the zircono–imine bond of the intermediary metallacycle (**3**).

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5 We noticed one example of intramolecular reductive cyclization of nitrile with an alkyne rather than an alkene. Namely, 1-cyanohept-5-yne treated with zirconocene affords metallacycle. However, the yield was not reported: P. J. Fagan and W. A. Nugent, *J. Am. Chem. Soc.*, 1988, **110**, 2310.

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‡ The reaction mechanism for the formation of (**16**) is unclear. Presumably, the enamino-form of metallacycle (**13**) reacts with O_2.

§ Satisfactory elemental analyses or high resolution mass spectra and spectroscopic data were obtained for all new compounds.