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# Synthesis of Cyclopentylamines using Zirconium Chemistry

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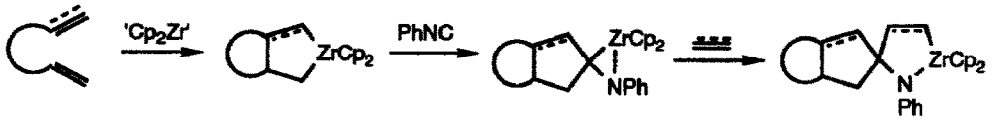
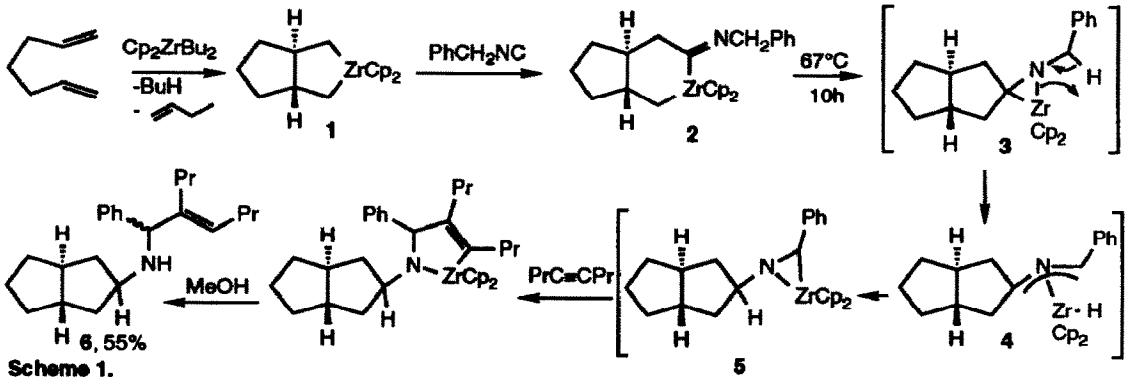
**Abstract.** Insertion of alkyl or trialkylsilyl isocyanides into zirconacyclopentanes gives iminoacyl complexes which rearrange to zirconocene $\eta^2$-imine complexes on heating. These may insert alkynes to give 1-vinyl-1-cyclopentylamines on work up, or decomplex the zirconium to afford, after hydrolysis, cyclopentanones. With benzyl isocyanide 1,2-migration of the $\eta^2$-imine complexes occurs before quenching.

We recently reported[1] that insertion of phenyl isocyanide into various zirconacyclo-pentanes and -pentenes derived from the intramolecular co-cyclisation of 1,n-dienes and enynes[2] was followed by rearrangement to afford zirconocene $\eta^2$-imine complexes[3] (Eq. 1). These reactive intermediates inserted a range of unactivated alkenes and alkynes to afford elaborated systems on work-up. The main drawback of this method as a tool in organic synthesis was the restriction to the production of anilines. We now report our investigations aimed at removing this limitation.

Eq. 1.



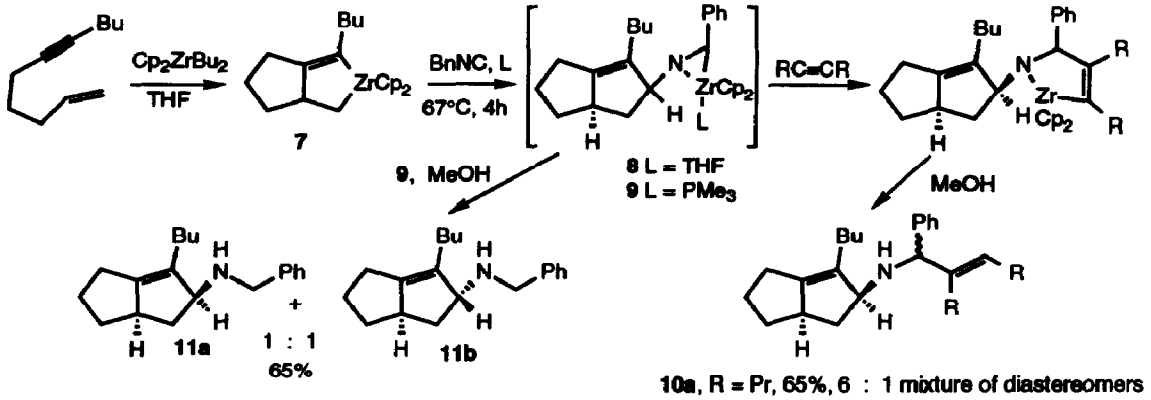

The ideal alternative to phenyl isocyanide in the transformations described in Eq. 1 seemed to be benzyl isocyanide since reductive removal of the benzyl group from the products could afford primary amines. To this end benzyl isocyanide was added to the saturated zirconacycle **1**, prepared *in-situ* from the 1,6-diene and




**Scheme 1.**

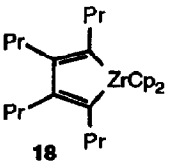
dibutylzirconocene[4] in THF, to give the iminoacyl complex **2**. Warming to 67°C for 15h in the presence of 4-octyne gave a clean conversion to a new complex which on protic work-up afforded not the product of insertion into the expected $\eta^2$-imine complex **3**, but **6**[5] derived from the $\eta^2$-imine complex **5**. The formation of **5** can be accounted for by a 1,3-hydride shift from the first formed $\eta^2$-imine complex **3** *via* a zirconocene 2-azaallyl hydride species[6] **4** (Scheme 1).

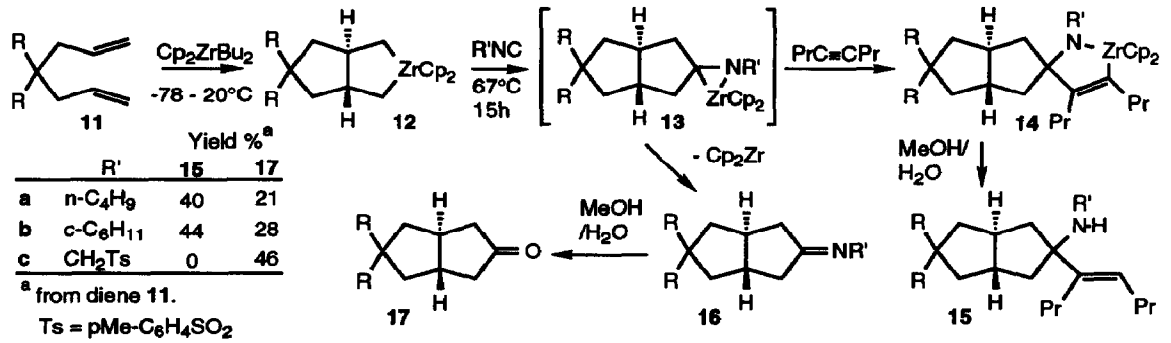
The insertion of benzyl isocyanide into the bicyclic zirconacyclopentene **7** followed by trapping with 4-octyne and protonolysis gave the product **10a** also derived from a 1,2-rearrangement of the expected $\eta^2$-imine complex. **10a** was obtained as a 6 : 1 mixture of diastereomers[7] whereas with 2-butyne as the trap the diastereoselectivity was 9 : 1. Surprisingly when the isolated $PMe_3$ adduct of the $\eta^2$-imine complex **9** was quenched with water **11** is obtained as a 1:1 mixture of diasteromers - a lack of stereoselectivity which is we cannot explain.




**Scheme 2.** Bn = $CH_2Ph$

The successful insertion / rearrangement of benzyl isocyanide, though not giving the desired products, demonstrated that a phenyl substituent on the nitrogen is not necessary for the rearrangement of iminoacyl to $\eta^2$-imine complexes. The benzylic nature of the hydrogen which was transferred probably accelerates the 1,2-migration of the $\eta^2$-imine complex so we next examined n-butyl- and cyclohexyl-isocyanides. Much to our delight reaction of the zirconacycle **12** with these isocyanides in the presence of 4-octyne gave the adducts **15** resulting from insertion into the first formed $\eta^2$-imine complexes (Scheme 3). A new complication was the formation of substantial amounts of the ketone **17** as a by-product, presumably arising by hydrolysis of the imine **16**. **16** is formed by transfer of the $Cp_2Zr$ moiety from **13** to 4-octyne, eventually giving the zirconacyclopentadiene **18**. Since '$Cp_2Zr$' is the active species in the initial co-cyclisation of **11** to give **12** this implies that a catalytic




| | R' | Yield %[a] 15 | 17 |
|---|---|---|---|
| a | n-$C_4H_9$ | 40 | 21 |
| b | c-$C_6H_{11}$ | 44 | 28 |
| c | $CH_2Ts$ | 0 | 46 |

[a] from diene **11**.

Ts = pMe-$C_6H_4SO_2$

**Scheme 3.** R,R = -$CH_2OC(CH_3)_2OCH_2$-

process should be possible. Buchwald has recently demonstrated an analogous titanocene catalysed co-cyclisation of enynes in the presence of isocyanides[8]. The easily handled, crystalline, tosylmethyl isocyanide gave only the ketone **17** and none of the 'inserted' product **15c** despite the presence of 4-octyne.

*Acceleration of the iminoacyl - $\eta^2$-imine interconversion by methanol.* A remarkable observation was that when the iminoacyl complex **19** derived from insertion of cyclohexyl isocyanide into **12** was quenched at room temperature by the addition of methanol followed by aqueous work-up the sole product isolated was the cyclised amine **20** (Eq. 2). This presumably arises from protonation of the $\eta^2$-imine complex **13b** despite that fact that **19** shows no reaction with 4-octyne after 48 h at room temperature. We would expect[9] protonation of **13b** to be much faster than of the iminoacyl complex **19** but simple displacement of a rapid equilibrium is unlikely. The methanol probably acts as a general-acid catalyst for the rearrangement.[10] We have already reported[1a] that the iminoacyl complex derived from **12** and *tert*-butyl isocyanide does not rearrange to an $\eta^2$-imine complex even under forcing conditions, but does yield the ketone **17** on work-up with *tert*-butyl hydroperoxide.

Eq. 2 **12** —(CyNC, THF, r.t., 1h; Cy = c-$C_6H_{11}$)→ **19** —(i. MeOH, ii. $H_2O$, 73%)→ **20**

*Insertion of trialkylsilyl isocyanide.* Trimethylsilyl cyanide exists in equilibrium with trimethylsilyl isocyanide which may insert into carbon-metal bonds. Recently the reaction with titanacyclopentenes has been used in a synthesis of cyclopentenones[8]. We were delighted to find that exposure of the zirconacycle **12** to $Me_3SiCN$ in the presence of an alkyne gave, on aqueous work-up, a good yield of the primary amine **21** together with small amounts of the ketone **17** (Eq. 3). The use of $^tBuMe_2SiCN$ gave less inserted product and more ketone. Attempts to trap the intermediate $\eta^2$-trimethylsilylimine complex with terminal alkenes failed.

Eq. 3 **12** —(i. $Me_2RSiCN$, $R^1C{\equiv}CR^2$, THF, 67°C, 2h; ii. MeOH, $H_2O$)→ **21** + **17**

| | | | Yield % | |
|---|---|---|---|---|
| R | $R^1$ | $R^2$ | **21** | **17** |
| Me | Pr | Pr | 63 | 8 |
| Me | Me | $SiMe_3$ | 54 | 19 |
| $Bu^t$ | Pr | Pr | 21 | 41 |

*Double insertion of benzyl isocyanide.* Finally reaction of **1** with excess benzyl isocyanide at room temperature followed a quite different course to the reactions described above. Instead of the initial iminoacyl complex rearranging to a cyclopentyl-$\eta^2$-imine complex a second molecule of the isocyanide inserts before ring closure to give the cyclohexenone derivative **23** on work-up[11] (Eq. 4).

Eq. 4 **1** or **12** —(i. 2.5 eq. BnNC, r.t, 4h; ii. 67°C, 4h; iii. MeOH, $H_2O$)→ **22** → **23**

50% : R = H
38% : R,R = -$CH_2OCMe_2OCH_2$-

**Conclusion.**

The insertion of alkyl isocyanides into 3-zircona-bicyclo[3.3.0]octanes provides access to 3-alkylamino-bicyclo[3.3.0]octanes either unsubstituted at the 3-position (quenching the intermediate iminoacyl complex with methanol) or with a 3-vinyl substituent (trapping with an alkyne). The insertion of

trimethylsilyl isocyanide provides an excellent synthesis of primary amine analogues. The extension of this chemistry to monocyclic cyclopentylamines is under investigation. Double insertion of benzyl isocyanide can also occur to give 2-aminocyclohexenones.

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4. $Cp_2ZrBu_2$ is an excellent 'zirconocene ($Cp_2Zr$) equivalent' : Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829-2832. The active reagent is zirconocene(1-butene) formed *in-situ*: Buchwald, S.L.; Watson, B.T.; Huffman, J.C. *J. Am. Chem. Soc.* **1987**, *109*, 2544-2546.

5. All organic compounds were characterised by high field $^1H$ and $^{13}C$ NMR, IR,and Mass spectra, and either HRMS on $M^+$ or microanalysis. All isomers were separated with the exception that the minor isomers of **10a** & **b** were not obtained free of the major. All yields quoted are for isolated compounds, pure by NMR, and are based on the initial 1,6-enyne or -diene.

6. We recently characterised a 1-azaallyl zirconocene hydride analogous to **4** and demonstrated that there was a rapid equilibrium between this and a zirconocene $\eta^2$-imine complex: Coles, N; Harris, M. C. J.; Whitby, R. J.; Blagg, J. *Organometallics* in press. Similar migrations of zirconocene $\eta^2$-alkene complexes have also been reported: Maye, J.P.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 3359-3362.

7. There is good precedent[1b] for the formation of the initial $\eta^2$-imine complex with the zirconium on the *exo*-face. The H transfer from the metal should thus occur from the *exo*-face giving the *endo*-amine though this has not yet been proven.

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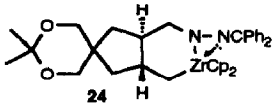
9. Donation of electron density from the iminoacyl nitrogen lone pair to the formally 16e metal centre will slow the rate of hydrolysis, e.g. complex **24** where the exocyclic N is strongly coordinated to the metal takes 8 days at r.t. to complete protonolysis with excess methanol c.f. a few seconds for **1**: T.Luker & R. J. Whitby, unpublished.



**24**

10. Lewis acids ($Me_2AlCl$) are known to induce the rearrangement of acyl- to $\eta^2$-ketone complexes of zirconocene: Waymouth, R.M.; Clauser, K.R.; Grubbs, R.H. *J. Am. Chem. Soc.* **1986**, *108*, 6385-6387.

11. The oxidation state of the quenched product **23** is not that expected from **22**. One explanation is that the '$Cp_2Zr$' moiety decomplexes from the diazadiene before or during the aqueous quench.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