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A Practical Procedure for the Elaboration of Amines *via* Zirconocene η^2-Imine Complexes

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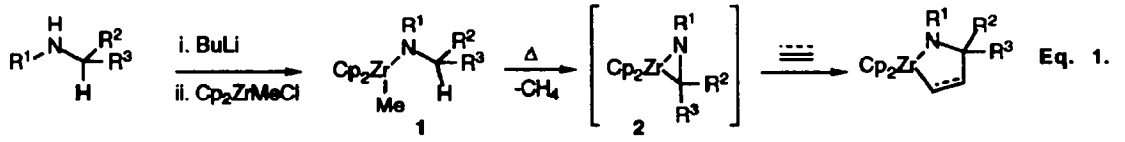
Abstract. Sequential addition of a magnesium amide and methyl magnesium chloride to zirconocene dichloride provides a practical synthesis of zirconocene methyl amides. Thermolysis of these zirconocene complexes in the presence of unactivated alkenes and alkynes gives, on protonolysis, α-alkylated or α-vinylated amines.

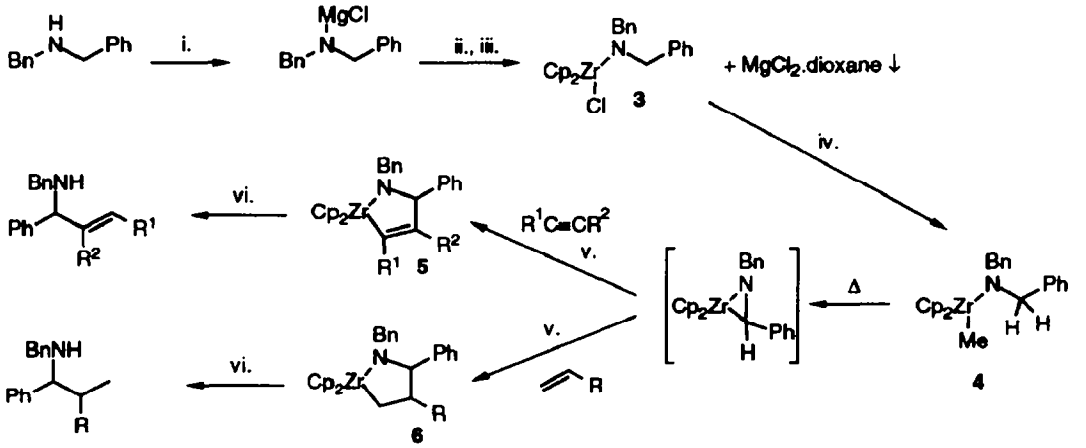
Zirconocene η^2-imine complexes (zirconaziridines) **2** are useful carbometallating reagents for unactivated alkenes and alkynes[1]. When these are formed by β-hydrogen activation of zirconocene methyl amide complexes **1** the overall sequence comprises a useful method for the elaboration of amines (eq. 1). N-Trimethylsilyl- and N-aryl-amines undergo this transformation readily, the facility of the β-hydrogen elimination being greatly enhanced by the reduced basicity of the nitrogen lone pairs with these substrates[1b,c]. Amines which lack this activation, but where the proton to be eliminated is benzylic, may also successfully undergo this transformation[2].



A limitation to the routine use of this chemistry in synthesis is the need for zirconocene methyl chloride as one of the reagents[3]. This is available *via* a two step synthesis[4] but the use of trimethylaluminium, and the requirement for the manipulations to be carried with rigorous exclusion of air, make the preparation inconvenient. We now report the direct *in situ* formation of the required zirconocene methyl amide complexes from commercially available zirconocene dichloride. This chemistry is illustrated with a range of α-aryl and α-heteroaryl amines, trapping the intermediate zirconocene η^2-imine complexes with both alkenes and alkynes - a significant extension in the reported scope of the reaction.

As part of an investigation[1c] into the mechanism of the β-hydrogen activation process **1** - **2** we wished to investigate leaving groups other than methyl on zirconium. This required the preparation of zirconocene chloroamide complexes e.g. **3** as precursors. Whereas those derived from aromatic amines were formed in good yield from zirconocene dichloride and the lithiated amines[1a], the reaction between lithium dibenzylamide and Cp_2ZrCl_2 consistently gave a multitude[5] of products in which the desired complex **3** accounted for only 15 - 30%. Changing to the magnesium salt of the amine gave a remarkably clean reaction -

the required chloroamide **3** being the only new zirconium complex formed, even if a large excess of the magnesium amide and long reaction times were used. This suggested a one-pot preparation of the zirconocene methyl amide **4** by addition of methyl magnesium chloride to the solution of **3** formed as above. Initially results were disappointing, the overall yield of **4** being only 40-50%. Careful examination of the reaction mixture after each stage showed that not all the Cp_2ZrCl_2 was reacting in the first step, and that it was converted to the inert[6] Cp_2ZrMe_2 (consuming MeMgCl) in the second stage. Even using an excess of magnesium dibenzylamide over Cp_2ZrCl_2 and long reaction times left unreacted dichloride suggesting that an equilibrium is set-up. Addition of dioxane (1eq.) and hexane to precipitate the magnesium chloride allowed this equilibrium to be displaced in favour of the required product **3**. Addition of a further equivalent of MeMgCl then gave the wanted zirconocene methyl amide **4** in high yield. It was important to use only 1 equivalent of dioxane in the first step otherwise the second step was inhibited by the formation of unreactive Me_2Mg. Thermolysis of **4** in the presence of a variety of alkynes and alkenes afforded the azametallacycles **5** and **6** and, on aqueous work-up, elaborated benzylamines (Table, entries 1-9)[7]. Generally the yields were as



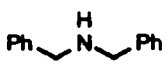
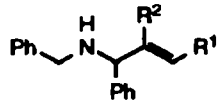
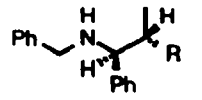
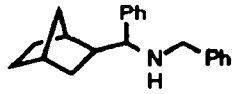
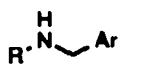
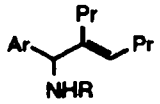
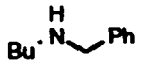
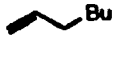
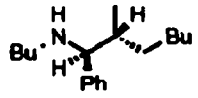
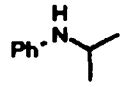
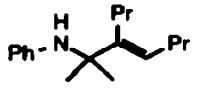
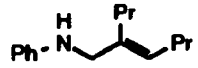
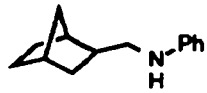
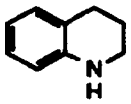
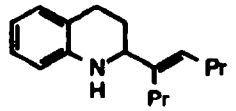
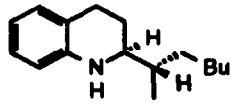
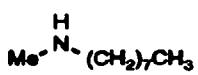
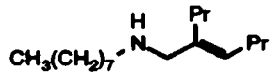
Scheme. *Reagents and conditions:* i. 1 eq. MeMgCl, THF, r.t., 1 h; ii. add to 1 eq. Cp_2ZrCl_2 in THF at -30°C, warm to r.t., 1 h; iii. add hexane (25% by vol.) and 1 eq. dioxane, 14 h, r.t.; iv. 1eq. MeMgCl, -30°C - r.t., 8 h; v. add alkene or alkyne (1.5 eq.), boil under reflux, 15 h; vi. MeOH, r.t.

good as, or better than those previously obtained using zirconocene methyl chloride (i.e. eq. **1**). The excellent regiocontrol obtained with trimethylsilyl- and trimethylstannyl-alkynes (entries 3 & 4) is notable. Terminal alkenes gave reasonable diastereocontrol (entries 5 - 8) although this is not as good as found in other systems[1a,d]. Under the thermolysis conditions used to generate **4** the addition of alkenes to form the azametallacycles **6** is reversible. Initially **6** is formed with >20:1 diastereocontrol but this slowly falls on further heating, the values given in the table being typical for reactions which were heated for 15 h to ensure complete consumption of the starting amide. Higher diastereoselectivities may be obtained at the expense of a slight reduction in yield by heating for only 2 h.

The general procedure developed for dibenzylamine was then applied to a variety of other amines (Table). N-alkyl benzylamines gave exclusively C-H activation on the benzylic side to afford the alkyne and alkene inserted products (entries 10-13 and 18). The use heteroaromatic groups to activate the amine α-proton also worked well (entries 14-16). With a 3-pyridyl substituted amine (entry 16) instability of the magnesium amide[8] caused problems. This was solved by adding MeMgCl rapidly to the amine in THF at 0°C and as soon as bubbling had stopped (≈30s) rapidly (≈10s) transferring the mixture by cannula into a suspension of Cp_2ZrCl_2 in THF at -30°C.

Tetrahydroquinoline (entries 22 & 23) underwent the general procedure well, but simple anilines (entries 19 & 20) gave poor yields. The problem was found to be poor reaction between the N-aryl

Table. Elaboration of amines *via* zirconocene η^2-imine complexes

Entry	Amine	Alkene / Alkyne	Product			Yield (%)[a]	
				R^1	R^2		
1		$R^1C{\equiv}CR^2$		Pr	Pr	78	(53[b])
2				Me	Me	64	
3				$SiMe_3$	$n\text{-}C_5H_{11}$	76	
4				$SnMe_3$	Bu	58	
				R	threo:erythro		
5				$(CH_2)_4CH_3$	14 : 1	71	
6				$(CH_2)_2Ph$	10 : 1	64	
7				$(CH_2)_3OTBDMS$	12 : 1	60	
8				$(CH_2)_3OBz$	8 : 1	49	
9						55	
				Ar	R		
10		PrC≡CPr		Ph	Bu	61	(55[b])
11				Ph	i-Pr	54	
12				p-$MeOC_6H_4$	Pr	64	
13				p-ClC_6H_4	Bu	54	(56[b])
14				2-thiophene	Bu	65	
15				2-furyl	Bu	69	
16				3-pyridyl	Bu	69[d]	
17				2-naphthyl	Bu	34	
18					threo : erythro 14 : 1	64	
19		PrC≡CPr				78[d]	(92[b])
20		PrC≡CPr				72[d]	(80[b])
21						67[d]	
22		PrC≡CPr				73	(85[b])
23						66	(57[c])
24		PrC≡CPr				39[d]	(46[b])

[a] isolated yield based on the amine using the conditions given in the scheme; [b] ref 1c; [c] ref 1a; [d] see text for change in conditions.

magnesium amides and zirconocene dichloride and was overcome by using the lithium amides in the first step. Finally the substrate N-methyloctylamine which lacks activation either on the nitrogen, or of the proton to be eliminated, was tried. By changing the solvent for the thermolysis step to toluene and heating at 110°C for 17 h we obtained a moderate yield of the 4-octyne adduct (entry 24). Attempts to trap with alkenes failed.

In summary, we have developed a convenient access to zirconocene methyl amides from the amine, zirconocene dichloride and methylmagnesium chloride. Thermolysis of these complexes in the presence of alkenes or alkynes affords α-alkylated or -vinylated amines in good overall yields *via* zirconocene η^2-imine complexes. This experimentally simple procedure should encourage wider use of a powerful synthetic method. The successful generation and trapping of a range of zirconocene η^2-imine complexes derived from α-phenyl or α-heteroaromatic alkylamines demonstrates a significant extension in the range of substrates which may be used.

Typical experimental. *N-((E)-1-phenyl-2-propyl-hex-2-enyl)-benzylamine.* To a solution of dibenzylamine (1.18 g, 6 mmol) in THF (6 ml) under argon at room temperature was added dropwise MeMgCl (2 ml of a 3M solution in THF, 6 mmol). After stirring for 1 h this solution was added dropwise to a suspension of Cp_2ZrCl_2 (1.75 g, 6 mmol) in THF (8 ml) at -30°C. The mixture was warmed to room temperature, stirred for 1 h, then hexane (5 ml) and dioxane (0.5 ml, 6 mmol) were added and the resulting heterogenous mixture stirred for 14 h. After cooling to -30°C MeMgCl (2 ml of a 3M solution in THF, 6 mmol) was added dropwise, the solution allowed to warm to room temperature, and stirred for 8 h. 4-Octyne (0.99 g, 9 mmol) was added and the mixture heated under reflux for 15 h, allowed to cool to room temperature, and methanol (2 ml) added. The reaction mixture was poured into water (50 ml), extracted with ether, dried ($MgSO_4$), and the product purified by column chromatography (7% ethyl acetate in light petroleum) and Kugelrohr distillation (120°C, 1 mmHg) to afford the *title amine* as a colourless oil (1.44 g, 78%).

Acknowledgements. We would like to thank Pfizer Central Research, U.K. and the S.E.R.C. for a CASE studentship.

References and Notes

1. Zirconocene η^2-imine complexes by C-H activation: (a) Coles, N.; Whitby, R. J.; Blagg, J. *Synlett* **1990**, 271-272; (b) **1992**, 143-145; (c) Coles, N.; Harris, M.C.J.; Whitby, R. J.; Blagg, J. *Organometallics* in press; (d) Buchwald, S.L.; Watson, B.T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486-4494; (e) Grossman, R.B.; Davis, W. M.; Buchwald, S.L. *J. Am. Chem. Soc.* **1991**, *113*, 2321-2322. By rearrangement of zirconocene iminoacyl complexes: (f) Davis, J. M; Whitby, R. J.; Jaxa-Chamiec, A. *Tetrahedron Lett.* **1992**, *33*, 5655-5658. By ligand exchange: (g) Jensen, M; Livinghouse, T. *J. Am. Chem. Soc.* **1989**, *111*, 4495-4496; (h) Ito, H; Taguchi, T; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 4469-4472.
2. Buchwald reported the formation of a PMe_3 stabilised η^2-imine complex from dibenzylamine (ref 1d). We have reported the formation and trapping with 4-octyne of zirconocene η^2-imine complexes derived from dibenzylamine, $pXC_6H_4CH_2NHBu$ (X = Cl, OMe, CH_3), dibutylamine, and methyloctylamine as part of a mechanistic study (ref 1c).
3. Reaction of Cp_2ZrCl_2 with ^tBuLi affords, after rearrangement, $Cp_2Zr(^iBu)Cl$ which may be used *in situ* as a $Cp_2Zr(Me)Cl$ replacement: Buchwald, S.L.; Watson, B.T.; Barr, K.J. *Tetrahedron Lett.* **1991**, *32*, 5465-5468.
4. Wailes, P.C.; Weigold, H.; Bell, A.P. *J. Organomet. Chem.* **1971**, *33*, 181.
5. We believe that this is due to deprotonation of one of the cyclopentadienyl rings by the strongly basic reagents although hydride transfer from the lithiated amine is also possible.
6. Reaction of Cp_2ZrMe_2 with R_2NMgCl did not result in the formation of $Cp_2Zr(Me)(NR_2)$ unlike the analogous metathesis with RMgX: Takahashi, T.; Nitto, Y.; Saburi, M; Negishi, E. *Chem. Lett.* **1990**, 2259-2262.
7. All organic products were characterised by high field ^1H and ^{13}C nmr, IR, mass spectra, and either HRMS on the amine or microanalysis of the HCl salts.
8. It is likely that the product of kinetic deprotonation - the magnesium amide - rearranges to the more stable anion where the 'benzylic' proton has been removed.

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