Pergamon

Tetrahedron Letters, Vol. 38, No. 13, pp. 2335-2338, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00308-0

Zirconium-Catalysed Enantioselective 2-Aluminoethylalumination of Alkenes.

Graham Dawson, Charles A. Durrant, George G. Kirk and Richard J. Whitby*

Department of Chemistry, The University, Southampton, SO17 1BJ, U. K.

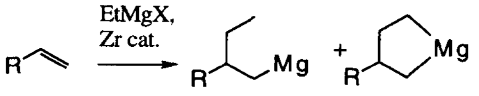
Raymond V. H. Jones and Michael C. H. Standen

Zeneca Fine Chemicals Manufacturing Organisation, Grangemouth, Stirlingshire, FK3 8XG, U. K.

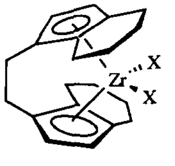
Abstract: Asymmetric 2-aluminoethylalumination of mono-substituted alkenes and 2,5-dihydrofurans catalysed by (R,R)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)zirconium (R)-1,1'-binaphth-2,2'-diolate **4** and η^5-cyclopentadienyl-η^5-(1-neomenthyl-4,5,6,7-tetrahydroindenyl)zirconium dichloride **5**. gave 30 - 99% enantiomeric excesses. The so formed organoaluminium has potential for further elaboration leading to enantiomerically enriched products. © 1997 Elsevier Science Ltd.

The zirconium catalysed ethylmagnesiation of alkenes (**Eq. 1**, product **1**) is a useful method for carbon-carbon bond formation.[1,2] Recently the enantioselective ethylmagnesiation reaction catalysed by Brintzingers ethylene-1, 2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)zirconium dichloride ([ETBHI]$ZrCl_2$) **3**[3] and the cheap and easily synthesised η^5-cyclopentadienyl-η^5-(1-neomenthyl-4,5,6,7-tetrahydroindenyl)zirconium dichloride **5**[4] were reported.[5,6] Unfortunately, apart from a small number of exceptional cases, the carbomagnesiation reaction is limited to the addition of an ethyl group.

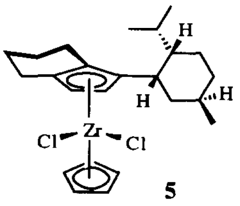
In certain cases the dicyclopentadienylzirconium dichloride catalysed addition of diethylmagnesium to alkenes gives mainly the 1,4-magnesium product **2** (2-magnesioethylmagnesiation),[1,7] a potential means to introduce more complex fragments. Unfortunately, even under conditions previously optimised for the formation of **2** the chiral catalysts **4** and **5** gave only the ethylated product **1**. Dzhemilev has shown that zirconocene dichloride catalysed addition of triethylaluminium to alkenes gives aluminacyclopentanes, and has reported several useful elaborations of them.[8] Negishi has reported the asymmetric alkylalumination of alkenes in good enantioexcesses by a fundamentally different mechanism to the reactions described below.[9] Herin we report an enantioselective 2-aluminoethylalumination of alkenes and hence potential access to a wide variety of enantiopure fine chemicals.



Eq. 1 **1** **2**

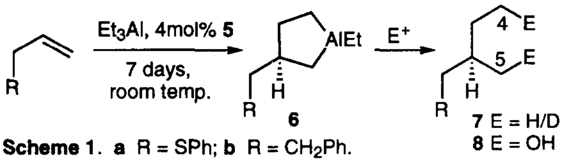


3 X = Cl
4 X,X = (R)-BINOL



5

Reaction of allylphenylsulphide with triethylaluminium (3 equiv., 1.0M concentration) in hexane using 4 mol% of **5** as the catalyst was slow, but gave a good yield of phenyl(2-methylbutyl)sulphide **7a** on protic work-up. The enantiomeric excess of **7a** was determined as 64% by chiral g.c. on a FS Hydrodex-β-3P column.[10] We were pleased to find that quenching with D_2O gave good incorporation of deuterium at both C4 and C5 proving that the aluminacycle **6a** (or a 1,4-dialuminium reagent) had been formed. Ethylation of 4-phenyl-1-butene under the same conditions also went to completion but we could not assay the enantiomeric excess of the protonated product. Work-up with oxygen gave the 1,4-diol **8b** in good yield demonstrating that the aluminacycle **6b** had been formed, but with only 30% enantiomeric excess (hplc on chiralcel® OD-H).

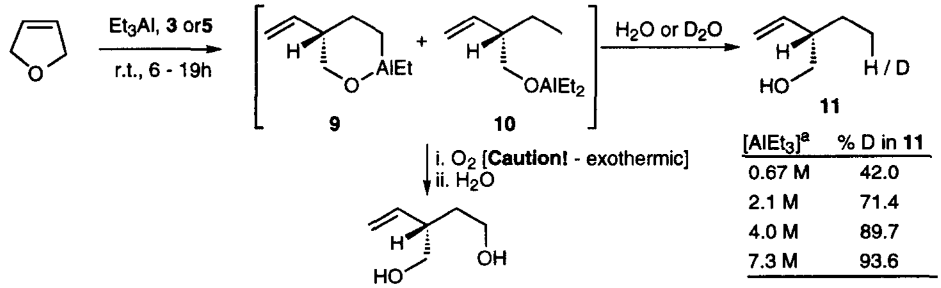


Scheme 1. **a** R = SPh; **b** R = CH2Ph.

R	E^+	E	Yield (%)	e.e. (%)
SPh	H_2O	H	76	64
SPh	D_2O	D	71[a]	62
CH_2Ph	O_2	OH	69	30

a - 100% D at C5; 84% D at C4.

Ethylmagnesiation of 2,5-dihydrofuran catalysed by **3**[6] or **5**[5] gives 2-ethyl-3-buten-1-ol **11** in excellent enantiomeric excesses, the initial carbometallation of the alkene being followed by elimination. Examination of the corresponding reaction with triethylaluminium showed that with **5** 2-aluminoethyl-alumination was the major pathyway giving the organoaluminium compound **9** together with the ethylated product **10**. Quenching with D_2O allowed the relative amounts of **9** and **10** to be measured, and it was found that increasing the concentration of triethylaluminium increased the percentage of **9** (**Scheme 2**). With neat triethylaluminium excellent deuterium incorporation (94%) was obtained. Under these conditions quenching with water gave (S)-2-ethyl-3-buten-1-ol in reasonable yield, and good enantiomeric excesses (**Table 1**). Work-up with oxygen gave the trifunctionalised chiral compound **12** in good isolated yield and enantiomeric excess. Brintizngers catalyst **4** gave excellent e.e.'s in the carboalumination, but the deuterium incorporation in **11** was poor, and hence the yield of diol **12**.



$[AlEt_3]^a$	% D in 11
0.67 M	42.0
2.1 M	71.4
4.0 M	89.7
7.3 M	93.6

[a] Using **5** as catalyst.

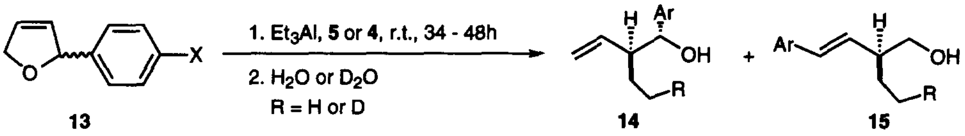
Scheme 2

Table 1. Asymmetric Zirconium Catalysed 2-Aluminoethylalumination of 2,5-Dihydrofuran[a].

		Using 5 as catalyst		Using 4 as catalyst	
Quench	Product	Yield (%)	e.e. (%)[c]	Yield (%)	e.e. (%)[c]
H_2O	11	67[b]	90	90[b]	>99
D_2O	11	67[b] (94% D[d])	85	90[b] (67% D[d])	>99
O_2	12	68[e]	90	45[e]	99

a. conditions: 5 mol% 4 or 2 - 4 mol% 5, 3 equivalents of Et_3Al, no solvent, room temp., 6-19 h; b. yield calculated by GC analysis with an internal standard; c. e. e. determined by GC analysis: 11 on a chiraldex B-TA column and 12 as its bis-trifluoroacetate derivative on FS-Hydrodex-β-P; d. deuterium incorporation determined by ^{13}C NMR; e isolated yield.

In order to extend the scope of the asymmetric 2-aluminoethylalumination reaction we applied the optimised conditions to the substituted dihydrofurans **13a** and **13b**. As shown in **Scheme 3** two products (**14** and **15**) may be formed depending on the regiochemistry of the initial carbometallation. With a chiral zirconium catalyst the enantiomers of the racemic starting material give predominantly different products (kinetic resolution) yielding enantiomerically enriched compounds **14** and **15**.[5,11] The chiral catalyst **5** gave moderate to high enantiomeric excesses of both **14** and **15** (**Table 3**). Furthermore, reactions quenched with D_2O showed moderate to good incorporation of deuterium on the methyl group. Carboaluminations carried out in the presence of (EBTHI)Zr(BINOL) **4** (**Table 3**, entries 4-8) gave high yields and excellent enantiomeric excesses, but when quenched with D_2O deuterium incorporation was disappointingly low.



Scheme 3. a X = H; **b** X = F.

Table 3: Zirconium-Catalysed Kinetic Resolution of 2-Substituted 2,5-Dihydrofurans[a].

			14[b]		15	
Entry	Ar	Quench	Yield(%)	e.e.(%)[d]	Yield(%)	e.e.(%)[e]
			Reactions using catalyst **5**			
1	C_6H_5	H_2O	45[c]	84	50[c]	65
2	C_6H_5	D_2O	22; 53%D[f]	81	28; 84%D[f]	72
3	*p*-F-C_6H_5	H_2O	32[c]	81	40[c]	65
4	*p*-F-C_6H_5	D_2O	40; 70%D[f]	82	46; 71%D[f]	64
			Reactions using catalyst **4**			
5	C_6H_5	H_2O	32	97	39	>99
6	C_6H_5	D_2O	37; 0%D[f]	97	40; 33%D[f]	>99
7	*p*-F-C_6H_5	H_2O	31	96	34	99
8	*p*-F-C_6H_5	D_2O	35; 0%D[f]	96	36; 30%D[f]	99

a. Reaction conditions: 4-5mol% Zr catalyst, 3-4equiv. Et_3Al, r.t., 24-48h; b. 100% *anti* isomer was obtained; c. yield based on recovered starting material; d. e.e. calculated using GC FS Hydrodex β-3p column; e. e.e. calculated using hplc - Chiralcel® OB-H column; f. Deuterium incorporation calculated using ^{13}C NMR analysis.

Conclusion

We have shown that the 2-aluminoethylalumination of alkenes may be catalysed enantioselectively using chiral zirconium catalysts, particularly the recently developed complex **5**. The potential for elaboration of the carbon-aluminium bond(s) in the products make this a versatile route to chiral fine chemicals. Notable is the preparation of (S)-3-hydroxymethyl-4-penten-1-ol.

Acknowledgements

We thank Zeneca Fine Chemicals Manufacturing Organisation for a studentsip (CAD), and the EPSRC for postdoctoral support (Catalysts and Processes Initiative grant GR/K71127 and ROPA grant GR/K63108).

REFERENCES AND NOTES

1. Lewis, D. P.; Muller, P. M.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron Lett.* **1991**, *33*, 6797. Lewis, D. P.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron* **1995**, *51*, 4541.
2. Dzhemilev, U. M.; Ibragimov, A. G.; Zolotarev, A. P.; Mulukhov, R. R.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR Ser. Khim.* **1989**, *38*, 207. Dzhemilev, U. M.; Sultanov, R. M.; Gaimaldinov, R. G.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR Ser. Khim.* **1990**, *12*, 2831. Dzhemilev, U. M.; Ibragimov, A. G. *J. Organomet. Chem.* **1994**, 4661. Dzhemilev, U. M. *Tetrahedron* **1995**, *51*, 4333; Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266. Rousset, C. J.; Negishi, E. I.; Suzuki, N.; Takahashi, T. *Tetrahedron Lett.* **1992**, *33*, 1965. Houri, A. F.; Didiuk, M. T.; Xu, Z. M.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6614. Hoveyda, A. H.; Xu, Z. M.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950; Hoveyda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z. M. *J. Am. Chem. Soc.* **1992**, *114*, 6692; Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079.
3. Racemic (EBTHI)$ZrCl_2$ was prepared by the method of Brintzinger (Wild, F. W. R. P.; Wasiuciomek, M.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.*, **1985**, *288*, 63) and resolved (to give (EBTHI)Zr(BINOL) **4**) by the method of Buchwald: Grossman, R. B.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.*, **1991**, *113*, 2321.
4. Jones, R. V. H.; Standen, M. C. H.; Whitby, R. J.; Bell, J. L. International patent WO 96/25420, publication date 22.08.96.
5. Bell, L.; Whitby, R. J.; Jones, R. V. H.; Standen, M. C. H. *Tetrahedron Lett.* **1996**, 37, 7139.
6. Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.*, **1993**, *115*, 6997. Didiuk, M. T.; Johannes, C. W.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.*, **1995**, *117*, 7097. (d)
7. Dzhemilev, U. M.; Sultanov, R. M.; Gaimaldinov, R. G.; Muslukhov, R. R.; Lomakina, S. I.; Tolstikov, G. A. *Bull. Russ. Acad. Sci., Div. Chem. Sci.* **1992**, *41*, 770. Dzhemilev, U. M.; Sultanov, R. M.; Gaimaldinov, R. G. *J. Organomet. Chem.* **1995**, *491*, 1.
8. Dzhemilev, U. M.; Ibragimov, A. G.; Zolotarev, A. P.; Muslukhov, R. R.; Tolstikov, G. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1990**, *39*, 2570. Dzhemilev, U. M.; Ibragimov, A. G. *J. Organomet. Chem.* **1994**, *466*, 1.
9. Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.*, **1995**, *117*, 10771. Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577.
10. Analysis of enantiomeric excesses were carried out on a Hewlett-Packard 6890 g.c. or HP 1050 h.p.l.c using ChemStation software to analyse peak sizes. The following chiral columns were used. G.c.: FS-Hydrodex-β-3P (Machery-Nagel) and Chiraldex™ B-TA (Astec). H.p.l.c: Chiralcel® OB-H and OD-H (Diacel). Absolute stereochemistries of the major enantiomers are as shown, proven by comparison with authentic samples, except for **8b** which was not proven.
11. Visser, M. S.; Hoveyda, A. H. *Tetrahedron*, **1995**, *51*, 4383.

(*Received in UK* 22 *January* 1997; *revised* 13 *February* 1997; *accepted* 14 *February* 1997)