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Catalytic Asymmetric Carbomagnesiation of Unactivated Alkenes. A New, Effective, Active, Cheap and Recoverable Chiral Zirconocene.

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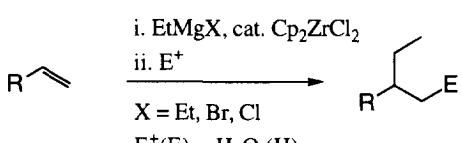
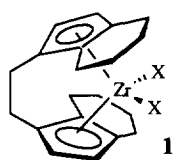
Abstract: The ethylmagnesiation of terminal alkenes catalysed by (*R,R*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)zirconium (*R*)-1,1'-binaphth-2,2'-diolate gave low turnovers and enantioexcesses. A novel C_1 symmetric zirconocene dichloride CpCp'$ZrCl_2$ (Cp = C_5H_5, Cp' = 1-neomenthyl-4,5,6,7-tetrahydroindenyl) was prepared which gave better enantioselectivity, is cheaper to make, catalytically more active, and recoverable. Copyright © 1996 Elsevier Science Ltd

The search for reactions which may be catalysed by chiral transition metal complexes to yield non-racemic products is an important goal . We,[1] and others[2,3] have explored the zirconocene catalysed ethylmagnesiation of unactivated alkenes originally noted by Dzhemilev[4] (**Eq. 1**). Many closely related reactions catalysed by zirconocene dichloride have also been described recently.[5] Herein we report our efforts to induce asymmetry in the carbomagnesiation reaction culminating in the design and synthesis of novel chiral complexes and useful enantioinductions.

The most widely used[6,7,8] chiral zirconocene is the C_2-symmetric ethylenebis(tetrahydroindenyl)zirconocene dichloride **1** first reported by Brintzinger.[9] We synthesised the racemic complex[9] and kinetically resolved it using (R)-2,2'-dihydroxy-1,1'-binapthol.[10] It was convenient to store and use the complex as the binol adduct **2** as this proved to be an active catalyst for the ethylmagnesation reaction of terminal alkenes.[11] Reasonable conversion of substrate generally required 10 mol% of **2** (c.f. 2% of Cp_2ZrCl_2) and the enantiomeric excesses obtained were consistently around 27% (**Table 1**).[12] The high cost of the synthesis of **2**, its low activity and poor enantioselectivity led us to investigate alternatives. Several other literature zirconocenes were tried,[13] but it became clear that we faced a general problem in asymmetric induction - a trade-off between enantioselectivity and catalytic activity - and a new class of chiral zirconocenes was needed.

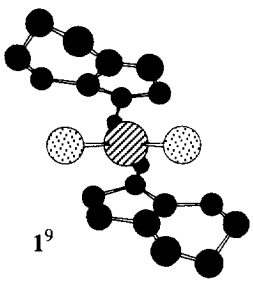
Eq. 1





1 X = Cl
2 X,X = (R)-BINOL

A reasonable model for enantioinduction using the Brintzinger catalyst **1** is shown in **Fig 1** where the alkene may, by virtue of the C_2 symmetry of the complex, approach from either side of the proposed zirconacyclopropane intermediate in the ethylmagnesiation. Interaction of the alkene substituent with the 6-membered ring favours the orientations shown, and hence chiral induction. In order to provide greater flexibility in the design of new complexes we chose a C_1-symmetric model (**Fig 2**) where the alkene may only approach from one side, enantioinduction again being provided by interaction between the 'roof' and alkene substituent. By combining the two control elements required to induce asymmetry in one cyclopentadienyl ligand we allow the use of an unsubstituted cyclopentadienyl ring as the other in the hope of regaining some of the catalytic activity of the parent system.



1[9]

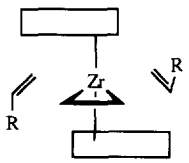


Fig. 1

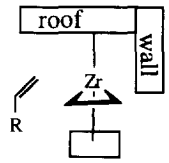
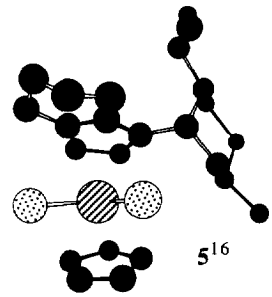


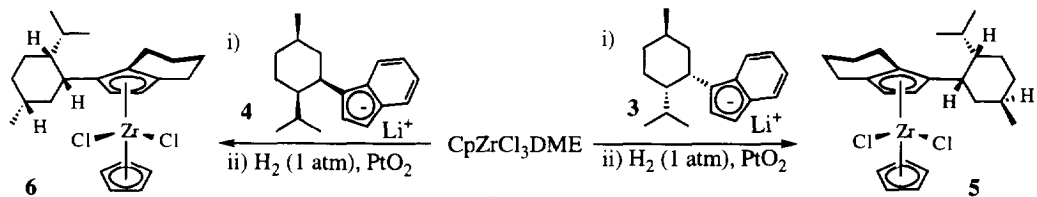
Fig. 2



5[16]

One feature of **1** which we felt important to retain was the planar chirality of the non-symmetrically substituted cyclopentadiene bound to the metal. To avoid a resolution step in the synthesis of the new complexes the planar chirality should ideally be induced from a chiral substitutent. The 1-neomenthylindene ligand **3** reported by Erker[14] is an important advance since in the lowest energy rotomer about the indenyl-neomenthyl bond the isopropyl substituent partially blocks one enantioface of the indene leading to face-selective metallation.[14] The side chain chirality thus induces planar chirality on complexation. Isoneomenthylindene **4** works similarly, although with lower selectivity.

Reaction of the lithium neomenthylindene **3** with cyclopentadienylzirconium trichloride dimethoxyethane complex[15] followed by hydrogenation gave the novel complex **5**[16] as a single diastereomer in 25 - 35% yield after recrystallisation from toluene (the crude product contained a 6 : 1 ratio of diastereomers). Lithium isoneomenthyindene **4** reacted similarly to afford **6** (30-35% yield). In **5** the menthyl ring provides the wall, and the reduced ring from the indene the 'roof' of our model (**Fig 2**). In **1** the orientation of the tetrahydroindenyl ligands are fixed by the ethylene bridge. In **5** the substituted tetrahydroindenyl ligand adopts the particular orientation shown in the X-ray structure (above) since it minimises steric interactions with the unsubstituted cyclopentadienyl ligand.

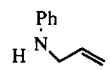
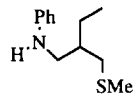
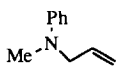
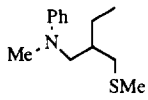
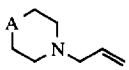
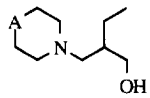
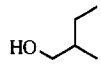


6 **5**

Scheme 1

We were delighted to find that **5** and **6** were catalytically much more active than **2** (as little as 2 mol% was required for complete conversion) and the enantiomeric excess obtained consistently higher (**Table 1**). As expected **5** and **6** gave opposite enantioselectivities since metallation is directed to opposite enantiofaces of the indene moieties and the planar chirality dominates enantioinduction. Better enantioinductions were obtained with **5** and, since **ent-5** is also readily available (from (+)-menthol), is the catalyst of choice. An important extra benefit was that unlike **1** or **2** the complex **5** could be efficiently recovered (>90%) from the

Table 1. Asymmetric ethylmagnesiation of terminal alkenes

Alkene	Electrophile	Product[a,b]	Cat:	Yield (ee%) 2	5	ent-5	6
	$(MeS)_2$			39% (26)[c]	95% (75)[c]	52% (79)[c]	73% (36)[c]
	$(MeS)_2$			34% (26)[c]	61% (52)[c]		65% (29)[c]
	O_2		A = $CHCH_2Ph$		37% (52)[c]	36% (55)[c]	
			A = NPh		50% (42)[c]		
	H_2O			35% (27)[d]	75% (56)[d]		43% (28)[d]

[a] Reaction as Eq. 1. Conditions: i. Et_2Mg (3 eq), THF, room temp., 16 - 48h, 10 mol% of **2** or 2 - 4 mol% **6**, **5** and **ent-5**; ii. Electrophile. [b] In all cases **2** and **5** gave one enantiomer in excess ((*R*)-2-methylbutan-1-ol in the last example), and **6** and **ent-5** the opposite. [c]measured by HPLC on Diacel OA. [d] Measured by NMR of Moschers ester.

reaction mixture by work-up with 6M hydrochloric acid followed by extraction, removal of solvent and recrystallisation.

Hoveyda has shown that with complex **1**, *cis*-alkenes give excellent enantioselectivities in the carbomagnesiation when the reaction is driven by elimination of the initial adduct.[6] Application of **5** to the ethylmagnesiation / elimination reaction of 2,5-dihydrofuran gave (*S*)-2-ethyl-3-butene-1-ol[6] in excellent e.e. (**Scheme 2**), the sense of enantioinduction being consistent with the model shown in **Fig. 3**. In preliminary studies on the kinetic resolution (in the sense that the enantiomers give predominantly different products) of 2-substituted dihydrofurans[7] using **5** we obtain good enantioinductions (**Scheme 2**), although lower than reported for **1**.

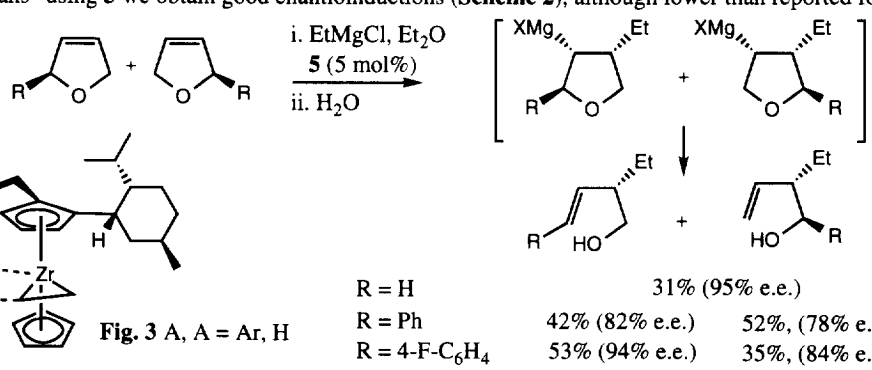


Fig. 3 A, A = Ar, H

R = H	31% (95% e.e.)	
R = Ph	42% (82% e.e.)	52%, (78% e.e.)
R = 4-F-C_6H_4	53% (94% e.e.)	35%, (84% e.e.)

Scheme 2. E.e.'s by chiral hplc (Diacel OA) or chiral g.c. (FS-Hydrodex-β). Absolute configurations are as shown, determined by comparison with the known (ref 7) products using **1**.

Conclusion. We have designed and synthesised a C_i symmetric chiral zirconocene featuring induced planar chirality in one cyclopentadienyl ligand which also provides both control elements (a 'roof' and 'wall') needed for chiral induction. The complex is cheap to make, substantially more active in the ethylmagnesiation of alkenes than other chiral zirconocenes tried, gives higher enantioexcesses, and is efficiently recoverable.

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11. Hoveyda (ref. 3) has used **1** for the carbomagnesiation of chiral terminal alkenes with an allylic hydroxy or ether group. The d.e.'s reported show that the diastereocontrol is dominated by the chirality of the hydroxy/ether group, but the additional influence of the catalyst chirality (matched / mismatched pairs) is consistent with our reported 26-27% e.e's:
12. All new compounds were fully characterised. All yields refer to pure isolated products.
13. For example the complexes (1,2,3,4-tetrahydro-**3**)$_2$$ZrCl_2$ and (1,2,3,4-tetrahydro-**4**)$_2$$ZrCl_2$ (ref 14) were inactive. The complexes (**3**)$_2$$ZrCl_2$ and (**4**)$_2$$ZrCl_2$ were poorly active: allyl aniline, 18% yield (28% e.e.), and 16 (3) respectively; N-methylallylaniline 5 (16) and 31 (22); and for allyl alcohol 10 (20) and 26 (12). Negishi obtains good activities and enantioinductions in ethylaluminations using (**3**)$_2$$ZrCl_2$, but under conditions which favour a different mechanism (direct insertion of the alkene into a cationic ethyl zirconocene). Under conditions which favour the same mechanism to herein he obtains low conversions and around 30% e.e.'s consistent with our results: Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577.
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16. International Patent Application no. PCT/GB96/00264. X-Ray structure of **ent-5** determined by Dr. C. Ceccarelli, Zeneca Pharmaceuticals, Wilmington, Dellaware, U.S.A. Full details will be reported shortly.

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