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Application of *N*,*S*-chelating chiral ligands and zinc complexes in catalytic asymmetric hydrosilylation using polymethylhydrosiloxane

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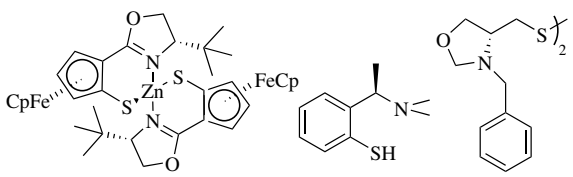
Abstract—A new *N*,*S*-chelating zinc catalyst was synthesised and evaluated for the enantioselective reduction of ketones in the presence of polymethylhydrosiloxane (PMHS).

1. Introduction

The stereoselective synthesis of optically active alcohols is a well studied topic in organic chemistry. In this way, the search for economical methods for enantioselective reduction of prochiral ketones is a rewarding goal. Polymethylhydrosiloxane (PMHS), a polymer coproduct of the silicone industry, is a safe and inexpensive reducing silylating agent, which can transfer its hydride to a variety of metal catalysts (Ti, Sn, Zn, etc.).[1] For example, Buchwald and co-workers have reported its use with chiral titanocene catalysts activated by *n*-butylithium for the enantioselective reduction of ketones with enantiomeric excesses (ee's) up to 97%.[2] Recently, Mimoun has shown that various bidentate ligands, such as diamines and diimines, are effective chiral inductors for the zinc catalysed asymmetric hydrosilylation of prochiral ketones by PMHS. The best results were obtained with chiral C_2 symmetric diamines providing good isolated yields and ee's up to 88%.[3] PMHS was also used for Zn-diamine reduction of ketones and imines.[4] Structural modifications on the backbone of various C_2 symmetric diamine ligands were also recently studied by Walsh and co-workers and Carpentier and co-workers with enantioselectivities reaching 91% for the reductions of acetophenone being achieved.[5]

Our group previously focused on copper based catalysts for the asymmetric hydrosilylation of ketones.[6] With this system, up to 92% ee was achieved. Extension of our studies prompted us to develop another low cost transition metal catalytic system focusing on *N*,*S*-zinc catalysts. Indeed many studies have demonstrated the superiority of catalysts incorporating amino and sulfur groups compared to amino alcohols.[7] Applications in asymmetric catalysis such as hydrogenation,[8] allylic alkylation,[9] organozinc additions,[7] Grignard cross-coupling and hydrosilylation of imines and ketones[9] have demonstrated the interest of these classes of chiral ligands. The electronic properties of sulfur compared to oxygen and the higher affinity of thiols and thiolates towards soft metal, especially zinc, could explain these results.

Herein we report the design of a new *N*,*S*-chelating zinc catalyst **1** and its evaluation in asymmetric hydrosilylation of ketones using the cheap and safe PMHS, by comparison with the chiral ligands **2** and **3** (Scheme 1).



1 **2** **3**

Scheme 1. *N*,*S*-chelating Zn ligands and catalyst.

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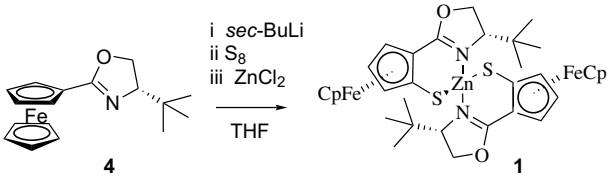
In view of the promising results obtained by van Koten and co-workers with amino thiol **2** for the enantioselective addition of dialkylzincs to aldehydes,[10] which have been recently developed by Perrio and co-workers in the diastereoselective alkylation of sulfenate anions,[11] we became interested by its evaluation in our hydrosilylation conditions. Disulfide **3** was also evaluated due to the result obtained by Braga et al. in the asymmetric addition of diethylzinc to aldehydes.[12]

2. Results and discussion

The ferrocene oxazoline **4** was prepared by a two-step procedure, involving first the formation of an α-hydroxyamide by combination of ferrocene carboxylic acid and *tert*-leucinol followed by cyclisation.[13] Starting from this ferrocene oxazoline **4**, treatment with *sec*-BuLi generated with high diastereoselectivity the *ortho*-lithiated ferrocene (Scheme 2). Reaction with electrophilic sulfur gave the corresponding lithium thiolate, which reacted with anhydrous zinc chloride yielding the *N*,*S*-zinc complex **1** in 81% after aqueous work-up and chromatographic purification. This air-stable zinc complex, obtained by this one pot procedure, has been fully characterised by all spectroscopic methods.[14]

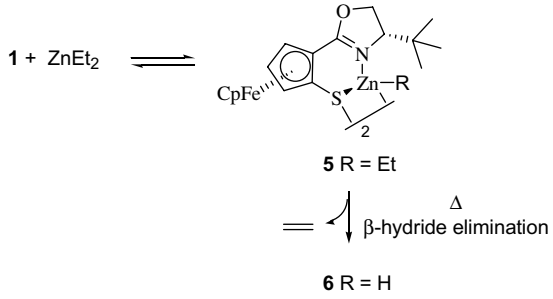


Scheme 2. Reagents and conditions: (i) *sec*-BuLi (1.2 equiv), THF, −78 °C, 2 h, then 0 °C, 5 min; (ii) S_8 (1.2 equiv), −78 °C, 1 h; (iii) $ZnCl_2$ (0.5 equiv), rt, 15 h.

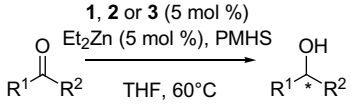
The enantiopure thiophenol **2** could be prepared from 1-(*R*)-phenylethylamine following the methodology of van Koten and co-workers,[10] recently modified by Perrio and co-workers,[11] that is, selective ortho-lithiation of (*S*)-methylbenzyldimethylamine, trapping of the intermediate with elemental sulfur, acidic work-up and purification by sublimation gave the dimethylamino thiol **2** in only moderate yield. The chiral disulfide **3** could be prepared according to the procedure developed by Braga et al. starting from L-cysteine.[12]

A standard experimental protocol was devised for testing the complex **1** in asymmetric reduction of acetophenone with PMHS. A solution of complex was thus mixed with an equimolecular amount of diethylzinc under atmosphere to generate the dimeric oxazolino-thiolate zinc complex **5**.[10] The complex was then activated by heating the solution to generate the corresponding zinc hydride dimer **6** by a β-hydride elimination from the ethyl ligand (Scheme 3). In the case of ligands **2** and **3**, the active catalysts were generated by a similar procedure before the addition of the substrate and the reducing agent.

A preliminary optimisation was carried out by studying the effect of various solvents and temperature on both conversion and enantioselectivity (Scheme 4). According to Table 1, THF gave the best results regarding both conversion and enantiomeric excess with the shorter reaction time (entry 5). Formation of zinc hydride active catalyst at 60 °C and hydrosilylation of the substrate at room temperature increased enantioselectivity but decreased the reaction rates (entries 5 and 6). Lastly, change in concentration and catalyst loading lead unfortunately to a decrease in enantioselectivity (entries 7–9).



Scheme 3. Formation of the hydride zinc catalyst **6**.



Scheme 4. Reduction of ketones by Zn catalysts/PMHS system.

Table 1. Solvent, temperature and catalyst load effects

Entry	Solvent	*T* (°C)[a]	Time (h)	Concn (mol/L)	Conv (%)[b]	ee (%)[b]
1	CH_2Cl_2	35	18	0.25	46	18
2	Toluene	80	1.5	0.25	100	42
3	Et_2O	35	18	0.25	57	43
4	Dioxane	60	21	0.25	100	45
5	THF	60	2	0.25	100	51
6	THF	Rt	24	0.25	100	61
7	THF	60	2	6.25	100	41
8	THF	60	5	0.125	85	43
9	THF	60	5	0.05	46	42

[a] Addition temperature of acetophenone.
[b] Determined by chiral GC analysis (see note).

Ligands **2** and **3** gave low activities and almost racemic alcohols compared to complex **1** (Table 2, entries 2–3).[3] As shown in the table, complete reduction of arylketones proceed in a few hours (2–5 h) with ee up to 55%. Longer reaction time was required for non-aromatic ketone (entry 4).

Different alkyl group (*n*-propyl, cyclohexyl, trifluoromethyl, cyclic chain) in α-position were examined. If the reactivity was not modified, we could notice a decrease in the enantioselectivity except for the bulkier α-tetralon (Table 2, entries 5–9). Introduction of an electron-withdrawing group at the *para* position sensibly modifies the reaction rate and slightly reduced the enantioselectivity while a donor group in this position did not affect the reactivity but decreases the ee (entries

Table 2. Asymmetric hydrosilylation of various prochiral ketones with complex **1** (Scheme 4)[a]

Entry	Ligand	R^1	R^2	Time (h)	Conv (%)[b]	ee (%)[b]
1	**1**	Ph	Me	2	100	51
2	**2**	Ph	Me	6	23	3
3	**3**	Ph	Me	6	69	8
4	**1**	C_6H_{10}	Me	5	6	42
5	**1**	Ph	*n*-Propyl	5	100	13
6	**1**	Ph	C_6H_{10}	2	100	24
7	**1**	Ph	CF_3	2	100	14
8	**1**	α-Indanon		2	100	9
9	**1**	α-Tetralon		2	100	55
10	**1**	*p*-ClPh	Me	5	100	45
11	**1**	*p*-MeOPh	Me	2	100	41
12	**1**	Me	CH_2COOEt	2	100	15
13	**1**	Fc	Me	3	89[c]	44

[a] Typical experimental procedure for the reduction of ketones: To a dry 20 mL Schlenk flask under argon, the chiral ligand or complex (5 mol %) was dissolved in 3 mL of dry THF. A freshly prepared solution of $ZnEt_2$ in THF (5 mol %) was dropwise added to the mixture and the solution was heated and stirred at 60 °C for 10 min (PMHS 1.1 equiv SiH) and acetophenone were then successively injected to the solution. Conversions and enantiomeric excesses were determined by GC analysis (CHIRASIL cyclodextrine B column (25 m × 0.25)) after quenching a sample with 1 mL of NaOH in MeOH solution and filtration on SiO_2.

[b] Determined by chiral GC analysis (see note).

[c] Isolated yield after chromatography purification.

10 and 11). Chelating substrates such as an α-ketoester were also cleanly reduced, albeit with a low ee (entry 12).

3. Conclusions

We have synthesised a new chiral *N*,*S*-chelating zinc complex, which proved to be air and moisture stable.

Although the enantioselectivities remain still modest for the reduction of various ketones, this study shows that new families of chiral ligands can be effectively used for the enantioselective hydrosilylation of prochiral ketones. More studies are still required to optimise the structure of such chiral complexes. Current efforts are also directed towards the identification of the active catalysts generated during this process.

Acknowledgements

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14. Synthesis of complex **1**: The ferrocenyl oxazoline **4**[13] (310 mg, 1 mmol) was dissolved in 17 mL of freshly distilled THF under argon and cooled to −78 °C. *sec*-Butyl lithium (0.92 mL of a 1.3 M solution, 1.22 mmol) was injected dropwise and the solution was stirred at −78 °C for 1 h and at 0 °C for 5 min. The solution was cooled again at −78 °C and solid sulfur (38 mg, 1.2 mmol) was added in one portion under a stream of argon. After stirring at −78 °C for 1 h, the temperature was allowed to slowly reach room temperature. A freshly prepared solution of anhydrous zinc chloride (68 mg, 0.5 mmol) in THF was injected and the reaction mixture was stirred at room temperature overnight. After concentration, the crude reaction mixture was taken up in dichloromethane and washed with brine. The solution was concentrated and the zinc complex was purified by flash chromatography on silica gel (1% MeOH in DCM, $R_f = 0.29$). Data for compound **1**: Orange solid, 78% isolated yield (290 mg), ^1H NMR ($CDCl_3$, 500 MHz): δ 0.99 (s, 9H, $C(CH_3)_3$); 3.25 (dd, 1H, $J = 5.8$ Hz, $J = 9.3$ Hz, CH–CH_2); 4.03 (pseudo t, 1H, $J = 9.3$ Hz, CH–CH_2); 4.16 (s, 5H, Cp); 4.27–4.31 (m, 2H, CH–CH_2 and Cp subs.); 4.53 (m, 1H, Cp subs.); 4.69 (m, 1H, Cp subs.). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.0 ($C(CH_3)_3$); 33.6 ($C(CH_3)_3$); 64.7 (C–CNO); 67.4 (Cp subs.); 68.6 (CH–CH_2), 71.5 (Cp); 74.3 (CH–CH_2); 75.0 (Cp subs.); 96.5 (C–S); 175.2 (CN). IR: 1606 (C═N). MS (APCI): 749.2 $[M+H]^+$.