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Tetrahedron Letters 45 (2004) 9215–9217

Tetrahedron Letters

Diastereo- and enantioselective syntheses of ansa-metallocenes from metal halide complexes with tropos biphenol and atropos binaphthol ethers

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Received 13 August 2004; revised 6 October 2004; accepted 15 October 2004

Abstract—A diastereo- and enantioselective route to synthesize ethylene-bis(4,5,6,7-tetrahydro-1-indenyl)-titanium and -zirconium dichlorides is described using titanium trichloride or zirconium tetrachloride complexes with tropos (chirally flexible) biphenol and atropos (chirally rigid) binaphthol ethers.

ansa-Metallocene derivatives represent a class of chiral organometallic reagents or catalysts in organic syntheses.[1,2] Especially, chiral C_2-symmetric ethylene bridged bis(indenyl) group 4 ansa-metallocene complexes (**1a**: Ti and **1b**: Zr)[3] have received considerable attentions (Fig. 1) as highly active soluble catalysts for stereocontrolled polymerization[3] and stereoselective synthetic transformations.[4–6] However, in their previous syntheses, the metallocene complexes were obtained as a mixture of racemic (*d*,*l*) and *meso* diastereomers, with the latter as the major isomer in the titanium case. We report here a new approach to allow the synthesis of ethylene-bis(4,5,6,7-tetrahydro-1-indenyl)-titanium and -zirconium dichlorides (**1a** and **1b**) diastereo- and enantioselectively.

We found by chance the diastereoselective synthesis of *d*,*l*-ethylene-bis(4,5,6,7-tetrahydro-1-indenyl) titanium dichloride (*d*,*l*-**1a**), using commercially available titanium tetrachloride THF complex at −20 °C.[7] This *d*,*l*-selective synthesis is in sharp contrast to the precedent method[3] using titanium tetrachloride to give *meso* isomer as the major product (Table 1, entries 1 vs 2). Likewise, 2,5-dimethyltetrahydrofuran titanium tetrachloride complex, which was prepared in situ, also gave the desired *d*,*l*-**1a** as the major product (entry 3). These *d*,*l*-selective syntheses are in sharp contrast to the precedent method[3] using titanium tetrachloride to give *meso* isomer as the major one (entry 1). Thus, sterically bulky ethers were examined to induce higher diastereoselectivity (Scheme 1). First, hydrobenzoin dimethyl ether was tested, and highly diastereoselective synthesis of *d*,*l*-**1a**

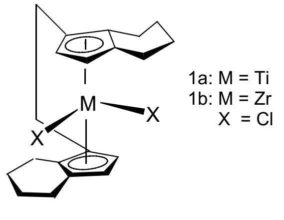

Figure 1. ansa-Metallocenes.

Table 1. Diastereoselective synthesis of titanocenes **1a** with titanium-ether complexes

Entry	Ethers	$TiCl_x$	Yield[a] (%)	*d*,*l*:*meso*[b]
1[c]	—	$TiCl_4$	22	1:2–10
2	THF	$TiCl_4$	42	80:20
3	2,5-Me_2THF	$TiCl_4$	31	77:23
4	Hydrobenzoin dimethyl ether	$TiCl_4$	10	>95:5
5[d]	—	$TiCl_3$	40	1:1.1
6	BIPOL dimethyl ether	$TiCl_3$	46	*d*,*l* only
7	BINOL dimethyl ether	$TiCl_3$	52	*d*,*l* only

[a] Refers to that of the isolated product (**1a**).
[b] Determined by ^{1}H NMR analysis.
[c] Lit. 3a.
[d] Lit. 5b.

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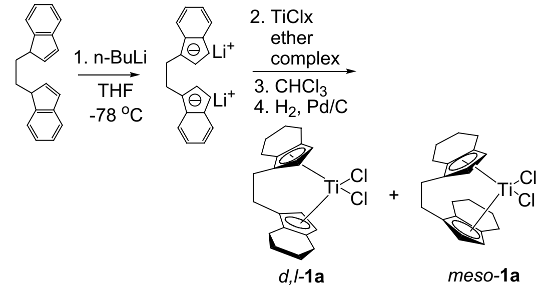
doi:10.1016/j.tetlet.2004.10.094



Scheme 1. Diastereoselective synthesis of titanocene (*d,l*-**1a**) with titanium chloride ether complexes.

was indeed confirmed (entry 4). Only a trace amount of *meso* isomer was observed by ^{1}H NMR analysis. A higher diastereoselectivity was obtained when chirally flexible (tropos)[8] biphenol (BIPOL) dimethyl ether was used. Considering the order[9] of crystal radius of Ti^{4+} (0.745 Å) < Ti^{3+} (0.810 Å) < Zr^{4+} (0.860 Å), titanium trichloride is larger in ionic radius, and hence less steric demanding than titanium tetrachloride in their complexes. Titanium trichloride was thus utilized to give higher yield of the isolated ansa-metallocene complex (*d,l*-**1a**) as the sole diastereomer (Table 1, entries 6 and 7).

These results suggest the association between metal center and C_2-symmetric ether might control the absolute configuration of C_2-symmetric ansa-metallocenes highly diastereo- and enantioselectively (Scheme 2). This strategy was applied to the syntheses of zirconocenes **1b** using zirconium tetrachloride complexes with chirally rigid atropos[8] binaphthol (BINOL) ethers. The complex formation with atropos BINOL ether was confirmed by the down field chemical shift of the dimethyl groups after complexation with $ZrCl_4$ in ^{1}H NMR analysis (Fig. 2).

It should be noted that high enantioselectivity was obtained as determined by chiral CD-HPLC[10] (Fig. 3). Especially, when BINOL dimethyl ether was utilized, higher enantioselectivity was observed, as compared with that of dibenzyl ether (Table 2, entries 1 and 2 vs 3). Its worth noting here that 95% ee was obtained from either (*S*)- or (*R*)-BINOL dimethyl ether (entries 1 and 2).

The enantiopurity of ansa-zirconocene (**1b**) was further confirmed after transformation[11] to the complexes with tropos BIPOL (**2b**) at two different temperatures, via addition of an excess amount of racemic BIPOL in toluene or CH_2Cl_2 (Scheme 3). A mixture of enantiomeric **2b** was obtained with varying degree of enantiopurity.

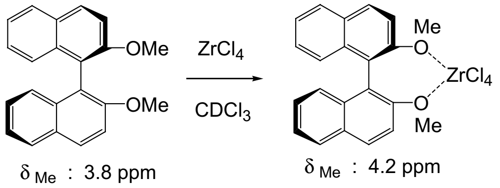
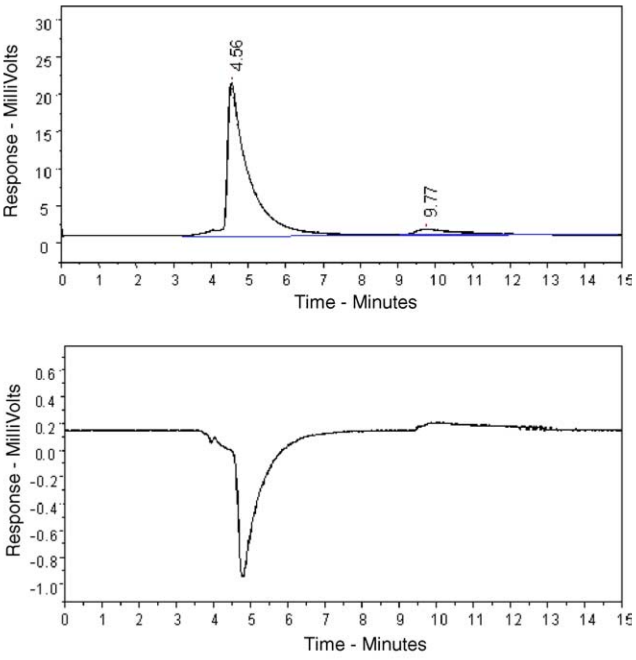


Figure 2. Formation of zirconium tetrachloride BINOL ether complex.



(*R*,*R*)-**1b** (Table 2, entry 1)

Figure 3. CD-HPLC analyses: Chiralcel OD*-H (25 × 0.46) cm; eluent: hexane/ethyl acetate 85/15 (v/v); flow rate: 1.0 mL/min; temperature: −10 °C; monitored at UV 254 nm, CD 250 nm.

Table 2. Diastereo- and enantioselective synthesis of zirconocene **1b** with zirconium tetrachloride BINOL ether complex

Entry	BINOL ethers	Yield[a,b] (%)	ee[c] (%)
1	(*R*)-Dimethyl ether (R = Me)[d]	38 (33)	95 (*R*,*R*)
2	(*S*)-Dimethyl ether (R = Me)[d]	39	96 (*S*,*S*)
3	(*S*)-Dibenzyl ether (R = Bn)[d]	27	78 (*S*,*S*)

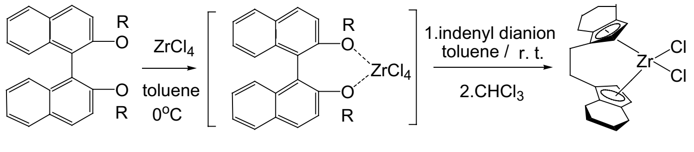
[a] Determined by ^{1}H NMR analysis.

[b] Value in parenthesis refers to that of the isolated product (**1b**).

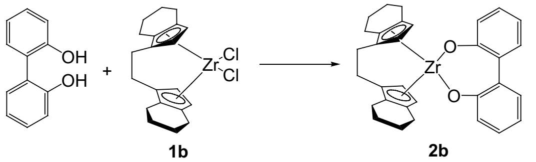
[c] Determined by chiral CD-HPLC analysis.

[d] See Scheme 2.

The enantiopurity critically depends on the reaction temperature with BIPOL to suggest racemization to some extent (Table 3).



Scheme 2. Diastereo- and enantioselective synthesis of zirconocene **1b** with zirconium tetrachloride chiral BINOL ether complexes.



1b **2b**

Scheme 3. Further determination of enantiopurity of zirconocene derivatives **2b**.

Table 3. Enantiopurity of zirconocene **1b**

Entry	Substrate	ee[a] **1b**	Method[b] (%)	Yield (%)	ee[a] (%) **2b**
1	(*S*,*S*)-**1b**	95	A (80 °C)	72	58
2	(*S*,*S*)-**1b**	96	B (rt)	67	88

[a] Determined by chiral HPLC analysis: chiralcel OD*-H (25 × 0.46) cm; eluent: hexane/ethyl acetate 85/15 (v/v); flow rate: 1.0 mL/min; temperature: 25 °C; monitored at 254 nm.

[b] Method A: Na/toluene, 80 °C, 4 h (Lit. 3a); Method B: Et_3N/CH_2Cl_2, rt, 2 h (Lit. 5b).

In summary, we have devised a simple route to synthesize ansa-metallocene derivatives diastereo- and enantio-selectively by use of titanium and zirconium chloride complexes with tropos BIPOL and atropos BINOL ether. Further works along this line are now under way.

Acknowledgements

We are so grateful to Dr. Atsushi Onishi of Daicel Chemical Industries Ltd for his useful discussions and technical assistance.

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