

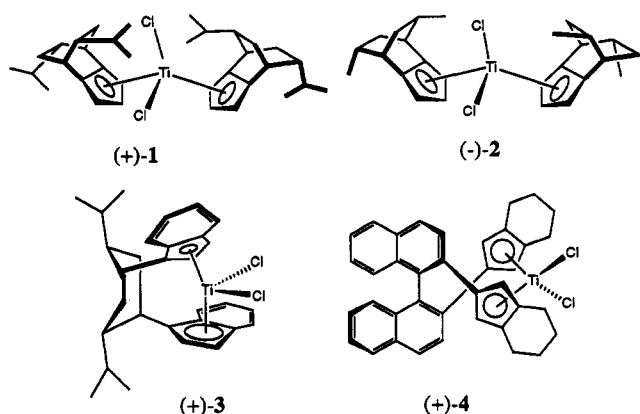
## Catalytic Asymmetric Hydrosilation of Aryl Alkyl Ketones with C<sub>2</sub>-Symmetric Chiral Metallocene Complexes

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In an ongoing effort to prepare and evaluate new chiral C<sub>2</sub>-symmetric metallocenes as catalysts for asymmetric transformations,<sup>1</sup> we have applied our recently published catalysts<sup>2</sup> 1-4 to the catalytic asymmetric hydrosilation of aromatic ketones. We report here that complexes 1-4 catalyzed enantioselective hydrosilation of prochiral aromatic ketones with triethoxysilane to yield enantiomerically enriched alcohols in high yield but with low to fair enantioselectivity.



While several chiral transition-metal complexes<sup>3</sup> have been successfully employed to catalyze the asymmetric hydrosilation of prochiral ketones, there are no reports of titanium-catalyzed asymmetric hydrosilations. Nakano and Nagai<sup>4</sup> have reported that Cp<sub>2</sub>TiPh<sub>2</sub> could catalyze the hydrosilation of ketones in the presence of diphenylsilane or phenylsilane at relatively high temperature (90-100 °C). Buchwald<sup>5</sup> has reported the use of parent titanocene dichloride as a precatalyst to effect the hydrosilation of esters under milder conditions to yield primary alcohols. Prompted by the mildness of reductions under Buchwald's conditions with an achiral titanocene, we examined the asymmetric hydrosilation of several prochiral aromatic ketones applying chiral titanocene dichlorides 1-4 whose syntheses we have previously reported.<sup>2</sup>

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Table 1. Asymmetric Hydrosilation of Aryl Alkyl Ketones

(R <sup>*</sup> Cp) <sub>2</sub> TiCl <sub>2</sub>	0.010 eq.	0.005 eq.	0.010 eq. n-BuLi	(1) 2.5 eq. silane / -78 °C	(2) 1.0 eq. ketone / -78 °C - π	(3) 3N NaOH / π	R	OH	H	CH <sub>3</sub>
ketone	catalyst	time (h)	% yield	% ee <sup>a</sup>	confgn					
	4	80	40	5	(S)-(-)					
	4	58	87	0						
	1	2	84	12	(S)-(-)					
	2	2	78	5	(R)-(+)					
	3	2	77	7	(S)-(-)					
	4	13	100	14	(S)-(-)					
	4	2	100	32	(S)-(-)					
	4	0.7	100	2	(S)-(-)					
	1	6	84	13	(S)-(-)					
	2	6	99	6	(R)-(+)					
	3	6	96	20	(S)-(-)					
	4	24	90	40	(S)-(-)					

<sup>a</sup> Determined by chiral GC. Absolute configuration determined by optical rotation in agreement with literature values.<sup>11</sup>

The homogeneous asymmetric hydrosilation reaction was conducted by reducing 0.5% or 1.0% of complexes 1-4 in THF at 0 °C with 2 equiv of n-BuLi. At -78 °C the silane was slowly added followed by the appropriate ketone and decane as an internal standard. The ratio of complex to substrate was 1:200. The results reported in Table 1 are the average of at least two runs. The reaction was monitored by GC until all the starting material was consumed or the reaction had virtually stopped. The enantioselectivity was determined by chiral GC with decane as an internal standard. In all cases the reaction was clean with either ketone or alcohol accounting for virtually 100% of the mass. Yields of alcohol are thus reflective of percent conversion in the allotted time. It was noted that the enantiomeric excess remained consistent throughout the course of the reactions. It was also noted that substituting diphenylsilane or phenylmethylsilane for triethoxysilane and maintaining a low reaction temperature did not effect the enantioselectivity, but merely increased the reaction time.

It has been hypothesized<sup>5</sup> that the hydrosilation of carbonyl compounds results from the initial reduction of Ti(IV) to Ti(III) employing 2 equivalents of n-BuLi with subsequent β-hydride elimination of butyl titanocene(III) forming the active titanocene(III) hydride species. The active catalyst then incorporates the ketone functionality into the chiral cleft and transfers a hydride to the prochiral carbonyl carbon followed by cleavage of the titanium oxygen bond by triethoxysilane, regenerating the active catalyst. A radical silyl<sup>6</sup> side product was also postulated, yet when a radical scavenger (di-tert-butyl nitroxide) was introduced into the reaction mixture in our system the

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Table 2

entry	substrate	temp programming			$t_R$ (min)		
		$T_i$	ramp	$T_f$ (°C/min)	ketone	alcohol	decane
1	4'-methoxyacetophenone	110/10	10/1	185/1 at 15 psi	15.39	14.20	4.08
2	4'-methylacetophenone	100/1	5/1	200/1	8.20	7.58	4.38
3	acetophenone	90/10	10/1	120/1	9.81	9.34	6.39
4	4'-bromoacetophenone	100/1	10/1	207/1	16.31	16.84	4.98
5	4'-(trifluoromethyl)acetophenone	100/1	5/1	176/1	5.41	6.32	4.36
6	2-acetylnaphthalene	120/16	10/1	200/1 at 20 psi	17.9	23.4	2.81

Table 3

entry	substrate	temp programming			$t_R$ (min)	
		$T_i$	ramp	$T_f$ (°C/min)	enantiomeric resolution	
1	4-methoxy- $\alpha$ -methylbenzyl alcohol	125/10	2/1	180/1 at 15 psi	37.16 (minor), 37.39 (major)	
2	4-methyl- $\alpha$ -methylbenzyl alcohol	100/1	2/1	150/1	24.39 (minor), 24.59 (major)	
3	sec-phenylethanol	110/10	2/1	150/1	16.93 (minor), 17.13 (major)	
4	4-bromo- $\alpha$ -methylbenzyl alcohol	145/1	2/1	200/1	26.04 (minor), 26.22 (major)	
5	4-(trifluoromethyl)- $\alpha$ -methylbenzyl alcohol	100/1	2/1	150/1	23.78 (minor), 24.20 (major)	
6	sec-naphthylethanol	160 (isothermal, at 25 psi)			42.40 (minor), 42.81 (major)	

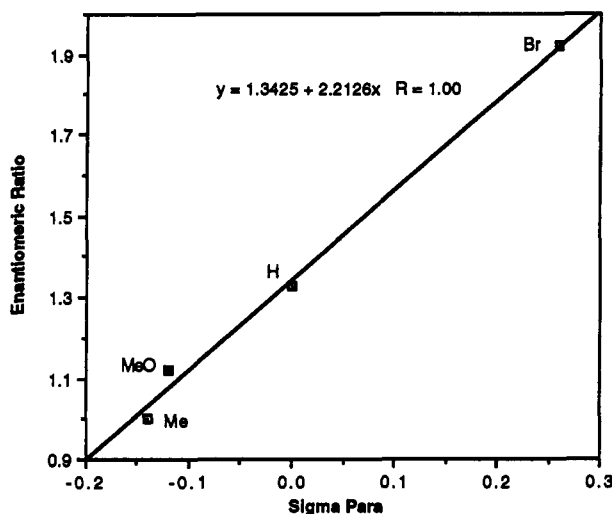


Figure 1. Enantiomeric ratio of 4-XPhCH(OH)CH<sub>3</sub> produced using 4 vs  $\sigma_p$ .

enantioselectivity was unchanged. The yield, however, was reduced substantially.

The highest selectivity (40% ee with 2-acetylnaphthalene) was observed with the binaphthyl-bridged tetrahydroindenyl titanium complex 4. The hydrosilylation of 2-acetophenone with either 1 (12% ee) or 4 (14% ee) gave similar results, while complexes 2 and 3 gave both lower yield and lower selectivity. Reductions of aliphatic ketones (2-decanone, pinacolone) provide a significantly lower enantiomeric excess ( $\leq 5\%$  ee).

We also investigated the influence of various substituents in the *para*-position of acetophenone on the enantiomeric excess in reactions involving binaphthyl-bridged complex 4. Introduction of a *p*-methyl or a *p*-methoxy group greatly reduced the asymmetric induction and gave a lower yield of alcohol and slower reactions. However, the enantiomeric excess and the rate of reduction increased with the addition of a *p*-bromo group. A plot of enantiomeric ratio for the reductions of substituted acetophenones (X = Br, MeO, H, Me) catalyzed by 4 vs  $\sigma_p$  suggests a correlation between the electronic effects of various electron-withdrawing and electron-donating substituents (Figure 1). However, the very strong electron-withdrawing trifluoromethyl group reduced the enantiomeric excess in a much more rapid reaction, perhaps indicating an alternative reaction mechanism.

Related results by Brunner and Kurzinger<sup>7</sup> for the hydrosilylation of acetophenone derivatives with [Rh(cod)-Cl<sub>2</sub>] and diphenylsilane indicate no substantial change in the enantioselectivity in the cases of acetophenone, 4-chloroacetophenone, and 4-methylacetophenone but a substantial reduction in the enantiomeric excess with 4-methoxyacetophenone substrate. One notable difference in the comparison of our results with those of Brunner is the difference in the selectivity of the 4-methylacetophenone where we observed a significant drop in selectivity.

In summary, we have demonstrated that our C<sub>2</sub>-symmetric titanium complexes 1–4 catalyze the asymmetric reduction of alkyl phenyl ketones in high yields and fair enantioselectivity. *p*-Bromoacetophenone gave increased enantiomeric excess and yield, while electron-donating groups lowered both the yield and the enantiomeric excess.

## Experimental Section

**General.** Standard experimental methods were followed.<sup>8</sup> Response factors for ketones and alcohols in decane were determined as described by Colletti.<sup>9</sup>

**General Procedure for Hydrosilylation of Aromatic Ketones.** To an oven-dried Schlenk tube under argon and charged with 0.5% (S)-(+)-1,1'-binaphthyl-2,2'-diyl-bridged ansabis-(4,5,6,7-tetrahydro-2-indenyl)titanium dichloride (4) (3 mg, 0.005 mmol) was added THF (1.5 mL). The red solution was cooled to 0 °C, and 2 equiv of *n*-BuLi (2.2 M, 9  $\mu$ L, 0.02 mmol) was added dropwise to the center of the solution to reveal an orange/yellow color. After being stirred for 15 min at 0 °C, the solution was cooled to -78 °C and 500 equiv of triethoxysilane (457  $\mu$ L, 2.47 mmol) was slowly trickled down the side of the Schlenk tube into the reaction solution. A mixture of 200 equiv of ketone and 103 equiv of decane (100  $\mu$ L, 0.513 mmol) was added in the same manner. The orange/yellow solution was allowed to gradually warm to room temperature and was monitored by GC, taking aliquots beginning at 0.25 h to reaction completion. The aliquots were quenched with aqueous 3 N NaOH (0.5 mL), dried with K<sub>2</sub>CO<sub>3</sub> before injecting into the GC. Reactions with complexes

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1-3 were carried out in the same manner.<sup>10</sup> Characterization of all products agreed with known compounds, and absolute configuration was assigned via polarimetric measurements.<sup>11</sup>

**GC Conditions for Ketones, Alcohol, and Decane.** Achiral Hewlett-Packard HP-5 crosslinked 5% Ph Me silicon 25-m  $\times$  0.2-mm  $\times$  0.33- $\mu$ m capillary column (see Table 2). Hewlett-Packard chiral fused silica WCOT CP-Cyclodex- $\beta$ 236 M 25-m  $\times$

0.02-mm  $\times$  0.33- $\mu$ m capillary column (see Table 3).

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