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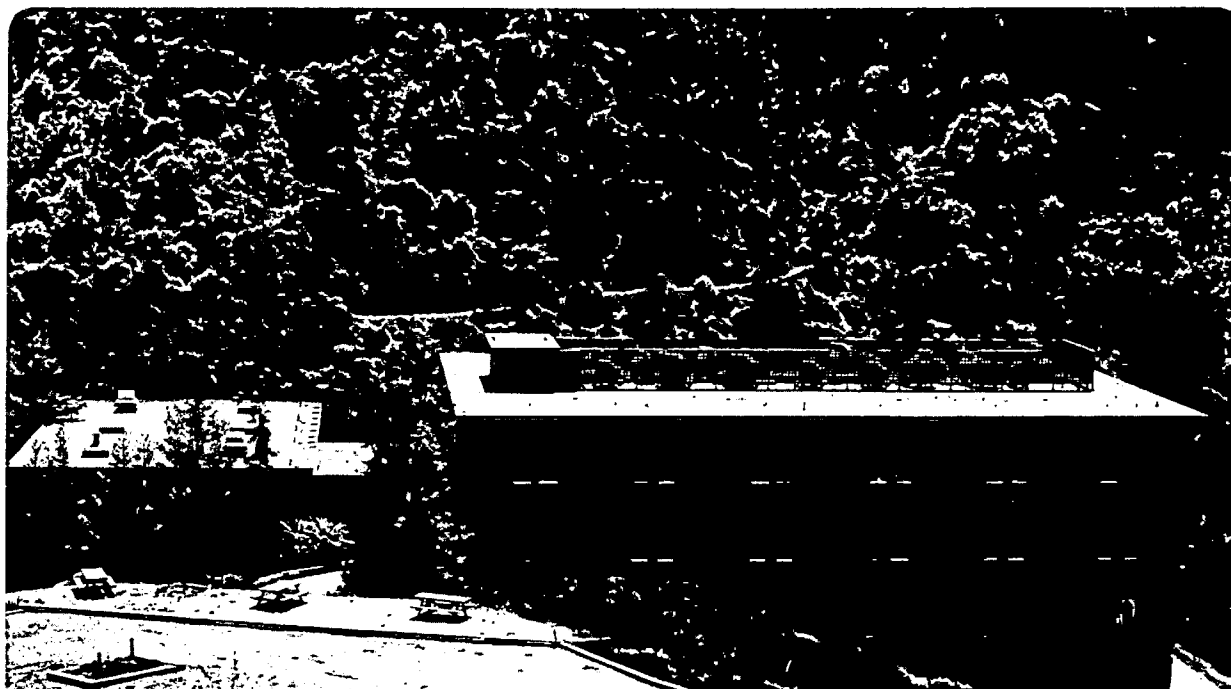
### Organolanthanide Catalysis of a Mukaiyama Addition Reaction

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## Organolanthanide Catalysis of a Mukaiyama Addition Reaction

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The stereoselective formation of carbon-carbon bonds remains an important goal of modern synthetic chemistry. Many approaches have been used to alter the ratio of diastereomers produced in aldol-type addition reactions with varying degrees of success.<sup>1</sup> In 1973, Mukaiyama, Banno and Narasaka<sup>2</sup> introduced the condensation of carbonyl compounds with silyl enol ethers promoted by Lewis acids such as titanium tetrachloride. This method is often superior to the use of lithium enolates or metal salts in the aldol condensation reaction because it prevents di-, poly- or self-condensation products but has the disadvantage that stoichiometric amounts of the Lewis acid are normally required. Moreover, the reaction shows poor diastereoselection.<sup>3</sup> The reaction can be catalyzed by triphenylmethyl cation<sup>4</sup> or by fluoride ion<sup>5</sup> but these reactions also have poor stereoselectivity. More recently, the use of rhodium(I) diphosphine complexes with chiral phosphines has been shown to provide catalysis with enantioselection.<sup>6</sup>

Enolate salts of lanthanides have been shown to undergo condensation reactions with carbonyl compounds.<sup>7</sup> Of more immediate relevance was the recent demonstration that lanthanum chloride promotes the Mukaiyama addition of 1, the trimethylsilyl enolate of methyl isobutyrate, with benzaldehyde.<sup>8</sup> These reactions show no useful stereospecificity. Coordination to lanthanide cations is normally limited only by space and we thought that stereochemical discrimination could be induced by control of other ligands on the lanthanides, specifically with substituted cyclopentadienyls.

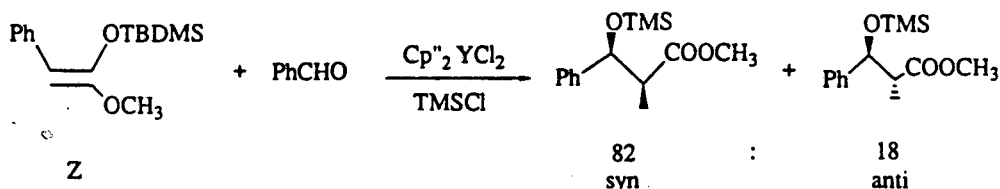
We now report that bis[bis(1,3-trimethylsilyl)cyclopentadienyl]ytterbium(III) chloride,  $\text{Cp}^*_2\text{YbCl}$ , 2,<sup>9</sup> is an effective catalyst for the reaction of 1 with benzaldehyde. Reaction occurs in

high yield in methylene chloride at various temperatures. Facile reaction requires the presence of trimethylsilyl chloride (TMSCl) and can be carried out with 0.01 moles of catalyst or less and at temperatures as low as -70 °C. In a typical procedure, One mole each of 1, the aldehyde and trimethylsilyl chloride was stirred in methylene chloride at room temperature with 0.01-0.1 moles of 2 for several hours. After hydrolysis with aqueous ammonium chloride, the mixture was extracted with pentane and the organic layer was washed, dried and evaporated. The pure aldol products were isolated by chromatography on silica gel.

The reaction is good for aromatic aldehydes with isolated yields of over 80%. The examples include p-tolualdehyde, 2-naphthaldehyde and furfural. Aliphatic aldehydes such as butyraldehyde, isobutyraldehyde and crotonaldehyde gave lower yields of >50% but the conditions were not optimized. Highly hindered aldehydes such as pivalaldehyde did not react, nor did the ketones acetophenone and cyclohexanone. Note that reaction with the  $\alpha,\beta$ -unsaturated aldehydes gave exclusively the 1,2-addition product.

The diastereoselectivity was studied with the use of isomeric silyl enol ethers from propionate and phenylacetate esters. Reaction of the ester in THF with LDA at -78 °C and treatment with TMSCl gives primarily the E-TMS enolate whereas reaction of the lithium enolate at room temperature in THF-hexamethylphosphoric triamide (HMPA) with t-butyldimethylsilyl (TBDMS) chloride gives mostly the Z-isomer.<sup>10</sup> The phenylacetate reaction gave the result in eq. 1.

Eq. 1



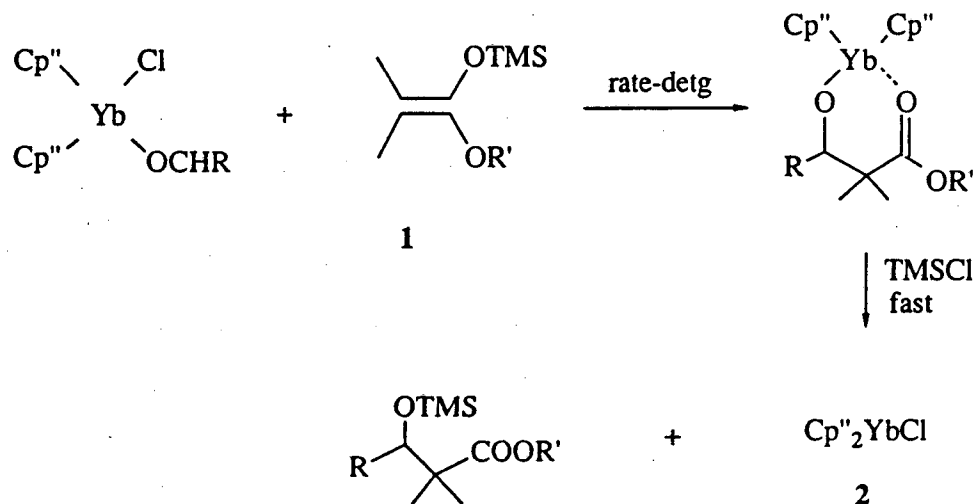
70% yield

The reactions of the silyl enol ethers of various propionate esters with either TMS or TBDMS groups are summarized in Table I. From these data it

appears that the E-isomers react with >95% diastereoselection whereas that of the Z-isomers is about 80-90%. The results are readily rationalized by a mechanism that is consistent with kinetic studies to be reported in the full paper.

The ytterbium compound 2 is a dimer in inert solvents but forms a solvated monomer in donor solvents such as THF.<sup>11</sup> Color changes and the IR spectrum indicate that 2 forms a complex with the aldehyde,  $\text{Cp}''_2\text{YbCl}\cdot\text{OCHR}$ , which undergoes rate-determining reaction with the silyl enolate to give a hypothesized internally coordinated Yb intermediate. The latter rapidly reacts with the  $\text{TMSCl}$  present to give the product which is hydrolyzed on workup. This mechanism is shown in Scheme 1 and is consistent with the kinetic observation that the rate is independent of the concentration of  $\text{TMSCl}$  so long as some is present.

Scheme 1



On the basis on this mechanism, the stereochemical results are readily rationalized by the transition state structures in Scheme 2. The favored pathway is shown by the heavy arrow. This scheme is an obvious extension of the Zimmerman-Traxler model<sup>12</sup> as extended to the Mukaiyama addition by Chan et al.<sup>13</sup>

The organolanthanide compound 2 thus shows promise as a useful addition to

the growing armory of reagents for promoting stereo-controlled aldol-type addition reactions. With many possibilities for structural modification of the cyclopentadienyl ligands, the central lanthanide metal and the leaving halide, much further refinement of the reagent is clearly possible and is currently in progress.

#### Acknowledgement

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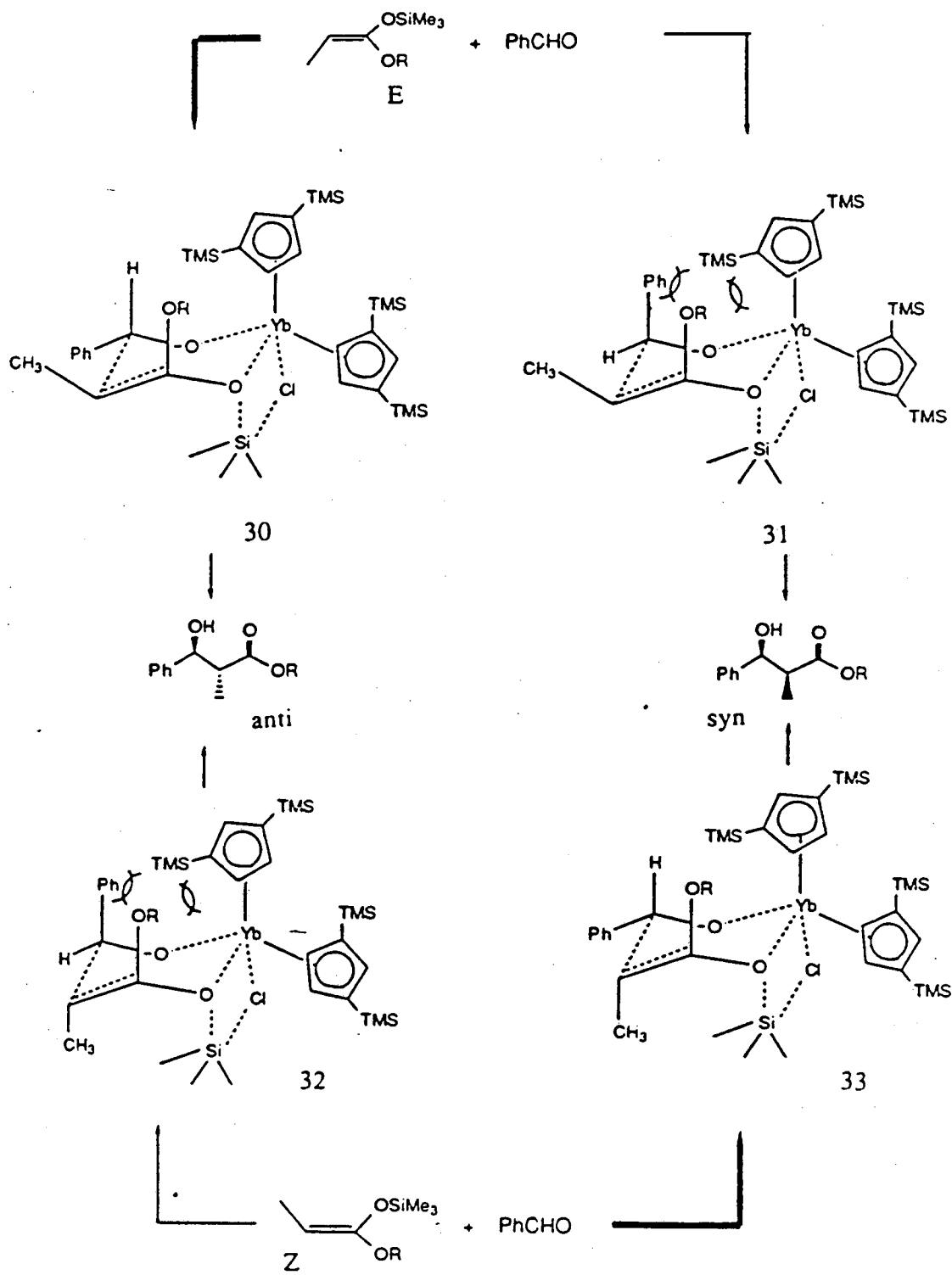
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Table I. Reactions of silyl enol ethers 3 with benzaldehyde (B), or cinnamaldehyde (C), TMSCl and 10-20% 2 in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C.

<u>R', R''</u>	<u>Z:E</u>	<u>Aldehyde</u>	<u>Syn:Anti</u>	<u>Yield(%)</u>
TBDMS, Et	97 : 3	B	78 : 22	60
		C	70 : 30	63
TMS, Et	15 : 85	B	19 : 81	58
		C	18 : 82	65
TBDMS, iPr	99 : 1	B	90 : 10	51
TBDMS, iPr	26 : 74	B	25 : 75	55
TBDMS, CHX <sup>a</sup>	82 : 18	B	74 : 26	52

(a) CHX - cyclohexyl



scheme 2

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