J. Org. Chem. **1990**, *55*, 6235–6236 **6235**

Organolanthanide Catalysis of a Mukaiyama Addition Reaction

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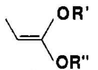
Received September 25, 1990

Summary: Bis[bis(1,3-trimethylsilyl)cyclopentadienyl]ytterbium(III) chloride, Cp''_2YbCl, **2**, is an effective *catalyst* in the presence of additional trimethylsilyl chloride for the reaction of silyl ester enolates, such as the trimethylsilyl enolate of methyl isobutyrate, **1**, with aliphatic and aromatic aldehydes, to yield β-silyloxy esters. The reaction shows good diastereoselection that is readily rationalized with a cyclic transition-state mechanism in which a key feature is the important role played by restricted coordination space around the lanthanide cation.

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.[1] In 1973, Mukaiyama, Banno, and Narasaka[2] 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- or polycondensation or self-condensation products but has the disadvantage that stoichiometric amounts of the Lewis acid are normally required. Moreover, the reaction shows poor diastereoselection.[3] The reaction can be catalyzed by triphenylmethyl cation[4] or by fluoride ion,[5] 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.[6]

Enolate salts of lanthanides have been shown to undergo condensation reactions with carbonyl compounds.[7] Of more immediate relevance is the recent demonstration that lanthanum chloride promotes the Mukaiyama addition of **1**, the trimethylsilyl enolate of methyl isobutyrate, with benzaldehyde.[8] These reactions of "bare" lanthanides 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, Cp''_2YbCl, **2**,[9] is an effective *catalyst* for the reaction of **1** with benzaldehyde. Use of other silyl ester enolates shows useful diastereoselection, making this the first such example of an organolanthanide catalyst.

Table I. Reactions of Silyl Enol Ethers 3 with Benzaldehyde (B) or Cinnamaldehyde (C), TMSCl, and 10–20% 1 in CH_2Cl_2 at –78 °C



3

R′, R″	*Z*:*E*	aldehyde	syn:anti[a]	yield, %
TBDMS, Et	97:3	B	78:22	60
		C	70:30	63
Et, TMS	15:85	B	19:81	58
		C	18:82	65
TBDMS, iPr	99:1	B	90:10	51
iPr, TBDMS	26:74	B	25:75	55
TBDMS, CHX[b]	82:18	B	74:26	52

[a] Analysis by NMR; cf.: Heathcock, C. H.; Buse, C. T.: Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. [b] CHX = cyclohexyl.

Reaction occurs in fair to good yield in methylene chloride at various temperatures. Facile reaction requires the presence of trimethylsilyl chloride (TMSCl) and can be carried out with as little as 0.01 mol of catalyst or less and at temperatures as low as –70 °C. In a typical procedure, 1 mol each of **1**, the aldehyde, and trimethylsilyl chloride was stirred in methylene chloride at room temperature with 0.01–0.1 mol 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 works well 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. In particular, **2** also promotes the Lewis acid self-condensation of butyraldehyde.[10] Highly hindered aldehydes such as pivalaldehyde did not react, nor did the ketones acetophenone and cyclohexanone. Reaction with an α,β-unsaturated aldehyde gave exclusively the 1,2-addition product.

The diastereoselectivity was studied with the use of isomeric silyl enol ethers from propionate 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 *tert*-butyldimethylsilyl (TBDMS) chloride gives mostly the *Z* isomer.[11] The *Z* isomers are generally more readily available in purer form than the *E* isomers;[12] the pure *Z*

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[1] For reviews, see: Heathcock, C. H. *Science* **1981**, *214*, 395; *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3, p 111. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

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[10] Gonzalez, H., unpublished results.

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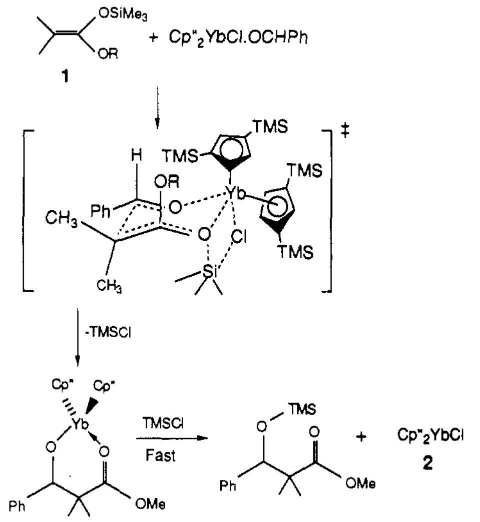
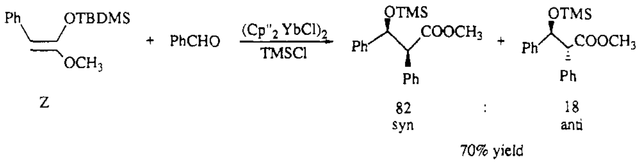
[12] However, see: Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.

Scheme I



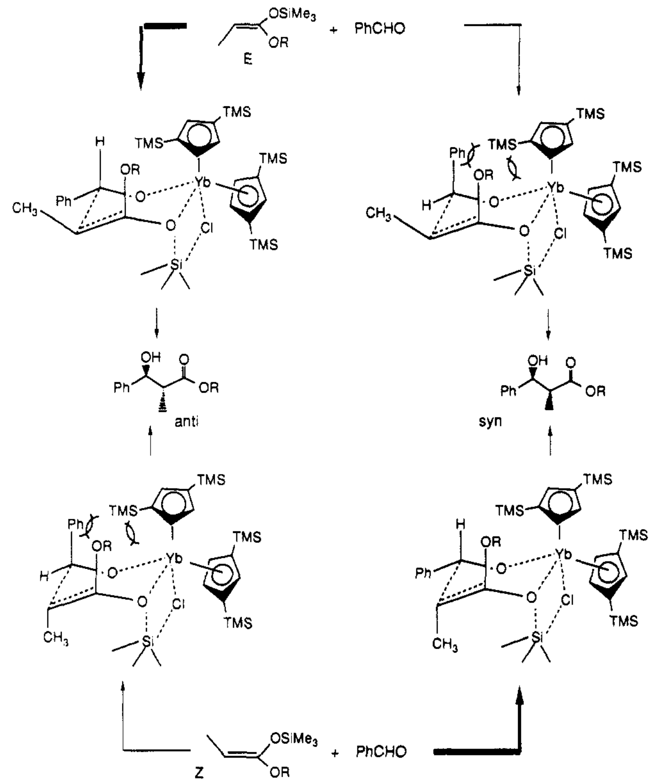
isomer is readily available from methyl phenylacetate and gave the result:



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.[13] The use of other Lewis acids in such reactions generally gives poor diasterioselection.[14]

The ytterbium compound **2** is a dimer in inert solvents but forms a solvated monomer in donor solvents such as THF.[15] Color changes and the IR spectrum indicate that **2** forms a complex with the aldehyde, $Cp''_2YbCl{\cdot}OCHR$, which undergoes rate-determining reaction with the silyl enolate to give a hypothesized internally coordinated Yb intermediate. The latter rapidly reacts with the TMSCl present to give the product which is hydrolyzed on workup. This mechanism is shown in Scheme I and is consistent with the kinetic observation that the rate is independent of the concentration of TMSCl so long as some is present.[13]

Scheme II



On the basis of this mechanism, the stereochemical results are readily rationalized by the transition-state structures in Scheme II. The favored pathway in each case is shown by the heavy arrow. This scheme is an obvious application of the Zimmerman–Traxler model[16] as extended to the Mukaiyama addition by Chan et al.[17] The organolanthanide compound **2** thus shows promise as a useful addition of the growing armory of reagents for promoting stereocontrolled 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.

Acknowledgment. This work was supported by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of the Department of Energy, under Contract Number DE-AC03-76SF00098.

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Total Synthesis of *dl*-Stenine

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Received October 8, 1990

Summary: Intramolecular Diels–Alder cycloadduct **10** was converted to the *Stemona* alkaloid stenine (**1**) via a reaction sequence that features a Curtius rearrangement (**12** → **13**), Eschenmoser–Claisen rearrangement (**19** → **20**) and stereoselective free radical allylation (**4** → **21**).

The roots of *Stemona tuberosa* and *Stemona japonica* have long been used in Chinese folk medicine as insecti-