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Diastereoselective Addition of Organoytterbium Reagents to Carbonyl Substrates

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Summary: Organoytterbium reagents, prepared by the addition of organolithiums or organomagnesiums to ytterbium(III) triflate, react in a highly diastereoselective fashion with a variety of chiral aldehydes and ketones.

Control of diastereofacial selectivity in carbonyl addition reactions is still a challenging problem for organic chemists. Development of organotitanium reagents by Reetz and co-workers[2] has contributed tremendously to progress in this area, and other organometallics have also been touted as providing excellent diastereoselectivity in carbonyl addition to chiral aldehydes and ketones.[3] Currently available methods are sometimes quite limited in scope, however. In particular, use of organotitanium reagents is restricted by the narrow range of organic ligands that can be tolerated on the metal.[2] Herein we report diastereofacial selectivities achieved in the addition of organoytterbium reagents to various chiral cyclic and acyclic carbonyl substrates. In addition to fulfilling the requirement for high diastereoselectivity, we have found that diverse organoytterbiums can be utilized in the process. Consequently, these reagents nicely complement the organotitanium reagents utilized so successfully by Reetz and others.[2]

Organolanthanide reagents have made a significant impact on selective organic synthesis[4] and in particular on those reactions involving carbonyl addition reactions. For example, organocerium reagents derived from a variety of organolithium reagents show little enolization in their reactions with carbonyl substrates.[5] Lanthanum reagents prepared from tris(trifluoromethanesulfonato)lanthanum and organolithium reagents have been added to amides, generating ketones in a highly selective process.[6]

Because of the imposing steric bulk of lanthanide complexes,[7] we felt that organolanthanide reagents would be suitable candidates to achieve high diastereofacial selectivity in addition to chiral aldehydes and ketones. After screening a number of organolanthanide reagents in carbonyl addition reactions, we found complexes derived from tris(trifluoromethanesulfonato)ytterbium [Yb(OTf)$_3$, ytterbium(III) triflate][8] exceptional for diastereocontrolled carbonyl addition reactions.

When Yb(OTf)$_3$ in THF at −78 °C was treated with 1 equiv of methyllithium, an intensely colored burgundy solution of the organoytterbium reagent was produced. Upon addition of 2-methylcyclohexanone the color faded rapidly, providing a nearly colorless solution. Analysis of the product alcohols[9] by capillary gas chromatography revealed that a 98.1:1.9 ratio of axial to equatorial alcohol had been produced, resulting from preferential equatorial attack of the methylytterbium reagent on the carbonyl substrate. Table I shows the diastereomeric ratios and yields of product obtained upon addition of methylytterbium reagents to a selected set of ketones and aldehydes. One equivalent of Me$_2$Mg/Yb(OTf)$_3$ provides similar results to those of MeLi/Yb(OTf)$_3$, whereas use of 2 equiv of methyllithium with 1 equiv of Yb(OTf)$_3$ gave slightly lower selectivities. Methylmagnesium bromide/Yb(OTf)$_3$ also gave a slightly lower equatorial/axial attack ratio with an increase in enolization. With the easily enolized ketone, 2-methylcyclopentanone, 46% enolization was observed under standard conditions utilizing MeLi/Yb(OTf)$_3$. However, addition of 1 equiv of tetramethylethylenediamine (TMEDA) reduced enolization to only 5%. In contrast, TMEDA showed little effect on the reaction with 2-methylcyclohexanone except that the diastereomeric ratio was slightly lower.

Somewhat diminished diastereoselectivities were observed as the stereogenic center was further removed from the carbonyl carbon. Thus, 3-methylcyclohexanone and 4-*tert*-butylcyclohexanone provided incrementally lower selectivities. Addition of the organoytterbium reagent to an acyclic aldehyde substrate (2-phenylpropanal) again provided high diastereofacial selectivity and yield, fully comparable to those achieved with organotitanium reagents.

Addition of other organolithium or organomagnesium reagents to Yb(OTf)$_3$ also produced highly colored solutions of stable organoytterbiums. Table II displays the results of our initial studies on addition of these organoytterbium reagents to 2-methylcyclohexanone. High yields of products were obtained in nearly all cases.[10] The high ratio of equatorial to axial attack upon this substrate is equal to or greater than the ratios observed with the widely used organotitanium reagents. Especially significant are the high yields and selectivities of both alkyl- and alkenylytterbium reagents, since the corresponding organotitanium reagents have provided incomplete conversion and/or low diastereofacial selectivities in addition to carbonyl substrates.[2,11]

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(4) For leading reviews, see: (a) Kagan, H. B.; Namy, J. L. In *Handbook on the Physics and Chemistry of Rare Earths*; Gschneidner, K. A., Jr., Eyring, L., Eds.; Elsevier: Amsterdam, 1984; Vol. 6, Chapter 50. (b) Molander, G. A. In *Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1989.

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(8) Prepared from Yb$_2$O$_3$ and triflic acid in water according to the published procedure. Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* 1987, *52*, 1017.

(9) All products were identified by comparison of spectral properties to those of authentic compounds. Yields in the tables refer to purified materials. All the compounds reported have been fully characterized spectroscopically.

(10) The following experimental procedure is representative: To a stirred solution of Yb(OTf)$_3$ (0.418 g, 0.67 mmol) in THF (15 mL) at −78 °C was added vinylmagnesium bromide (0.67 mmol) in THF (0.68 mL). After the mixture was stirred for 0.5 h at −78 °C, 2-methylcyclohexanone (0.073 mL, 0.61 mmol) was added dropwise. The solution changed color from orange to pale yellow. After 0.5 h at −78 °C the reaction was hydrolyzed with 1 mL of saturated NaHCO$_3$ solution and warmed to room temperature. The organic phase was separated, and the aqueous phase was extracted with Et$_2$O. The combined organic extracts were washed with brine and dried over MgSO$_4$. Capillary gas chromatographic analysis revealed that the product was generated as a 97.5:2.5 mixture of diastereomers. After removal of solvent the residue was purified by flash chromatography (silica gel, 9:1 hexanes–ethyl acetate) to provide 76 mg (89%) of 1-ethenyl-2-methylcyclohexan-1-ol.

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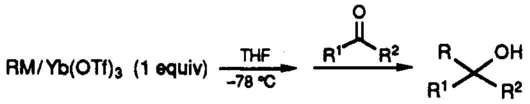
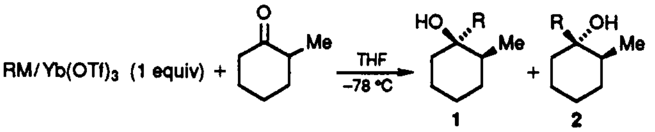
Table I. Diastereoselective Addition of Organoytterbium Reagents to Selected Ketones and Aldehydes



RM(X) (equiv)	substrate (equiv)	diastereomer ratio (% isolated yield)	% enolization	literature diastereo-selectivity
methyllithium (1.0)	2-methylcyclohexanone (0.81)	98.1:1.9[a] (91)	<1	96:4[b]
methyllithium (2.0)	2-methylcyclohexanone (0.97)	97.1:2.9[a] (99)[c]	<1	
methylmagnesium bromide (1.0)	2-methylcyclohexanone (0.85)	96.5:3.5[a] (87)[c]	13	88:12[d]
dimethylmagnesium (1.0)	2-methylcyclohexanone (0.9)	97.8:2.2[a] (94)	<1	80:20[e]
methyllithium (1.1) TMEDA	2-methylcyclohexanone (0.83)	96.6:3.4[a] (98)[c]	2	
methyllithium (1.1) TMEDA	2-methylcyclopentanone (0.85)	86.3:13.7[f] (81)	5	70:30[g]
methyllithium (1.0)	3-methylcyclohexanone (0.83)	85.3:14.7[a] (79)	3	89:11[b]
methyllithium (1.5)	4-*tert*-butylcyclohexanone (1.0)	82.2:17.8[a] (97)	0	94:6[b]
methyllithium (1.1)	2-phenylpropanal (0.86)	90.6:9.4[h] (88)	<1	93:7[b]

[a] Major product is axial alcohol. [b] Using MeTi(Oi-Pr)$_3$, see ref 2. [c] Yield determined by gas chromatography. [d] Using MeMgCl alone, see: Di Maio, G.; Pellegrini, M.; Tardella, P. *Ric. Sci.* **1968**, *38*, 240. [e] Using Me$_2$Mg alone, see ref 13. [f] Major product is (1*R**,2*S**)-1,2-dimethylcyclopentanol. [g] Using MeLi alone, see: Battioni, J.; Chadkiewicz, W.; Cadiot, P. *C. R. Acad. Sci., Ser. C* **1967**, *264*, 991. [h] Major product is (1*R**,2*R**)-3-phenyl-2-butanol.

Table II. Diastereoselective Addition of Organoytterbium Reagents to 2-Methylcyclohexanone



RM(X) (equiv)	equiv of ketone	ratio 1:2 (% isolated yield)	% enolization	literature diastereo-selectivity
n-butyllithium (2.0)	1.00	99.0:1.0 (91)	<1	83:17[a]
phenyllithium (1.1)	0.84	>99:<1 (73)	0	>99:<1[b]
trans-1-hexenyllithium (2.0)	1.00	96.7:3.3 (75)	3.5	95:5[c]
cis-1-hexenyllithium (2.0)	1.00	97.4:2.6 (78)	1	83:17[d]
vinylmagnesium bromide (1.0)	0.9	97.5:2.5 (89)	7.5	91:9[e]
tert-butyllithium (2.0)	1.00	200:1 (53)	14	100:0[f]

[a] Our experiment with *n*-BuLi and 2-methylcyclohexanone. [b] Using PhTi(Oi-Pr)$_3$, see ref 2. [c] Our experiment with *trans*-1-hexenyllithium and 2-methylcyclohexanone. [d] Our experiment with *cis*-1-hexenyllithium and 2-methylcyclohexanone. [e] Our experiment with vinylmagnesium bromide and 2-methylcyclohexanone. [f] Using *t*-BuLi alone, see ref 13.

Although at this time structural evidence for the nature of the reagents involved is rather sparce,[6,12] there is compelling circumstantial evidence that the diastereoselectivity is due to the generation of discrete organolanthanide species and not to a "complexing salt effect" as is observed with carbonyl addition reactions in the presence of LiClO$_4$.[13] For example, while the complexing salt effect (i.e., enhanced diastereoselectivity) observed with LiClO$_4$ is virtually nonexistent in THF, the reactions utilizing Yb(OTf)$_3$ appear to work best in THF. Lithium perchlorate is also reported to be ineffective at increasing diastereoselectivity when used in conjunction with dialkylmagnesium nucleophiles. In contrast, the reaction involving Me$_2$Mg in the presence of Yb(OTf)$_3$ shows greatly enhanced diastereoselectivity (Table I). That LiOTf is not the "complexing salt" involved has been demonstrated by performing carbonyl addition reactions on 2-methylcyclohexanone, 4-*tert*-butylcyclohexanone, and 2-phenylpropanal with MeLi/LiOTf. In these reactions LiOTf showed little or no effect on diastereoselectivity in the carbonyl addition reaction.

Regardless of the precise nature of the species involved, the generality of the procedure described herein and the high diastereoselectivities and yields obtained are attractive features that render organoytterbium reagents a useful alternative to other less selective organometallic reagents. We are continuing our investigations by performing structural studies of these and related lanthanide complexes and by conducting a comprehensive investigation into the reactions of organolanthanides with diverse electrophilic substrates. In addition, reactions will be performed with completely different ligands on the organolanthanide complex as a means to further increase selectivity.

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(12) Organolanthanide reagents prepared in this manner from organolithium reagents have been formulated as neutral species.[5,6] However, several "ate" complexes have been prepared and structurally characterized. See for example: (a) Schumann, H.; Müller, J.; Bruncks, N.; Lauke, H.; Pickardt, J. *Organometallics* **1984**, *3*, 69. (b) Schumann, H.; Müller J. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 276. (c) Wayda, A. L.; Evans, W. J. *J. Am. Chem. Soc.* **1978**, *100*, 7119.

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