

Yb(fod)₃-Promoted Ene Reaction of Aldehydes With Vinyl Ethers

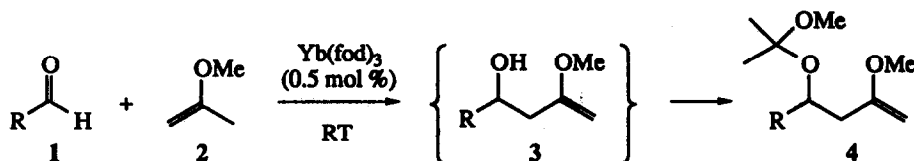
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ABSTRACT: Catalytic amounts of Yb(fod)₃ catalyze a bimolecular ene-like reaction between ordinary aldehydes and vinyl ethers, in which the oxygen functionality is located at the central carbon of an allylic system. These reactions proceed at room temperature in high yield.

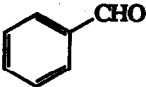
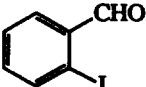
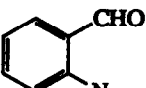
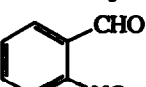
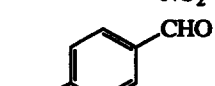
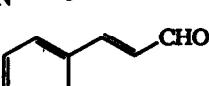
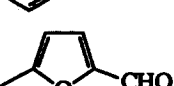
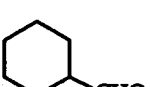
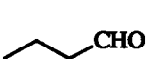
The synthetic possibilities offered by the ene reaction between carbonyl compounds and olefins have been amply recognized.² Intramolecular variants of such processes may be carried out in a truly catalytic mode,³ but bimolecular reactions normally require suprastoichiometric amounts of Lewis acids, unless very reactive aldehydes are used.⁴ We now report that traces of Yb(fod)₃ (0.5 mol %),⁵ catalyze a bimolecular ene-like reaction between ordinary aldehydes and vinyl ethers in which the oxygen functionality is located at the central carbon of an allylic system, e.g. 2-methoxypropene. The primary ene products, alcohols 3, undergo *in situ* reaction with excess vinyl ether, providing derivatives 4 directly (Scheme 1). Aromatic aldehydes react conveniently as solutions in excess ether (procedure A), while enolizable aldehydes react best in the presence of cosolvents such as CH₂Cl₂ (procedure B).⁶ The transformation takes place at room temperature under experimentally simple conditions, and the products emerge consistently in a state of high purity, eliminating completely any need for further chromatography or distillation. This appears to be the first example of a truly catalytic bimolecular ene-like reaction that occurs readily with unactivated aldehydes (Table 1).

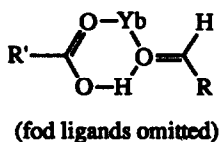
Scheme 1



Addition of a small amount of (insoluble) K₂CO₃ to a reaction mixture prevents formation of 4, and yields alcohols 3 instead. However, larger amounts of K₂CO₃ or soluble bases (e.g. Et₃N) completely inhibit the ene process itself. Similarly, rigorous purification of solvents, reagents and Yb(fod)₃ retards the reaction considerably. Catalytic activity is restored in the latter "slow" systems upon addition of traces of acetic acid (1-2 μL),⁷ and optimal activity is expressed upon addition of silica gel to the reaction mixture.⁸ These observations implicate protonic catalysis in the formation of 3. We believe that the species involved in the catalytic step may be a ternary lanthanide-carboxylic acid-aldehyde complex in which the aldehyde experiences "double activation," perhaps as shown in Scheme 2.⁹ We note that ordinary Brønsted- or Lewis acids do not promote our reaction; rather, they polymerize the vinyl ether. In accord with a recent discovery,¹⁰ it appears that unique catalytic properties pertain to hydroxylic units located within the coordination sphere of highly charged metal ions.

Table I: Reaction of Representative Aldehydes with 2-Methoxypropene.

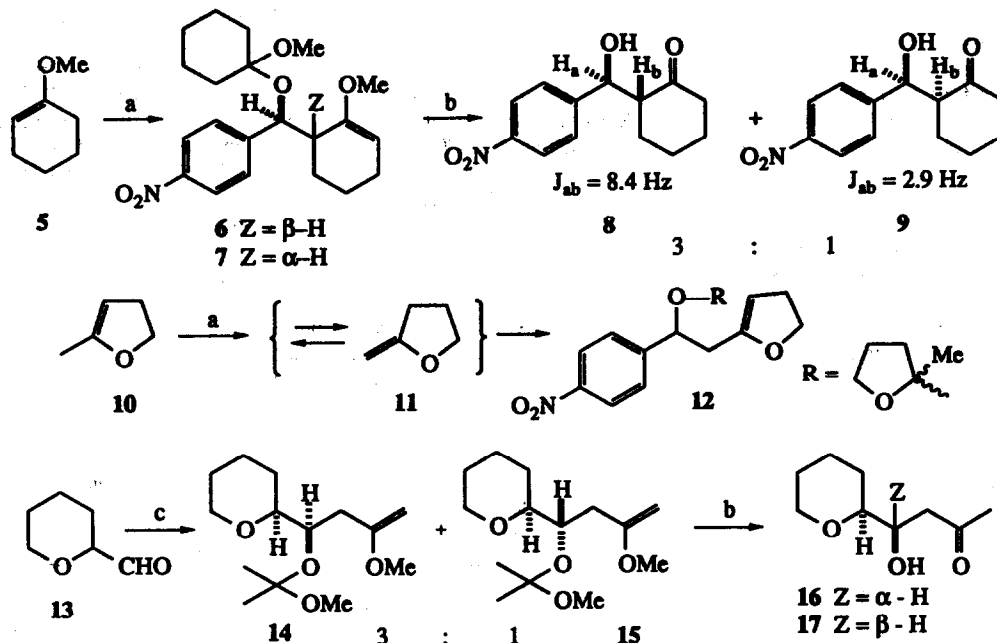
Aldehyde	Entry (1, 3-4)	Procedure	Isolated Yield of 4
	a	A	100
	b	A	99
	c	A	97
	d	A	100
	e	A	90
	f	A	83
	g	A	83
	h	B	80
	i	B	71

Scheme 2

The new reaction is not limited to methoxypropene, and indeed, it appears to have wide scope. Ether **5** combined with 4-nitrobenzaldehyde to give a 3:1 mixture of **6** and **7**. The stereochemistry was assigned after mild hydrolysis to ketols **8** and **9** on the basis of the coupling constant for the indicated protons.¹¹ Reaction of 4-nitrobenzaldehyde with ether **10** gave only **12** as a 1.5:1 mixture of unassigned diastereomers at the level of the OH blocking group. This result is interpreted in terms of rapid proton-mediated equilibration of **10** with its isomer **11**, and faster reaction of the

aldehyde with the less sterically encumbered **11**. Finally, reaction of aldehyde **13** with **2** proceeded with a 3:1 selectivity in favor of the Cram-Felkin diastereomer **14** (96%). Again, the stereochemistry was assigned after hydrolysis to ketols **16** and **17**, followed by comparison of these with the products of Sakurai reaction of **13** (Scheme 3).¹²

Scheme 3



(a) 1c, procedure A, 83 % (6 : 7 = 3 : 1), 90 % (12); (b) 1 N HCl, THF, 95 % (8 - 9), 90 % (16 - 17); (c) 2, procedure B, 96 % (14 : 15 = 3 : 1).

In summary, the transformation of Scheme 1 is experimentally simple, mild, and efficient. Products 4 may be readily converted into a variety of synthetically useful building blocks. The new reaction thus appears to have considerable synthetic potential. A number of synthetic applications are currently under study, and further results in this area will be described in due course.¹³

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REFERENCES AND FOOTNOTES

1. Recipient of the Robert A. Welch Predoctoral Fellowship.
2. Reviews: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* 1992, 92, 1021; (b) Snider, B. B. *Acc. Chem. Res.* 1980, 13, 426. Recent examples: cf. (c) Tanino, K.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.* 1990, 31, 2165; (d) Mikami, K.; Terada, M.; Sawa, E.; Nakai, T. *Tetrahedron Lett.* 1991, 32, 6571; (e) Tanino, K.; Shoda, H.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.* 1992, 33, 1337; (f) Nakamura, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* 1993, 34, 477.
3. Example of lanthanide catalysis in an intramolecular ene reaction: (a) Ziegler, F. E.; Sobolov, S. B. *J. Am. Chem. Soc.* 1990, 112, 2749. For related reactions, see, e.g.: (b) Gu, J. H.; Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* 1992, 33, 1465; (c) Kobayashi, S.; Hachiya, I. *Tetrahedron Lett.* 1992, 33, 1625, (d) Mikami, K.; Terada, M.; Nakai, T. *J. Org. Chem.* 1991, 56, 5456.
4. Catalytic ene reactions with glyoxylate esters: Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* 1990, 112, 3949. Uncatalyzed ene reactions normally proceed only with particular enophiles. Cf. (a) Magnus, P.; Mugrage, B. *J. Am. Chem. Soc.* 1990, 112, 462; (b) Beak, P.; Song, Z.; Resck, J. E. J.

- Org. Chem.* 1992, 57, 944.
- Europium-based shift reagents such as $\text{Eu}(\text{hfc})_3$ also promote this reaction. However, ytterbium complexes appear to possess superior catalytic activity.
 - Procedure A: silica gel (Merck 60-230 mesh, 100 mg) was added to a solution of aldehyde (2 mmol), $\text{Yb}(\text{fod})_3$ (10 mg), and acetic acid (1 μL) in 20 mmol of 2-methoxypropene. Stirring (argon) at 25° C was continued until all the initially formed 3 had been converted to 4 (6-48 hrs, TLC/NMR), then the mixture was poured into sat. aq. NaHCO_3 and extracted with CH_2Cl_2 . Evaporation yielded the crude product. Procedure B: same as procedure A, except that the aldehyde is introduced as a 10 % v/v solution in CH_2Cl_2 . The reaction accelerates appreciably at 40-50° C, but the yields decrease.
 - It is known that lanthanide fod complexes do not decompose in the presence of carboxylic acids: Sievers, R. E. *NMR Shift Reagents*. Academic Press: New York, N.Y. 1973.
 - The role of silica gel is not clear. In its presence, the reactions proceed faster and the products emerge in a state of greater purity. Perhaps the silica sequesters adventitious moisture / alcohol contaminants from the medium, thus preventing their coordination to catalytically active sites around the Yb complex.
 - The reaction may be induced simply upon addition of the lanthanide complex to a mixture of aldehyde and vinyl ether (no acetic acid or silica gel present), but under these conditions an induction period is observed. It is likely that oxidation of the aldehyde by adventitious air provides the acid necessary to initiate the reaction. No reaction whatsoever occurs without the lanthanide complex.
 - Cf. Hollis, T. K.; Robinson, N. P.; Bosnich, B. *J. Am. Chem. Soc.* 1992, 114, 5464.
 - (a) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* 1973, 95, 3310; (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* 1982, 13, 1.
 - The low selectivity may reflect an intrinsic property of 13: even the Sakurai reaction, which is often highly Cram-Felkin stereoselective in similar systems (Danishefsky, S.; DeNinno, M. P. *Tetrahedron Lett.* 1985, 26, 823) afforded a modest 5:1 Cram-Felkin selectivity with this aldehyde.
 - Spectral data for representative aldehyde - vinyl ether adducts: 4a ^1H : 7.30-7.19 (c. m, 5H), 4.93 (br. t, 1H, $J = 6.8$ Hz), 3.80 (d, 1H, B part of AB, $J = 1.9$ Hz), 3.76 (d, 1H, A part of AB, $J = 1.9$ Hz), 3.48 (s, 3H), 3.04 (s, 3H), 2.60 (dd, 1H, $J_1 = 13.7$ Hz, $J_2 = 7.4$ Hz), 2.31 (dd, 1H, $J_1 = 13.7$ Hz, $J_2 = 6.7$ Hz), 1.37 (s, 3H), 1.11 (s, 3H). ^{13}C : 161.0, 144.0, 127.9, 126.7, 126.3, 101.8, 83.1, 71.1, 54.5, 49.0, 45.4, 26.0, 24.9. IR: 3070, 3030, 2984, 2944, 2831, 1656, 1616, 1503, 1450, 1383, 1211, 1144, 1078, 1025, 951, 819, 753, 700. MS: 193 ($\text{M}^+ - \text{MeOC}=\text{CH}_2$), 179 ($\text{M}^+ - \text{Me}_2\text{COMe}$), 161, 147, 131, 129, 121, 105, 104, 103, 91, 89, 79, 78, 77, 73 (100%), 43. 4h: ^1H 3.89-3.87 (q, 2H, AB, $J = 1.8$ Hz), 3.81 (ddd, 1H, $J_1 = J_2 = 6.5$ Hz, $J_3 = 3.31$ Hz), 3.49 (s, 3H), 3.21 (s, 3H), 2.30-2.20 (c. m, 2H), 2.0-1.2 (c. m, 11 H), 1.33 (s, 3H), 1.85-0.9 (c. m, 11H), 1.32 (s, 3H), 1.30 (s, 3H). ^{13}C : 162.1, 100.7, 82.2, 73.3, 54.5, 49.0, 42.0, 37.6, 28.2, 26.8, 26.7, 26.6, 25.2, 25.0. IR: 2991, 2938, 2851, 1656, 1450, 1377, 1204, 1151, 1072, 1031, 799. MS: 225 ($\text{M}^+ - \text{OMe}$), 209, 162, 155, 115, 89, 73 (100%), 43. 3 : 1 Mixture of 8 and 9: ^1H : maj. & min.: 8.18 (app. br. d, 2+2 H, $J = 8.2$ Hz), 7.48 & 7.47 (two app. br. d, 2+2 H, $J = 8.2$ Hz), Major: 4.88 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.3$ Hz, CHOH), 4.12 (br. d, 1H, $J = 2.3$ Hz, OH), min.: 5.46 (br. s, 1H, decoupling shows dd, $J_1 = 3.0$ Hz, $J_2 = 2.9$ Hz, CHOH), 3.29 (br. d, $J = 3.0$ Hz, OH), maj. & min.: 2.70-2.25 (c. m, 3+3H), 2.10 (c. m, 1+1H), 1.90-1.40 (c. m, 5+5H). ^{13}C NMR: maj.: 216.0, 149.0, 148.3, 127.8, 123.4, 73.8, 57.0, 42.5, 30.6, 27.5, 24.5. min.: 214.0, 147.3, 146.5, 126.5, 123.3, 69.9, 56.6, 42.5, 30.6, 27.7, 25.8. IR: 3509, 2937, 2864, 1696, 1609, 1523, 1350, 1297, 1224, 1191, 865. MS: 249 (M^+), 231 ($\text{M}^+ - \text{H}_2\text{O}$), 214, 185, 184, 152, 151, 150, 98 (100%), 83, 77, 70. 1.5 : 1 Mixture of 12 ^1H : maj. & min.: 8.16 (app. br. d, 2+2H, $J = 8.4$ Hz), 7.48 & 7.47 (two app. br. d, 2+2H, $J = 8.4$ Hz); 4.53 (br. s, 1+1H), 4.26 (c. m, 2+2H), 3.93 (c. m, 1+1H), 2.65-2.45 (c. m, 3+3H), 2.40-1.60 (c. m, 5+5H); maj.: 4.96 (t, 1 H, $J = 6.7$ Hz), 2.90 (dt, 1H, $J_1 = 8.3$ Hz, $J_2 = 3.9$ Hz), 1.49 (s, 3H), min.: 5.05 (t, 1H, $J = 6.8$ Hz, CHOR), 3.56 (c. m, 1H), 1.09 (s, 3H). MS: 236 ($\text{M}^+ - \text{OH blocking group}$), 218, 200, 176, 170, 150, 141, 130, 128, 115, 103, 85 (100 %); 43. 3 : 1 Mixture 14 and 15: ^1H NMR: maj. & min.: 4.35 (c. m, 1 + 1H); 4.15 (d, 1H, min., $J = 1.4$ Hz); 4.08 (d, 1H, maj., $J = 1.6$ Hz); 3.93 (d, 1H, min., $J = 1.5$ Hz); 3.90 (d, 1H, maj. $J = 1.6$ Hz); 3.60 (c. m., 1 + 1H); 3.30 (s, 3H, maj.); 3.24 (s, 3H, min.); 3.22 (s, 3H, maj.), 3.17 (s, 3H, min.), 2.95 (dd, 1H, A part of AB, min., $J_1 = 13.7$ Hz, $J_2 = 4.8$ Hz); 2.76 (dd, 1H, A part of AB, maj., $J_1 = 14.2$ Hz, $J_2 = 6.2$ Hz), 2.55 (dd, 1H, B part of AB, maj., $J_1 = 14.2$ Hz, $J_2 = 7$ Hz); 2.52 (dd, 1H, B part of AB min., $J_1 = 13.7$ Hz, $J_2 = 7.5$ Hz); 1.8 - 1.0 (m., 8H); 1.47 (s, 3H, maj.); 1.43 (s, 3H, maj.), 1.39 (s, 3H, min.), 1.37 (s, 3H, min.). ^{13}C : 161.4, 100.9, 82.6, 79.9, 71.7, 68.5, 54.5, 49.2, 36.9, 26.8, 26.2, 25.2, 25.0, 23.6. IR: 2988, 2943, 2846, 1654, 1448, 1377, 1299, 1261, 1203, 1151, 1087, 1048, 900, 803. MS: 186 ($\text{M}^+ - \text{OC}(\text{OMe})\text{Me}_2$), 169, 137, 85, 73 (100%), 72, 55, 43.