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Regioselective Lewis Acid-Mediated [1,3] Rearrangement of Allylvinyl Ethers

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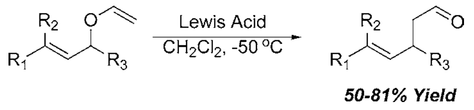
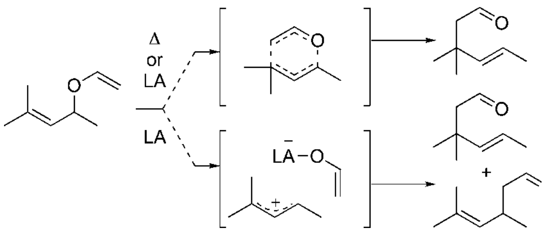
ABSTRACT



Aluminum and copper Lewis acids were implemented to effect a regioselective [1,3] rearrangement of allylvinyl ethers in moderate to good yields. The use of trisubstituted alkenes leads to depressed levels of Claisen products.

The formation of sterically congested carbon−carbon bonds with control of stereochemistry still represents a formidable challenge in organic synthesis. One tool that has met some of these challenges is the Claisen rearrangement, a [3,3] rearrangement of allylvinyl ethers.[1] This thermal sigmatropic rearrangement has been shown to relay stereochemical information from the cleaving C−O bond to the forming C−C bond via a concerted transition state.[2] More recently, the use of Lewis acids has provided rate acceleration for the Claisen rearrangement.[1] However, under the Lewis acid manifold, ionic intermediates have been proposed, which diverges from the generally accepted concerted mechanism.[3] If true ionic intermediates do exist, then other regioisomeric products should be observed. Yamamoto and co-workers reported that pentadienyl vinyl ethers undergo rearrangement to produce a mixture of [1,3], [3,3], and [5, 3] regioisomers in the presence of their bulky aluminum bisphenoxy Lewis acid.[3] Grieco and co-workers, under strongly ionizing conditions, were able to selectively produce [1,3] rearrangement products from sterically hindered allylvinyl ethers.[4] Gansauer has also illustrated a $Cu(OTf)_2$- and $B(C_6F_5)_3$-catalyzed regioselective [1,3] rearrangement of *tert*-butyl alcohol, benzyl alcohol, and isophorone-derived vinyl ethers.[5,6] In these cases, the Lewis acid-mediated [1,3] rearrangement of allylvinyl ethers necessarily proceeds through an allyl cation and metallo-enolate ion pair. As part of our efforts aimed at developing stereoselective [1,3] rearrangements,[7,8] we initiated a study to harness this reactivity, elucidate the factors that govern regioselectivity, and explore the scope of the [1,3] rearrangement of allylvinyl ethers (Scheme 1). Herein, we disclose our results.

Scheme 1. [3,3] vs [1,3] Rearrangement



Experimentation began with a brief Lewis acid screen using cinnamyl vinyl ether **1**. Cu(II), Sn(IV), and Ti(IV)

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(1) (a) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 223−247. (b) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, pp 827−873. (c) Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939−3002.

(2) For a mechanistic discussion, see: Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219−225.

(3) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316−322.

(4) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488−5489.

(5) (a) Gansauer, A.; Fielenbach, D.; Stock, C. *Adv. Synth. Catal.* **2002**, *344*, 845−848. (b) Gansauer, A.; Fielenbach, D.; Stock, C.; Geich-Gimbel, D. *Adv. Synth. Catal.* **2003**, *345*, 1017−1030.

(6) Other examples of [1,3] rearrangements include: (a) Shi, G.; Cai, W. *J. Org. Chem.* **1995**, *60*, 6289−6295. (b) Sperling, D.; Reissig, H.-U.; Fabian, J. *Eur. J. Org. Chem.* **1999**, 1107−1114. (c) Shiina, I.; Nagasue, H. *Tetrahedron Lett.* **2002**, *43*, 5837−5840. (d) Novikov, A. V.; Kennedy, A. R.; Rainier, J. D. *J. Org. Chem.* **2003**, *68*, 993−996. (e) Suzuki, T.; Inui, M.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2003**, *44*, 3713−3716. (f) Cai, Y.; Roberts, B. P. *Tetrahedron Lett.* **2003**, *44*, 4645−4648.

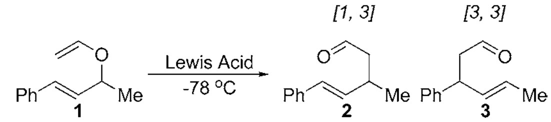
(7) Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720−9721.

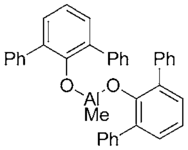
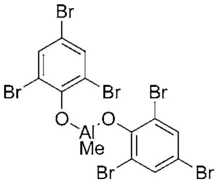
(8) Nasveschuk, C. G.; Rovis, T. *Angew. Chem., Int. Ed.* http://www3.interscience.wiley.com/cgi-bin/fulltext/110473806/PDFSTART.

10.1021/ol0505151 CCC: $30.25

Lewis acids provided mixtures of [1,3] and [3,3] adducts (entries 1−3, Table 1). The reaction worked equally well in CH_2Cl_2 or toluene. Lewis basic solvents were found to be inferior.

Table 1. Initial Lewis Acid Screen



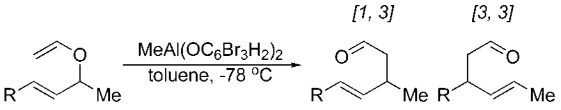
entry[a]	Lewis Acid	ratio [1, 3] : [3, 3]
1	$Cu(OTf)_2$[b]	50 : 50
2	$SnCl_4$	50 : 50
3	$TiCl_4$	67 : 33
4		5 : 95
5		78 : 22 (75%)[c]

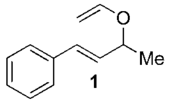
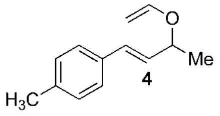
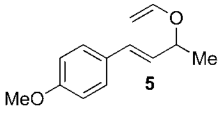
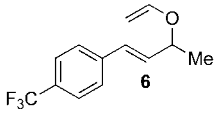
[a] Reactions conducted in toluene or CH_2Cl_2 using 1.05 equiv of Lewis acid. [b] Reaction performed at −50 °C. [c] Combined isolated yield.

Bisphenoxy Al complexes seemed to be better suited for this study due to the electronic and steric perturbations that could be achieved through substitution of the phenol ring.[9] We identified two different Lewis acids that gave complementary regioselectivity for the rearrangement of cinnamaldehyde-derived allylvinyl ether **1** (entries 4 and 5, Table 1). Steric bulk about the Al-metal center proved to be optimal for the [3,3] product, while halide substitution produced a stronger Lewis acid that was moderately [1,3] selective. While this dichotomy is not easy to rationalize, it is evident that there is a fine line between accelerating the concerted [3,3] rearrangement versus generating an ionic intermediate. An increase in the strength of the Lewis acid or in the stability of the allyl cation should result in increased [1,3] selectivity.

We next sought better [1,3] selectivity through electronic variation at the 4-phenyl position of the model substrate. As expected, on the basis of the above rationale, 4-methyl substitution (**4**) increased the [1,3] selectivity to 81:19 (entry 2, Table 2). However, 4-methoxy substitution (**5**) resulted in decreased regioselectivity (entry 3), a situation we ascribe to secondary Lewis acid coordination to the methoxy group. Electron-withdrawing substitution about the ring (**6**) resulted in recovered starting material, even upon warming the reaction mixture from −78 °C to ambient temperature (entry 4).

Table 2. Electronic Effect of a Para Substituent

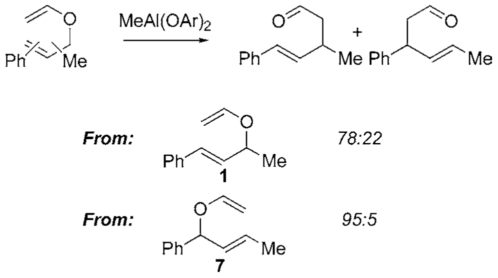


entry[a]	cinnamylvinyl ether	yield (%)[b]	ratio [1, 3] : [3, 3]
1		75	78 : 22
2		61	81 : 19
3		44	75 : 25
4		NP	No reaction[c]

[a] Reactions conducted using 1.05 equiv of Lewis acid. [b] Combined yield. [c] Reaction was warmed to 23 °C and starting material isolated.

To further explore why electronic variation of the substrate did not afford significant improvements in [1,3] regioselectivity, a control experiment was designed (Scheme 2). The regioisomeric allylvinyl ether **7** was synthesized and subjected to the optimized conditions. In the event both regioisomeric allylvinyl ethers provided the same major product. We hypothesize that if an ionic mechanism is operating, the allyl cation and enolate size determines the observed regioselectivity.[10] Indeed, a crossover experiment using deuterium-labeled vinyl ether illustrated nearly com-

Scheme 2. Control Experiment



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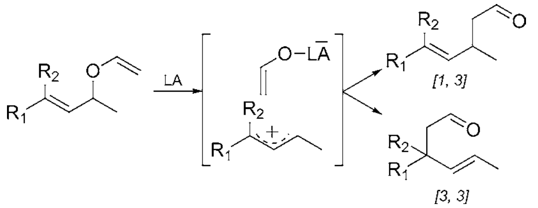
(9) (a) Yamamoto, H.; Maruoka, K. *Pure Appl. Chem*. **1988**, *60*, 21−26. (b) Yamamoto, H.; Yanagisawa, A.; Ishihara, K.; Saito, S. *Pure Appl. Chem*. **1998**, *70*, 1507−1512.

(10) Jia, Z. S.; Ottosson, H.; Zeng, X.; Thibblin, A. *J. Org. Chem*. **2002**, *67*, 182−187.

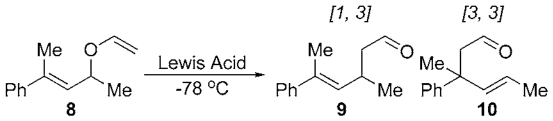
Scheme 3. Proposal for Regiocontrol

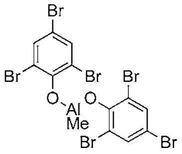


plete scrambling of the label.[11] In an attempt to further control regioselectivity, we turned our attention to allyl systems bearing trisubstituted alkenes. It is known that elevated temperatures are required in systems that undergo [3,3] rearrangement to form quaternary carbon centers.[1] We thought to apply this apparent characteristic of the Claisen rearrangement to our methodology: under ionic conditions, [3,3] recombination of the metallo enolate and allyl cation to form a quaternary carbon center at the tertiary cation should be slow relative to [1,3] recombination at the less hindered secondary cation (Scheme 3).

Trisubstituted allylvinyl ethers were easily prepared by carboalumination of commercially available alkynes,[12] trapping with aldehydes, and Hg(II)-catalyzed transvinylation.[13] A variety of Lewis acids afforded the [1,3] adduct in moderate to good yield and excellent regioselectivity (Table 3).

Table 3. Lewis Acid Screen

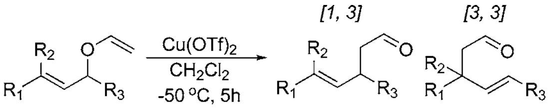


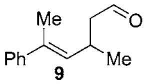
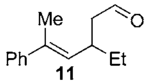
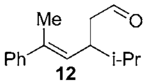
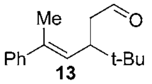
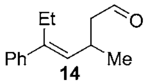
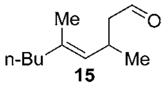
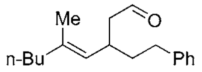
entry[a]	Lewis Acid	yield (%)	ratio [1, 3] : [3, 3]
1	$Cu(OTf)_2$[b]	81	>95 : 5
2	$SnCl_4$	40	80 : 20
3	$TiCl_4$	44	>95 : 5
4	Me_2AlCl	73	>95 : 5
5	$EtAlCl_2$	55	>95 : 5
6		44	>95 : 5

[a] Reactions conducted in toluene or CH_2Cl_2 using 1.05 equiv of Lewis acid. [b] Reaction performed using 10 mol % Lewis acid.

We were delighted to find that a broad range of trisubstituted allylvinyl ethers undergo [1,3] rearrangement in exceptionally high selectivity (Table 4).

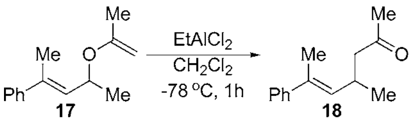
Table 4. Scope of [1,3] Rearrangement



entry[a]	product	yield (%)	ratio [1, 3] : [3, 3]
1	 **9**	81	>95 : 5
2	 **11**	70	>95 : 5
3	 **12**	53	>95 : 5
4	 **13**	63	85 : 15
5	 **14**	64	>95 : 5
6[b]	 **15**	50	80 : 20
7[b]	 **16**	84	69 : 31

[a] Reactions conducted using 5 mol % Lewis acid at −50 °C for 5 h. [b] Reaction conducted at −30 °C for 48 h.

The reaction seems to be somewhat insulated from electronic issues, albeit the yield and the selectivity decreased slightly by switching from aromatic to alkyl substitution of the double bond (entries 6 and 7). Intriguingly, we observe diminished selectivities when a *tert*-butyl group (**13**) is present at the 1-position and the reaction faces a choice between attack at the tertiary position ([3,3]) or the neopentyl position ([1,3]) (entry 4). Rearrangement of an isopropenyl vinyl ether produced a 50:50 mixture of regioisomers when using $Cu(OTf)_2$ as the Lewis acid (eq 1). Increasing the strength of the Lewis acid restored the regioselectivity. We believe this is consistent with our hypothesis that a weaker Lewis acid is capable of accelerating the Claisen via a concerted pathway, while the stronger Lewis acid results in bond ionization.



(1)

69%
90:10 ([1, 3]:[3, 3])

In conclusion, we have reported a regioselective [1,3] rearrangement of allylvinyl ethers. Reactivity issues concern-

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(11) See Supporting Information for details.

(12) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068−1071.

(13) Maruoka, K.; Banno, H.; Yamamoto, H. *Tetrahedron: Asymmetry* **1991**, *2*, 647−662.

ing regioselective [1,3] rearrangement of allylvinyl ethers in terms of Lewis acidity and substrate bias have been highlighted. Work in this area to identify chiral Lewis acids that effect an enantio- and regioselective [1,3] rearrangement of allyl vinyl ethers is currently under way.

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Supporting Information Available: Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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