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A Mild, Regioselective Ketal Claisen Rearrangement Promoted by Triisobutylaluminum

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The ketal Claisen rearrangement is a potentially powerful method to prepare new carbon–carbon bonds, but it has not been used as extensively as other Claisen variants,[2] due in part to the vigorous reaction conditions and to the modest and variable regioselectivity found with unsymmetrical acetals.[3] We report here a new ketal Claisen rearrangement that proceeds under very mild conditions, with regioselectivity that complements the standard acid-catalyzed thermal rearrangement.

While studying the generation of enol ethers using *i*-Bu_3Al-initiated cleavage of acetals,[4] we found that the 1-methyl-1-methoxyethyl ether of geraniol (**2**) not only cleaved to the enol ether, but that the enol ether underwent an unexpected Claisen rearrangement. A mixture of the mixed acetal **2** and the desired enol ether **3** was prepared by treating geraniol with 2-methoxypropene and catalytic $POCl_3$ as shown in Scheme 1. Cleavage of this mixture with *i*-Bu_3Al at 0 °C led to the unexpected rearranged and reduced product **4** in 89% overall yield.[5] There are many examples of Lewis acids catalyzing Claisen rearrangements,[2] and organoaluminum compounds are among the most effective catalysts for Claisen[6,7] and 3-aza-Cope rearrangements.[8] In particular, *i*-Bu_3Al has been shown to be an efficient and mild catalyst for the rearrangement and subsequent reduction of allyl vinyl ethers.[6,9] The most cumbersome part of these Claisen reactions is often generation of the requisite enol ether, and in our new procedure the enol ether is generated *in situ* from the readily available 1-methyl-1-methoxyethyl ethers. We decided to explore the scope of this simple and efficient new ketal Claisen rearrangement.

Our Claisen rearrangement using a variety of allylic alcohols and 2-methoxypropene is shown in Table 1. These reactions were carried out using a one-pot, two-step sequence.[10] The allylic alcohol was combined with 2-methoxypropene and catalytic PPTS in CH_2Cl_2. After acetal formation was complete, 3 equiv of *i*-Bu_3Al was added, and the mixture was stirred for 2 h at 0 °C. The yields range from moderate to excellent, with most of the remaining mass being recovered as starting alcohol. The final *i*-Bu_3Al reduction of the alcohols is generally not selective and leads to mixtures of stereoisomers. The yields are best with simple allylic alcohols and fall off with more reactive diene alcohols and allyl benzyl alcohols, as seen in entries 4 and 5. Acyclic secondary allyl alcohols lead to predominately the *E* alkene on rearrangement, as shown in entries 2, 3, and 5. This selectivity is in contrast to the 1:1 *E*/*Z* mixtures observed with *i*-Bu_3Al-catalyzed allyl vinyl ether rearrangements.[6] The difference can be attributed to the presence of a sterically demanding axial methyl group in the chairlike transition state. This one-pot procedure is a mild and efficient route to ketal Claisen products from simple allylic alcohols.

Scheme 1

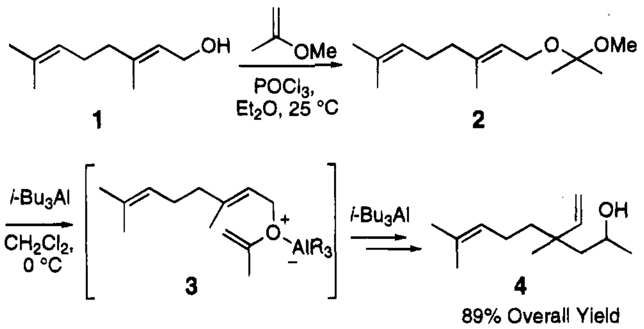
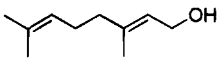
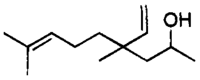
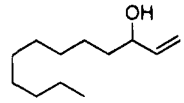
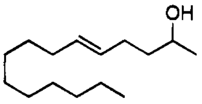
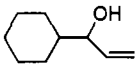
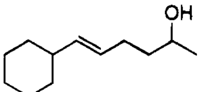
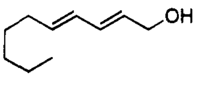
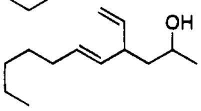
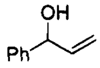
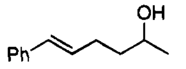
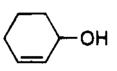
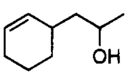


Table 1. Ketal Claisen Rearrangement with 2-Methoxypropene Catalyzed by *i*-Bu_3Al[a]

Entry	Allylic Alcohol	Yield	Product	E/Z ratio[b]
1		89%		
2		81%		88:12
3		80%		89:11
4		59%		
5		49%		87:13
6		88%		

[a] See ref 10 for a representative experimental procedure. [b] The *E*/*Z* ratio was measured by GC.

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[1] Camille and Henry Dreyfus Teacher–Scholar, 1990–1995. Alfred P. Sloan Research Fellow 1992–1994.

[2] (a) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds; Pergamon Press: New York, 1991; Vol. 5; pp 827–873. (b) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205–247.

[3] (a) Daub, G. W.; Sanchez, M. G.; Cromer, R. A.; Gibson, L. L. *J. Org. Chem.* **1982**, *47*, 745. (b) Daub, G. W.; McCoy, M. A.; Sanchez, M. G.; Carter, J. S. *J. Org Chem.* **1983**, *48*, 3876. (c) Daub, G. W.; Lunt, S. R. *Tetrahedron Lett.* **1983**, *24*, 4397.

[4] (a) Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 1363. (b) Naruse, Y.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 6021.

[5] Isolated as an approximately 1:1 mixture of two stereoisomers.

[6] (a) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 3985. (b) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 446.

[7] (a) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316. (b) Yamamoto, H.; Maruoka, K. *Pure Appl. Chem.* **1990**, *62*, 2063. (c) Maruoka, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 7791. (d) Maruoka, K.; Yamamoto, H. *Synlett* **1991**, 793.

[8] (a) Cook, G. R.; Barta, N. S.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 461. (b) Barta, N. S.; Cook, G. R.; Landis, M. S.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 7188. (c) Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1993**, *58*, 5095.

[9] See also: (a) Paquette, L. A.; Friedrich, D.; Rogers, R. D. *J. Org. Chem.* **1991**, *56*, 3841. (b) Philippo, C. M. G.; Vo, N. H.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 2762.

[10] A typical one-pot procedure is illustrated with the use of geraniol: To a solution of geraniol (**1**) (0.500 g, 3.24 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at 0 °C were added 2-methoxypropene (466 mL, 4.86 mmol, 1.5 equiv) and PPTS (ca. 10 mg, 32 μmol, 1 mol %). The mixture was stirred at room temperature and monitored by TLC. Upon formation of the ketal, a 1.0 M solution of *i*-Bu_3Al (9.72 mL, 9.72 mmol, 3 equiv) was added dropwise, and the reaction was stirred at 0 °C for 2 h. The mixture was poured into 20 mL of ice-cold 2 N NaOH, and the layers were allowed to warm and to separate. The aqueous layer was extracted with Et_2O (2 × 20 mL). The organic layers were combined, washed with H_2O (1 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (10% ethyl acetate/hexanes) afforded **4** (0.560 g, 2.85 mmol, 88%) as a thick, colorless oil.

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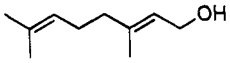
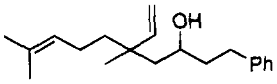
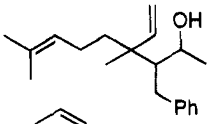
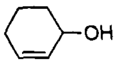
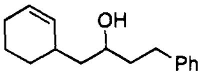
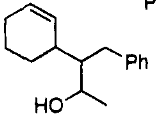
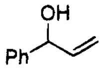
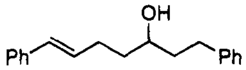
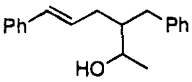
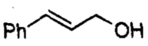
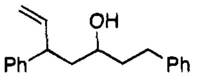
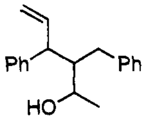
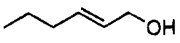
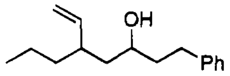
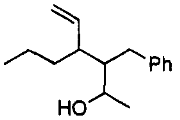
Table 2. Ketal Claisen Rearrangement with Enol Ether 5 Catalyzed by *i*-Bu$_3$Al[a]

Entry	Allylic Alcohol	Method	Yield	Linear: Branched[b]	Linear Product	Branched Product
1		A	67%	100:0		
2		A	63%	91:9		
3		A	30%	87:13		
4		B	49%	87:13		
5		C	50%	88:12		
6		A	43%	89:11		
7		B	38%	94:6		
8		C	40%	93:7		
9		A	49%	75:25		
10		B	58%	94:6		
11		C	69%	96:4		
12	(Daub's Thermal Conditions)	D	79%[c]	9:91[c]		

[a] Method A: (i) enol ether **5**, PPTS, 25 °C, CH$_2$Cl$_2$; (ii) *i*-Bu$_3$Al, 0 °C, CH$_2$Cl$_2$ (one-pot procedure). Method B: (i) enol ether **5**, PPTS, 25 °C, CH$_2$Cl$_2$; (ii) Et$_3$N; (iii) *i*-Bu$_3$Al, 0 °C, CH$_2$Cl$_2$ (one-pot procedure with Et$_3$N quench). Method C: (i) enol ether **5**, PPTS, 25 °C, CH$_2$Cl$_2$; (ii) *i*-Bu$_3$Al, 0 °C, CH$_2$Cl$_2$ (two-pot procedure). Method D: dimethoxy acetal **6**, propionic acid, 110 °C, 16 h (Daub's thermal conditions). [b] Ratios determined by GC and ^{1}H NMR. [c] The yield and ratio are for the corresponding ketone products formed under the Daub reaction conditions.

To evaluate the sequence using an unsymmetrical ketal, 2-methoxy-4-phenyl-1-butene (**5**) was prepared[11] and reacted with a variety of allylic alcohols, as shown in Table 2. The reactions were initially carried out using the same one-pot, two-step procedure described previously (method A).[10] All of the rearrangements were successful under these conditions, but the yields were moderate and starting alcohol was recovered in all cases. The most interesting aspect of these rearrangements is the regioselectivity of the enol ether formation and subsequent rearrangement. For each example, the major (linear) product derives from the less substituted enol ether, while the minor (branched) product derives from the more substituted enol ether. Presumably, the bulky *i*-Bu$_3$Al reagent coordinates to the less hindered acetal oxygen and removes a proton from the less hindered side of the acetal. The cleavage of 2,2-dimethoxy-4-phenylbutane (**6**) to **5** with *i*-Bu$_3$Al proceeds with 96:4 regioselectivity.[11] Thus, the 90:10 or better regioselectivity for the linear product was not unexpected.

We were surprised by the relatively low regioselectivity found in entry 9, where the linear and branched products were formed in only a 75:25 ratio. This rearrangement was repeated twice with the same result and was the impetus for the development of the two new rearrangement methods B and C. Method C is a two-pot procedure where the enol ether is isolated and examined by NMR before rearrangement. Entry 11 shows a significant improvement in overall yield compared to entry 9 and a dramatic increase in regioselectivity. The only obvious difference between entries 9 and 11 is the presence of PPTS in the rearrangement reaction. Apparently the PPTS persists after the addition of *i*-Bu$_3$Al and leads to partial enol ether equilibration before rearrangement. The PPTS can also catalyze the formation of dialkoxy acetals from alkoxy methoxy acetals, and dialkoxy acetals lead to starting allylic alcohol on *i*-Bu$_3$Al-promoted cleavage. Method B incorporated an *in situ* quench of the PPTS with Et$_3$N before addition of the *i*-Bu$_3$Al. Entry 10 shows that method B is not as good as method C for increasing the yield with 2-hexen-1-ol (**7**), but it does increase the regioselectivity. Methods B and C were applied to other allyl alcohol rearrangements and resulted in modest increases in yield over method A.

The *i*-Bu$_3$Al-catalyzed and thermal ketal Claisen rearrangements of 2-hexen-1-ol (**7**) with enol ether **5** or the corresponding dimethoxy acetal **6** are compared in Table 2, entries 11 and 12. As Daub previously demonstrated, acid-catalyzed thermal ketal Claisen reactions give the branched products with modest to very good selectivity.[3] Thus, the 9:91 ratio of branched to linear products, isolated as ketones, is what one would expect based on his results. Our *i*-Bu$_3$Al-catalyzed ketal Claisen reactions gave the linear product with very good selectivity, 90:10 following oxidation to the ketone, under mild conditions. This new procedure complements the Daub procedure and makes both regioisomeric ketal Claisen products available in good yield and good selectivity.

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Supporting Information Available: ^{1}H NMR spectra of Claisen rearrangement products (17 pages).

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(11) Enol ether **5** was readily synthesized by the following two-step route: conversion of the corresponding ketone to the dimethyl ketal (MeOH, HC(OMe)$_3$, CSA, 95%) and *i*-Bu3Al cleavage of the ketal to generate a 96:4 ratio of 2-methoxy-4-phenyl-1-butene (**5**) and 2-methoxy-4-phenyl-2-butene in 88% combined yield.