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Stereocontrolled Synthesis of (*E,Z*)-Dienals *via* Tandem Rh(I)-Catalyzed Rearrangement of Propargyl Vinyl Ethers

Dinesh V. Vidhani,* Marie E. Krafft, and Igor V. Alabugin*

Department of Chemistry & Biochemistry, Florida State University, Tallahassee, Florida 32306, United States

alabugin@chem.fsu.edu

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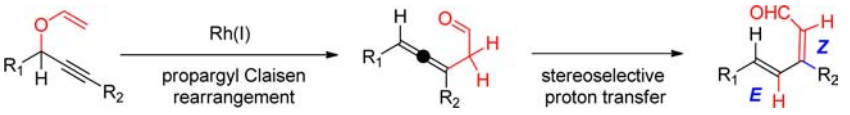
ABSTRACT



A novel Rh(I)-catalyzed approach to functionalized (*E,Z*) dienals has been developed via tandem transformation where a stereoselective hydrogen transfer follows a propargyl Claisen rearrangement. *Z*-Stereochemistry of the first double bond suggests the involvement of a six-membered cyclic intermediate whereas the *E*-stereochemistry of the second double bond stems from the subsequent protodemetalation step giving an (*E,Z*)-dienal.

Polyene motifs with (*E,Z*) stereochemistry are ubiquitous in biologically active and naturally occurring systems[1] and hence represent synthetically important targets (Figure 1).[2] Not only are synthetic routes to *Z*-alkenes relatively limited,[3] but such traditional approaches to unsaturated conjugated *Z*-polyenes as Wittig and Horner–Wadsworth–Emmons reactions cannot be used to directly deliver unsaturated aldehydes.

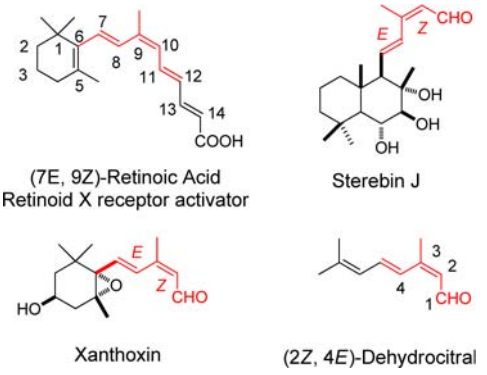


Figure 1. Selected (*E,Z*) dienal natural products.

The metal-catalyzed cross-coupling of two sp^2-hybridized reactants requires activating functionalities (e.g., organoboranes or organostannanes) which may be toxic, expensive, and/or deleterious for the overall atom efficiency. Methods for the direct incorporation of the unsaturated α,β carbonyl compounds with the *Z*-stereochemistry are limited.[4]

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In this work, we disclose a tandem transformation of propargyl vinyl ethers into dienals, where stereochemistry at *both* double bonds in the product is defined simultaneously by the nature of a common cyclic intermediate located at the Claisen rearrangement hypersurface connecting propargyl vinyl ethers with allene-aldehyde **1**. Trapping of such a cyclic structure via deprotonation coupled with the Grob fragmentation should lead to the conjugated dienals with *E,Z*-stereochemistry: the *Z*-geometry at the α,*β*-alkene is defined by the *syn*-arrangement of the endocyclic *σ*-bonds whereas the *E*-stereochemistry at *γ*,*δ*-alkene stems from the *syn*-arrangement of the exocyclic C−R1 and C−M bonds and proto-demetalation with retention of configuration (Figure 2).

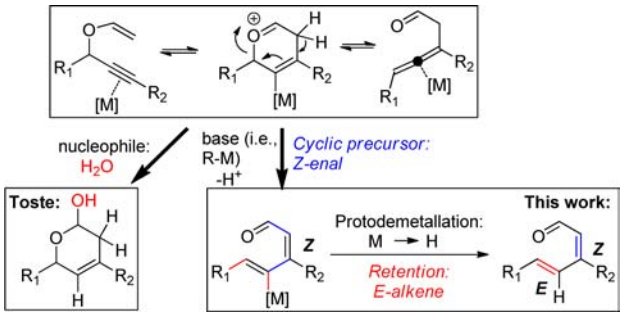


Figure 2. "*Two birds with one stone*": The proposed transformation of the six-membered intermediate in the metal-catalyzed propargyl Claisen rearrangement into (*E,Z*)-dienals defines stereochemistry in both double bonds of the product.

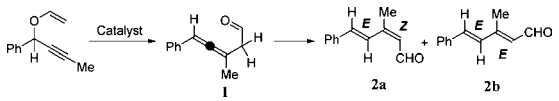
Au(I)-catalyzed Claisen rearrangements of propargyl and allenyl vinyl ethers were first reported by the groups of Toste[5] and Krafft,[6] respectively. In a recent mechanistic study of these two rearrangements,[7] we found that although the cyclic intermediate does not correspond to an energy minimum at the DFT potential energy hypersurface in the presence of the $R_3PAuSbF_6$-catalyst; the details of Au···substrate interactions at this stage suggest that a slight modification in the nature of the catalyst may be sufficient for creating and trapping such a cyclic structure.[8]

Although trapping via deprotonation has not been reported so far and our initial attempts with weak bases such as aniline led to deactivation of the Au-catalyst, we were further encouraged by the results of Toste and co-workers who found that the use of a multinuclear Au-catalyst provides access to such a cyclic structure trappable by a reaction with external nucleophiles (Figure 2).[8]

Because the equilibrium between the metal−alkyne, metal−vinyl ether, and metal−oxygen complexes should strongly depend on the nature of metal, we scanned a number of transition metal catalysts. Herein, we report that stereoselective tandem isomerization of propargyl vinyl ethers to (*E,Z*)-dienals can be achieved using Rh(I)-catalysis.

A screening of commonly used transition metals showed that Au-based catalysts promote the Claisen rearrangement step but only AuCl is efficient in moving the cascade further (Table 1). However, the stereoselectivity of the final step was, at best, modest. Pd-based catalysts were only successful in promoting the first step. The hard Lewis acids such as $Cu(OTf)_2$, $Zn(OTf)_2$, and $Sc(OTf)_3$ were even less efficient. On the other hand, $[Rh(CO)_2Cl]_2$ displayed remarkable reactivity, effectively promoting both the allene formation and its subsequent rearrangement into the desired (*E,Z*)-dienal **2a** (Table 1, entry 14). Donor phosphine ligands at the Rh center eliminated the catalytic activity (entry 15).

Table 1. Catalyst Screening[a]



entry	catalyst	**1**	**2a**	**2b**
1	AuCl	–[b]	28	72
2	$AuCl_3$	72	9	17
3	$Ph_3PAuSbF_6$	93	4	3
4	$[Au]SbF_6$	100	–	–
5	$IPr\text{-}AuSbF_6$	100	–	–
6	$PdCl_2$	12	–	–
7	$Pd(PPh_3)_2Cl_2$	100	–	–
8	$Pd(PPh_3)_4$	8	3	–
9	$Pd(PhCN)_2Cl_2$	100	–	–
10	$PtCl_2$	–	–	–
11	$Cu(OTf)_2$	16	–	–
12	$Zn(OTf)_2$	15	–	–
13	$Sc(OTf)_3$	10	–	–
14	$[Rh(CO)_2Cl]_2$	–[b]	98	2
15	$(PPh_3)_3RhCl$	–	–	–

[a] Standard reaction conditions: 0.1 M Substrate in toluene-d_8 at 50 °C in the presence of 10% metal catalyst for 24 h. Ratios determined by proton NMR. [b] Complete conversion of substrate into **1** was observed, followed by its full transformation into **2a** and **2b**.

Remarkably, $[Rh(CO)_2Cl]_2$ and AuCl provided cascade products in high yields but with the opposite stereochemistry. Table 2 summarizes further optimization of the Rh-catalyzed reactions. Coordinating solvents such as acetonitrile form a strong complex with Rh(I) and deactivate the catalyst.[9] Rearrangement in the mildly coordinating

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CH_2Cl_2 was sluggish (10% dienal **2a** and 35% allene-aldehyde **1**). The reaction in tetrahydrofuran gave 90% allene-aldehyde **1** at rt and proceeded slowly toward the 3:1 mixture of the dienals at 50 °C.

Table 2. Optimization Studies[a]

entry	solvent	temp	1	2a	2b
1	CD_3CN	25	N.R	–	–
2	CD_3CN	50	N.R	–	–
3	CD_3NO_2	25	trace[c]	–	–
4	THF-d_8	25	90	–	–
5	THF-d_8	50	89	8	3
6	CD_2Cl_2	25	35	10	–
8	toluene-d_8	25	100	–	–
7	toluene-d_8	50	–[b]	98	2
8	C_6D_6	25	95	–	–
9	C_6D_6	50	–[b]	95	5

[a] Standard reaction conditions: All reactions were performed at 0.1 M concentration in the presence of 10% $[Rh(CO)_2Cl]_2$. Relative ratios were determined by proton NMR. [b] Complete conversion of enol ether into **1** was observed that was subsequently fully converted into **2a** and **2b**. [c] Significant decomposition of substrate was observed.

On the other hand, conversions in benzene and toluene were clean and proceeded in high yield and remarkable *E,Z*-selectivity for substrates with a broad range of aromatic substituents at the carbinol carbon (Figure 3). Both donors and acceptors work well. Furthermore, other sp^2-substituents are also compatible with the cascade. For example, a cyclohexenyl substituted substrate gave a dienal product in 62% yield with excellent (*E,Z*)-stereoselectivity. Furthermore, the cascade tolerates steric hindrance; even with bulky substituents such as *tert*-butyl and mesityl, the Claisen products are quickly formed at 50 °C and smoothly converted to the dienals in ~80% yield and excellent stereoselectivity upon further heating.

The current limitations of this process seem to be associated with the possibility of further prototropic isomerizations. For substrates with an *n*-butyl group at the carbinol carbon, the dienal yields decrease to ~50% due to formation of several nonidentified nonpolar byproducts. In the presence of a secondary (cyclohexyl) substituent, formation of Claisen product proceeded efficiently (>90%) at 50 °C, but its subsequent rearrangement at 70 °C produced only a small amount of (*E,Z*) dienal product together with unknown nonpolar products. The cyclopropyl-substituted substrate was unreactive in the presence of Rh(I) at 50 °C and decomposed at higher temperatures.

DFT calculations at the M05-2X/LANL2DZ level suggest that the electron-rich vinyl ether dissociates the 16 electron Rh(I)-dimer to form a 16 electron Rh(I)-VE complex which is expected to be the catalyst resting state (Figure 4). The uncomplexed monomeric 14 electron precatalyst, $Rh(CO)_2Cl$, is unlikely to be persistent.[10]

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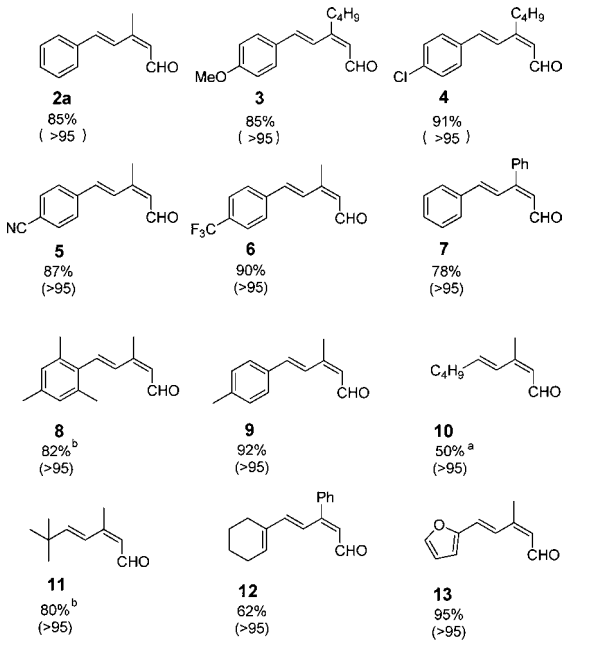

Figure 3. Products of Rh(I)-catalyzed rearrangements obtained from their respective propargyl vinyl ethers. Percentages correspond to the isolated yields. Values in parentheses show percentage of *E,Z* isomer determined by proton NMR. Reaction conditions: 0.1 M solution of 0.1 mmol of propargyl vinyl ether in toluene in the presence of 10% $[Rh(CO)_2Cl]_2$ at 50 °C. [a] Rearranges further into a mixture of products. [b] Requires 70 °C.

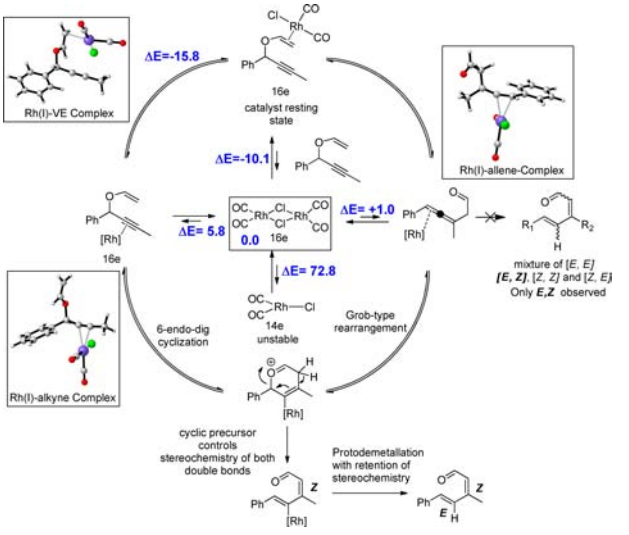

Figure 4. Proposed catalytic cycle. Numbers in blue correspond to the PCM-SCRF-M05-2X/LANL2DZ energies of the intermediate species relative to the uncomplexed Rh(I)-dimer.

Additional information regarding the mechanism of this isomerization was provided by DFT calculations. They revealed that the most stable complex produced *via* coordination of Rh(I) with the vinyl ether is catalytically

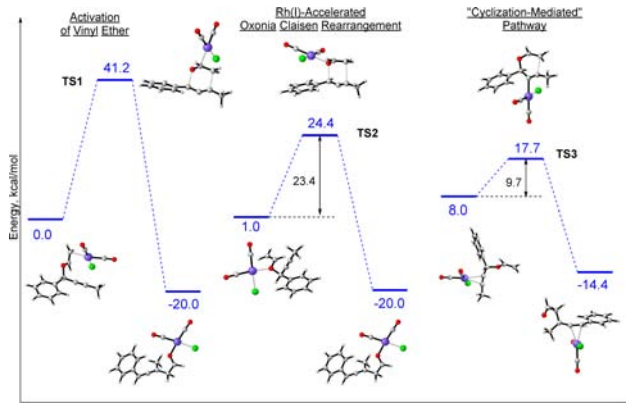

Figure 5. Curtin–Hammett analysis of the three mechanisms. Energies in toluene were calculated at the PCM-SCRF-M05-2X/LANL2DZ level on the gas phase optimized geometries.

unproductive due to the high barrier (Figure 4, TS1: 41.2 kcal/mol). DFT computations performed at the M05-2X level suggests that the less stable complexes formed via coordination of Rh(I) with the alkyne or the oxygen rearrange via considerably lower barriers.[11]

Coordination of Rh(I) to the oxygen initiates the oxonia-Claisen rearrangement which proceeds *via* a dissociative-TS with a 23.4 kcal/mol barrier (Figure 5, TS2). Coordination of Rh(I) with the alkyne directs rearrangement via a very low 9.7 kcal barrier (Figure 4, TS3). Even after the Curtin–Hammett correction, the latter route offers the lowest energy path for the Claisen rearrangement with the barrier of 17.7 kcal/mol (Figure 5).[12]

Although the interception of the pericyclic pathway is conceptually interesting and increasingly utilized in the design of cascade organic transformations,[13] the six-membered intermediate in the "cyclization-mediated pathway" is often elusive and its presence and lifetime depend on the intricate details of transition state complexation with the catalyst. For example, we had shown in our earlier work on Au-catalyzed rearrangement how coordination of Au stabilizes the TS for the subsequent Grob-type fragmentation into the allene-aldehyde product to the extent that the intermediate corresponds to a shallow inflection at the potential energy surface.[7] On the other hand, Siebert and Tantillo found that a combination of transition-state complexation with resonance stabilization converts a TS into a cyclic intermediate in Pd-promoted Cope rearrangement.[14]

At the M05-2X/LANL2DZ level of theory, we did not find an energy minimum corresponding to the six-membered organorhodium intermediate in the parent system (Figure 5). Further mechanistic exploration is needed to fully understand the subtleties of this transformation since the (*E,Z*)-stereochemistry of double bonds in the dienal is fully consistent with the suggested transformation of the six-membered intermediate in Figure 2. The stereochemistry of the two double bonds in **2a** and **2b** was confirmed by selective gradient-enhanced 1D NOESY (SELNOGP) and comparison to the known proton NMRs of the (*E,Z*) dienals **2a**, **7**, **8**, **10**, and **11**.[15]

In summary, Rh-catalyzed Claisen rearrangement followed by stereoselective hydrogen transfer converts propargyl vinyl ethers into the target (*E,Z*)-dienals in high yields, excellent stereoselectivity, and with minimal waste. The reaction tolerates steric hindrance and is compatible with substituents of different electronic demand. This atom economical method yields complex and stereochemically defined dienals in only three steps from commercially available aldehydes. Presently, we are exploring the mechanistic details of the catalytic cycle.

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Supporting Information Available. Detailed experimental procedures; spectra and HRMS of all new compounds; NOESY data for compounds **3a** and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.