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Rearrangement Reactions

Alkene Isomerization Revitalizes the Coates–Claisen Rearrangement

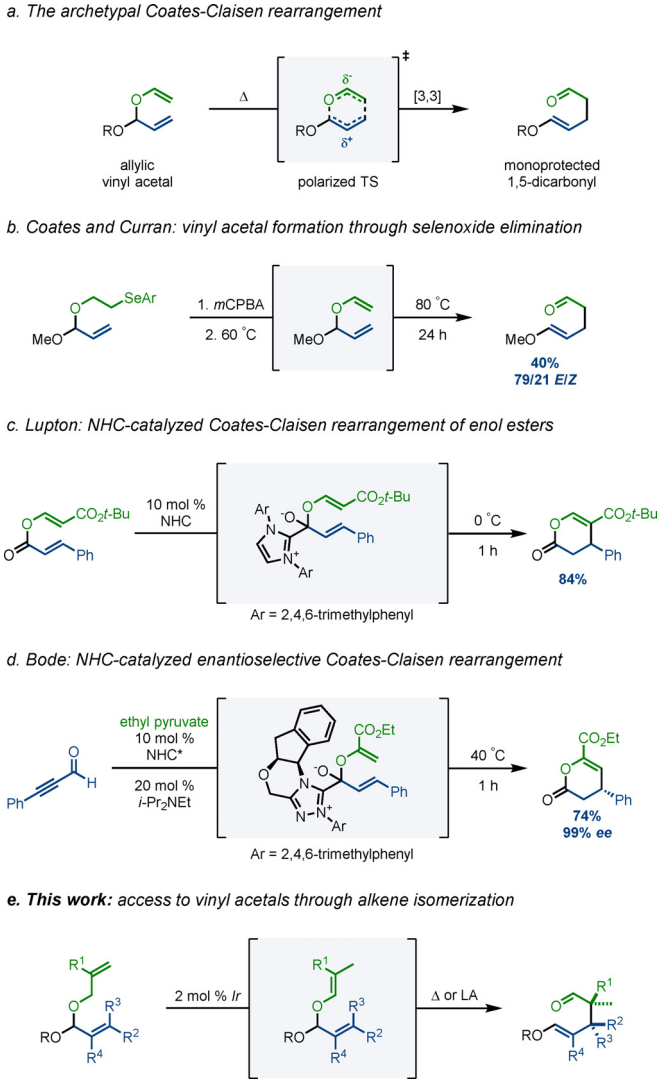
*Itai Massad and Ilan Marek**

Abstract: *The [3,3]-sigmatropic rearrangement of allylic vinyl acetals, first investigated by Coates nearly four decades ago, is set apart from other variants of the Claisen rearrangement owing to the versatile monoprotected 1,5-dicarbonyl motif featured in the products. Unfortunately, the synthetically elusive nature of the substrates has thus far precluded the widespread application of this attractive transformation. Herein, we show that the key allylic vinyl acetals can be efficiently generated through alkene isomerization of their readily available regioisomeric counterparts (derived from allylic alcohols and α,β-unsaturated aldehydes), thus enabling the first systematic study of the substrate scope of this rearrangement, as well as the discovery of exceptionally mild conditions for its mediation by Lewis and Brønsted acids.*

The Claisen rearrangement[1] is typified by its compatibility with substitution across the parent reactive scaffold, as reflected in the diverse functionality found in the products of its numerous modifications.[2] Consequently, the utility of a given variant of this rearrangement is often limited by the availability of the substrates, rather than the performance of the sigmatropic event. For example, facile access to stereodefined ester enolates[3,4] renders the Ireland-Claisen rearrangement[5,6] extremely synthetically appealing, while the challenge entailed in the preparation of stereodefined allyl vinyl ethers[7] explains why the "simpler" aliphatic Claisen rearrangement[8] has traditionally received more modest attention. In accord with this notion, the increasingly frequent application of the aliphatic Claisen rearrangement over the last two decades is directly traceable to the emergence of efficient and stereoselective strategies towards said ethers.[9–16]

The [3,3]-sigmatropic rearrangement of allylic vinyl acetals (Scheme 1 a), pioneered by Coates,[17,18] is a relatively underexplored member of the Claisen rearrangement family, even though the monoprotected 1,5-dicarbonyl motif embedded in the products, along with the rate-accelerating effect of the C2 alkoxy substituent over the rearrangement,[19] holds great promise for its use in synthesis. The fact that this promise is yet to be realized is most likely due to the shortage of methods providing the key enol-derived allylic acetals. To date, such species have only been prepared through multistep manipulations (Scheme 1 b) involving elimination reactions to form the vinyl ether moiety,[19] or transiently generated from stable enols or their esters under NHC catalysis (Scheme 1 c,d).[20–25]

Clearly, an approach which employs simple starting materials and forges the coveted allylic vinyl acetal moiety with complete regio- and stereocontrol would greatly broaden the scope of the Coates-Claisen rearrangement. Seeking to address this problem, our interest in the strategic application of alkene isomerization[26–29] pointed us to identify allyl

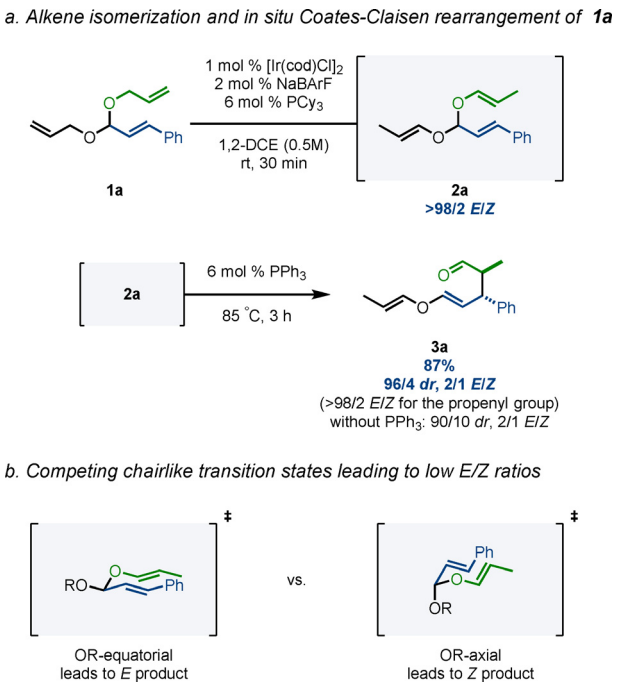


Scheme 1. Approaches towards the Coates–Claisen rearrangement.

[*] I. Massad, Prof. Dr. I. Marek
Schulich Faculty of Chemistry, Technion—Israel Institute of Technology
Technion City, Haifa, 3200009 (Israel)
E-mail: chilanm@technion.ac.il
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202105834.

acetals of α,β-unsaturated aldehydes[30] as convenient precursors to the regioisomeric vinyl acetals (Scheme 1e). Specifically, we posited that alkene isomerization catalysts operating through 1,3-hydride shift mechanisms would be ideal to realize this proposed transformation, considering their well-established prowess in site-, regio-, and stereoselective alkene isomerization.[31] Of this group of catalysts, we were drawn to Ir-based complexes, which have been extensively applied to the isomerization of allylic ethers,[32–37] as well as in sequential transformations comprising isomerization and sigmatropic rearrangements.[13–16,38–40]

Indeed, the readily available cinnamaldehyde diallyl acetal **1a** underwent completely site- and stereoselective alkene isomerization of both allyl groups at room temperature in the presence of 2 mol% of an in situ-generated cationic Ir-catalyst, furnishing the corresponding pure (*E,E*)-dipropenyl acetal **2a** (Scheme 2a), as characterized by NMR

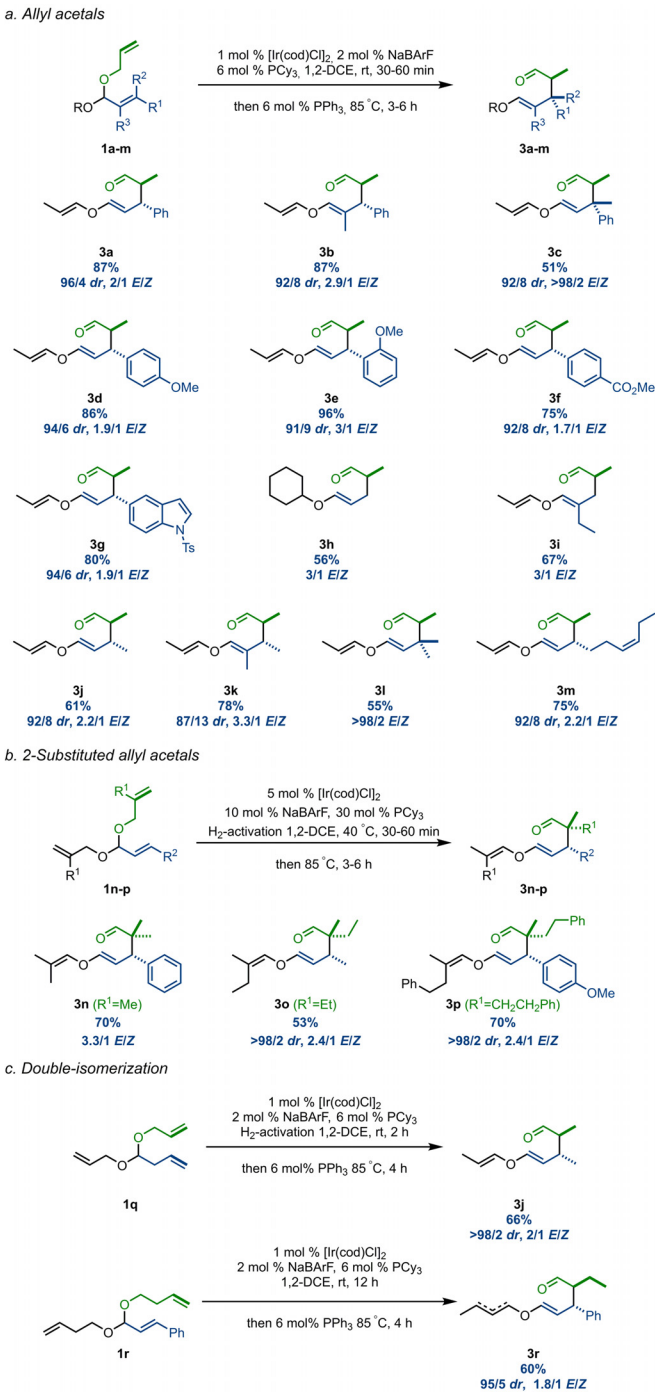


Scheme 2. Initial findings.

spectroscopy. Pleasingly, **2a** smoothly rearranged within 3 hours at 85 °C (with PPh_3 added to attenuate the Lewis acidity of the Ir-catalyst[13]), yielding aldehyde **3a** with satisfactory diastereoselectivity and yield. We were unable to test the rearrangement of **2a** without the presence of the Ir-based catalyst, since attempted purification on silica gel resulted in the isolation of the rearrangement product **3a** (SiO_2 catalyzes the rearrangement, see Scheme 4a).

Unlike most variants of the Claisen rearrangement, the stereochemistry of the alkene moiety generated through the rearrangement is not well controlled in our case (the stereochemistry of the alkene formed by isomerization remains well-defined), since the oxygen-based substituent is of little steric bulk compared to alkyl and aryl groups, in addition to the potential stabilization of the chairlike transition state leading to the *Z* vinyl ether by the anomeric effect (with the vinyloxy group in the pseudoaxial position, see Scheme 2b). Since the divinyl ether moiety in the product merely serves as a protected aldehyde, this stereochemical issue should be of little practical concern.

Substrates of various substitution patterns and electronic properties lend themselves to this isomerization Coates-Claisen rearrangement sequence, as outlined in Scheme 3. Aldehyde **3b**, containing a trisubstituted enol ether, was generated in similar yield and diastereoselectivity compared



Scheme 3. Substrate scope.

to its less substituted congener **3a**. In contrast, aldehyde **3c**, which features a quaternary carbon stereocenter at the β-position, required higher temperatures to undergo the rearrangement and is notably generated with complete *E*-selectivity. Both empirical details are accounted for by the presence of the *cis*-methyl group in the corresponding acetal substrate ($R^2 = Me$), which occupies a pseudoaxial position in the chairlike transition state.

Ortho-substitutions on the aromatic fragment do not hamper the rearrangement (compare **3e** and **3d**), nor ester or indole groups (**3f** and **3g**), showing the compatibility of the method with Lewis-basic functionality.

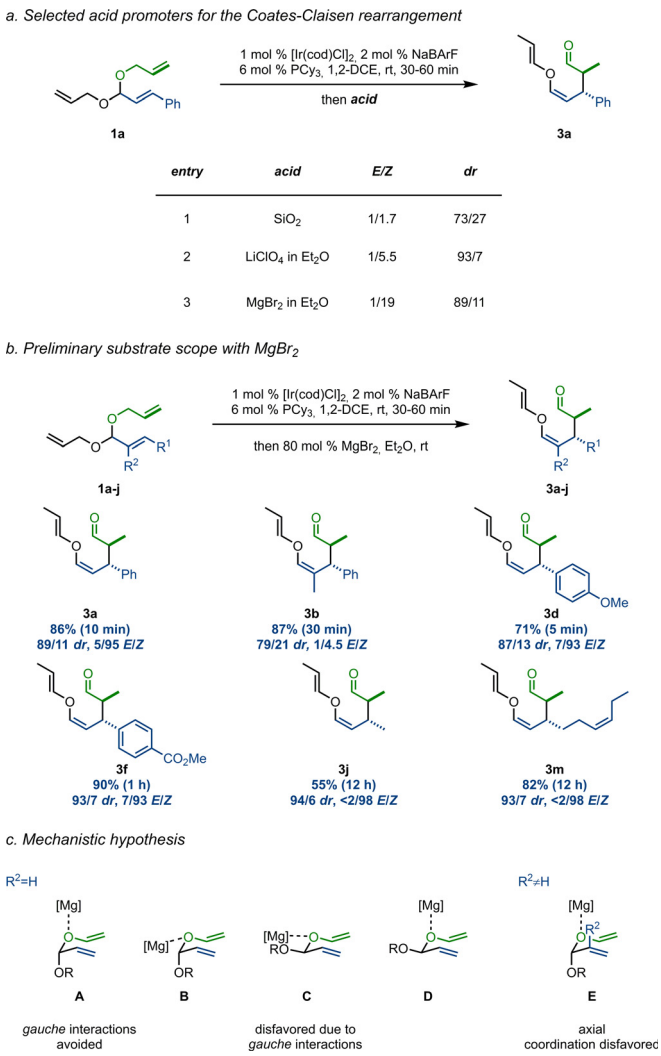
Aromatic substituents are not required to promote the rearrangement, as shown by the generation of aliphatic aldehydes **3h**–**3m** from aliphatic acetals of various substitution patterns. Aldehyde **3m** is generated without any competing isomerization of the neighboring *cis* alkene, illustrating the potential of this method in complex molecule synthesis.

This strategy is not limited to acetals of plain allyl alcohol, and acetals featuring 2-substituted allyl groups are also isomerized using an H_2-activated catalytic system,[37] leading to rearrangement products possessing a quaternary stereocenter at the α-position. Again, both aromatic (**3n**, **3p**) and aliphatic (**3o**) substituents lead to successful outcomes.

Interestingly, acetal **1q**, for which isomerization of both the O- and C-bound allyl groups precedes rearrangement, affords **3j** as a single diastereoisomer, thanks to the exquisite *E*-selectivity of the Ir-based catalyst. This improves upon the results achieved with the corresponding crotonaldehyde derived diallyl acetal (available only as a 9/1 *E*/*Z* mixture), which generates aldehyde **3j** with incomplete stereocontrol. Finally, a two-carbon isomerization and subsequent rearrangement of homoallyl acetal **1r** lead to aldehyde **3r** in 60% yield, demonstrating the feasibility of extending this method to long-range isomerization.

Having explored the thermal Coates-Claisen rearrangement of in situ generated allylic vinyl acetals, we were keen to find alternative conditions to carry out this transformation while addressing its key drawback, namely the *E*/*Z* ratio of the newly generated enol ether. In this context, the most promising alternative to the default thermal activation is the mediation of the Claisen rearrangement by Lewis acids,[41] which we predicted would positively influence the axial/equatorial preference of the vinyloxy group in the chairlike transition state.

In practice, the reactivity of in situ-generated divinyl acetal **2a** in the presence of Lewis and Brønsted acids exceeded our expectations, with 17 out of 25 acids screened facilitating the rearrangement to a considerable extent (see the SI for the full analysis). Along with well-precedented activators for the Claisen rearrangement such as Al-based Lewis acids,[42–44] much milder acids such as silica gel also promoted the desired rearrangement under ambient conditions (Scheme 4a). Out of the range of activators screened, the simple Lewis acids magnesium bromide and lithium perchlorate exhibited particularly impressive reactivity profiles, yielding rearrangement product **3a** with excellent diastereomeric ratios and only trace amounts of acetal



Scheme 4. Acid-mediated rearrangements.

hydrolysis products (even though no precautions were taken to exclude moisture from the reaction mixture). Furthermore, the $MgBr_2$-promoted rearrangement is almost completely *Z*-selective, a rare outcome in the Claisen rearrangement which so far has only been reported by Yamamoto using exceptionally bulky Al-based Lewis acids.[45]

Scheme 4b details a preliminary substrate scope for the $MgBr_2$-catalyzed Coates-Claisen rearrangement. The electronic properties of the starting material dramatically affect the rearrangement rate: Aldehydes **3a**, **3d** and **3f** were generated much more quickly than aliphatic aldehydes **3j** and **3m**, which required 12 hours for complete consumption of the starting acetals. The above five products were formed with impressive diastereo- and *Z*-selectivity. Strikingly though, product **3b**, which is generated from an acetal featuring internal substitution ($R^2 = Me$) afforded significantly lower stereoselectivity.

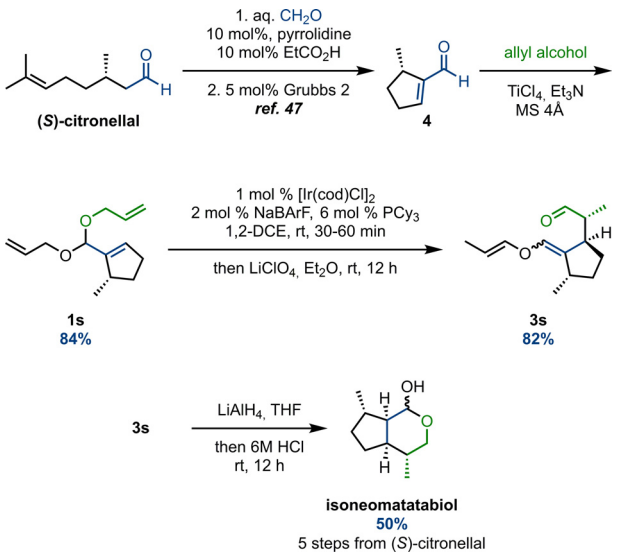
The latter observation led us to consider a mechanistic picture which includes coordination of the Mg-center to the pseudoaxially-oriented lone pair of the oxygen in the transition state (Scheme 4c). Such a mode of coordination avoids gauche interactions between the Mg-center and the

pseudoaxially oriented OR when both occupy pseudoaxial positions (compare **A** to **B**–**D**). This model also accounts for the detrimental effect of substitution at the 2-position, which would lead to 1,3-diaxial interactions with the Mg-center (**E**). Further investigations into the mechanism and origin of stereoselectivity of this Lewis acid-mediated rearrangement are ongoing.

To underline the utility of the monoprotected 1,5-dialdehyde motif featured in the rearrangement products, we developed a short total synthesis of the iridoid natural product isoneomatatabiol,[46] which also serves as an intermediate in reported syntheses of related iridoids.[47] The synthesis begins with acetal **1s**, available in three steps from (*S*)-citronellal.[48] **1s** was smoothly isomerized using the standard Ir-based system, and was found to display optimal reactivity towards the sigmatropic rearrangement using $LiClO_4$ in Et_2O. Since we were unable to determine the stereoselectivity of the Coates-Claisen rearrangement by NMR analysis, we directly subjected product **3s** to reduction with $LiAlH_4$, followed by quenching with 6 M HCl, which also serves to hydrolyze the divinyl ether moiety. Isomerically pure isoneomatatabiol was isolated by column chromatography in 50% yield for this reduction-hydrolysis sequence. Overall, the synthesis of this target molecule in five steps from citronellal augurs well for the synthetic relevance of this method, and specifically highlights the value of the monoprotected 1,5-dialdehyde motif for the elaboration of the rearrangement products.

In conclusion, the strategic application of alkene isomerization has allowed us to explore an underutilized variant of the Claisen rearrangement. The products of this Coates-Claisen rearrangement feature synthetically valuable functionality, which was leveraged in a concise total synthesis of the natural product isoneomatatabiol. Furthermore, the rate-accelerating effect of the acetal group enabled the orchestration of this rearrangement by Lewis and Brønsted acids as mild as $MgBr_2$ and silica gel, providing fertile ground for the development of enantioselective variants, an ongoing study in our research group.

From a broader perspective, we hope this work further demonstrates how the strategic use of alkene isomerization can uncover simple solutions to open problems in organic synthesis.



Scheme 5. Synthesis of isoneomatatabiol.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: acetals · alkene isomerization · Claisen rearrangement · iridium

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