Alkene Isomerization Revitalizes the Coates–Claisen Rearrangement

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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 stereo-defined ester enolates[3,4] renders the Ireland-Claisen rearrangement[5, 6] extremely synthetically appealing, while the challenge entailed in the preparation of stereo-defined 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 1a), 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 1b) involving elimination reactions to form the vinyl ether moiety,[19] or transiently generated from stable enols or their esters under NHC catalysis (Scheme 1c,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...
acetals of α,β-unsaturated aldehydes\cite{30} as convenient precursors to the regiosomeric vinyl acetals (Scheme 1c). 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\cite{31}. Of this group of catalysts, we were drawn to Ir-based complexes, which have been extensively applied to the isomerization of allylic ethers\cite{32–37}, as well as in sequential transformations comprising isomerization and sigmatropic rearrangements\cite{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 spectroscopy. Pleasingly, \(2a\) smoothly rearranged within 3 hours at 85 °C (with \(\text{PPh}_3\) added to attenuate the Lewis acidity of the Ir-catalyst \cite{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 \(3a\) (\(\text{SiO}_2\) 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 pseudoequatorial 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...
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 (R² = 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 H²-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 hydrolysis products (even though no precautions were taken to exclude moisture from the reaction mixture). Furthermore, the MgBr₂-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 MgBr₂-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 (R² = 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

**Scheme 4. Acid-mediated rearrangements.**
pseudoxially 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 LiClO₄ in Et₂O. Since we were unable to determine the stereoselectivity of the Coates-Claisen rearrangement by NMR analysis, we directly subjected product 3s to reduction with LiAlH₄ 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 Bronsted acids as mild as MgBr₂ 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.

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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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