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Stereoselective tandem iridium-catalyzed alkene isomerization-cope rearrangement of ω -diene epoxides: efficient access to acyclic 1,6-dicarbonyl compounds†

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The Cope rearrangement of 2,3-divinyloxiranes, a rare example of epoxide C–C bond cleavage, results in 4,5-dihydrooxepines which are amenable to hydrolysis, furnishing 1,6-dicarbonyl compounds containing two contiguous stereocenters at the 3- and 4-positions. We employ an Ir-based alkene isomerization catalyst to form the reactive 2,3-divinyloxirane *in situ* with complete regio- and stereocontrol, which translates into excellent control over the stereochemistry of the resulting oxepines and ultimately to an attractive strategy towards 1,6-dicarbonyl compounds.

1,6-Dicarbonyl compounds are widespread as targets and intermediates in organic synthesis.¹ Due to the “dissonant” polarizing effect induced by the two carbonyl groups,² these motifs are challenging to retrosynthetically disconnect into classical synthons. Unsurprisingly, many approaches toward 1,6-dicarbonyls rely on dimerization of α,β -unsaturated carbonyl compounds (Scheme 1a)³ or oxidative cleavage of substituted cyclohexene derivatives⁴ which significantly limits the range of possible products. Alternative strategies, such as the ring-opening of donor–acceptor cyclopropanes with enolate nucleophiles, efficiently form the 1,6-dicarbonyl skeleton, albeit with limited substrate scope (Scheme 1b).⁵ The Cope rearrangement of 1,5-dienes, featuring oxygen functionality in the 3- and 4-positions,⁶ represents a promising strategy towards 1,6-dicarbonyl compounds but suffers from lack of stereocontrol over the diene substrates, resulting in diastereomeric mixtures of products (Scheme 1c).

A conceptually related approach towards the preparation of 1,6-dicarbonyl compounds is through the hydrolysis of 3,4-dihydrooxepines (Scheme 1d), which are in turn generated through the Cope rearrangement of 2,3-divinyloxiranes.⁷ Such a sigmatropic rearrangement is also noteworthy as a rare example where an epoxide C–C bond is selectively cleaved over the usually more reactive C–O bond. This intriguing rearrangement has been studied but its use in synthesis is scarce, presumably due to difficulties in the stereoselective synthesis and handling of the key divinyl epoxides.

In line with our interest in the strategic application of alkene isomerization to generate reactive synthetic intermediates in stereodefined form,⁸ we posited to form the reactive 2,3-divinyloxiranes *in situ*, through alkene isomerization^{9,10} of the simpler allyl epoxides, which are accessible in enantiomerically enriched form.¹¹ Such a strategy might greatly facilitate access to these intermediates and therefore uncover a synthetically attractive route toward 1,6-dicarbonyl compounds featuring two contiguous stereocenters.

With this idea in mind, we first explored the isomerization and subsequent Cope rearrangement of allyl-vinyl epoxides **1** (Scheme 2). To induce isomerization, we employed a cationic iridium-based catalytic system,¹² which is known to reliably isomerize alkenes with high degrees of regio- and stereocontrol.¹³

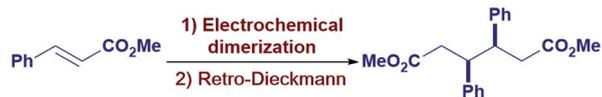
In line with our expectations, our model substrate **1a** ($R^2 = R^3 = H$, $R^4 = Me$, $R^5 = CO_2Et$) was smoothly isomerized at 65 °C in the presence of 1.5 mol% of Ir dimer to obtain the corresponding divinyl epoxide with a complete *E*-selectivity. With suitable conditions for alkene isomerization in hand, we exposed substrate **1a** to the Ir-based catalytic system at 120 °C and were equally pleased to observe the 4,5-dihydrooxepine product **2a**, resulting from the tandem isomerization-Cope rearrangement as a single diastereoisomer in 81% yield. We proceeded to test the generality of our protocol with respect to different alkene and epoxide substitution patterns. Pleasingly, product **2b** was generated with complete stereoselectivity, showcasing the compatibility of the reaction conditions with potentially labile tertiary stereocenters α to the ester group. We then wondered whether the *anti*-diastereomer could be accessed starting from the corresponding *cis* allyl-vinyl epoxide. Indeed, in line with the known stereospecific behavior of the Cope rearrangement, we obtained the complementary

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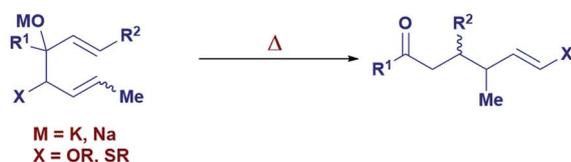
a) Nielsen and Utley: Electrodimerization of cinnamic acid esters



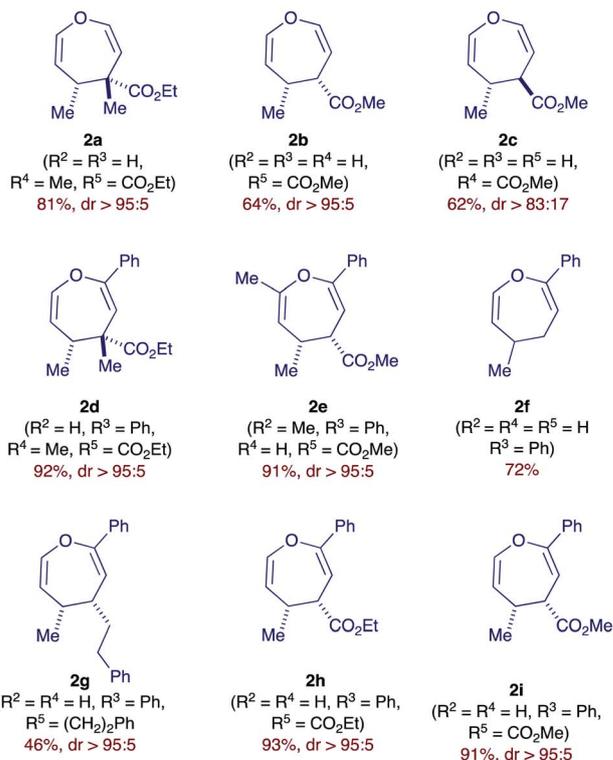
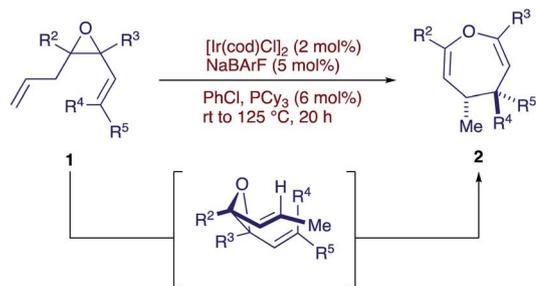
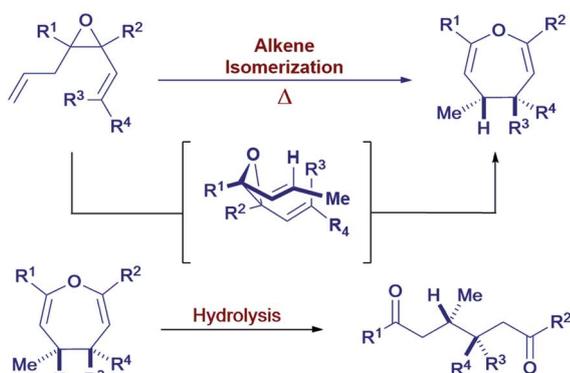
b) Zhan: Ring opening of donor-acceptor cyclopropanes



c) Evans: Base accelerated Oxy-Cope rearrangement

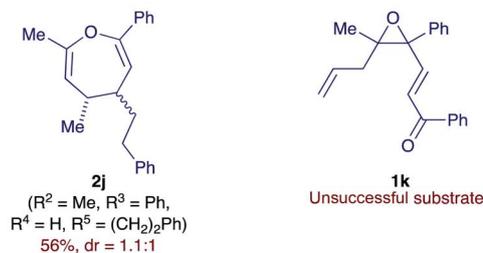


d) Our hypothesis: Alkene isomerization-Cope rearrangement and hydrolysis revealing 1,6-dicarbonyl compounds within acyclic systems



Scheme 1 Selected approaches towards the formation of 1,6-dicarbonyl compounds and our proposed approach.

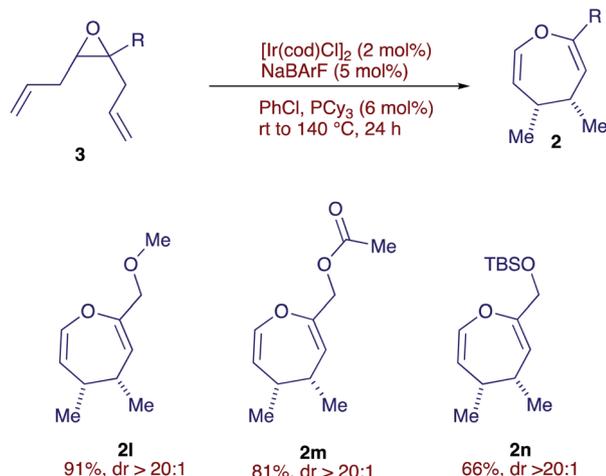
diastereomer **2c**. Turning our attention to more highly substituted epoxides, we were pleased to observe the formation of dihydrooxepines **2d** and **2e**, which correspond to 1,6-keto-aldehyde and diketone products, respectively. Substrate **1f** (R² = R⁴ = R⁵ = H, R³ = Ph), which features an unactivated vinyl group, also underwent the rearrangement, demonstrating that an activated alkenyl group is not required for a successful outcome. Similarly, product **2g** featuring two alkyl groups is also generated, with high diastereoselectivity albeit in moderate yield. Products featuring ethyl and methyl ester **2h**, **2i** could also be obtained in good yields and diastereoselectivity. We next tested substrate **1j** (R² = Me, R³ = Ph, R⁴ = CH₂CH₂Ph, R⁵ = H), as a geometric-mixture of the double bond (*E* : *Z* = 1.1 : 1) and in accordance with the stereospecificity of the process, the oxepine **2j** was obtained as a mixture of two diastereomers with the same ratio. Disappointingly, substrate **1k** did not undergo isomerization, presumably due to the Lewis basic nature of the ketone, likely poisoning the Ir-catalyst.



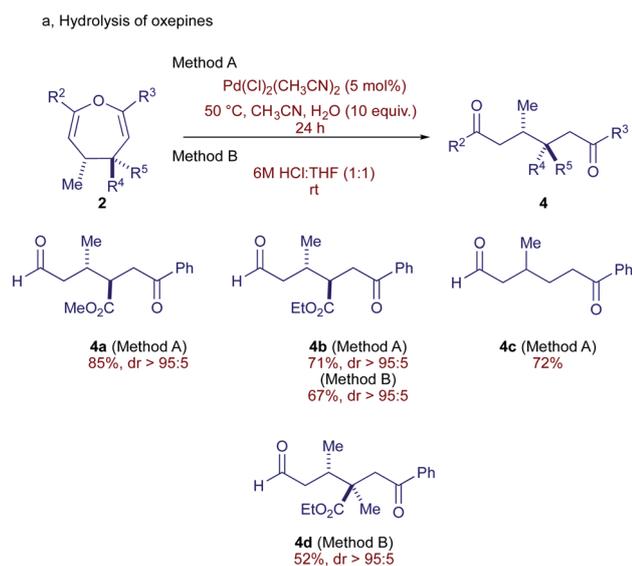
Scheme 2 Substrate scope for the tandem iridium-catalyzed alkene isomerization-Cope rearrangement of allyl-vinyl epoxides.

During our study, we noticed that allyl-vinyl epoxides bearing electron donating groups on the vinyl moiety tend to decompose during purification by column chromatography on silica gel. This obstacle further motivated us to explore diallyl epoxides **3** as substrates, where the reactive divinyl epoxide would be generated by isomerization of both allyl fragments. Notably, these diallyl epoxides are much more stable compared to their vinyl counterparts and can be readily prepared in two steps from simple alkynes.¹⁴ To our delight, diallyl epoxide **3a** (R =

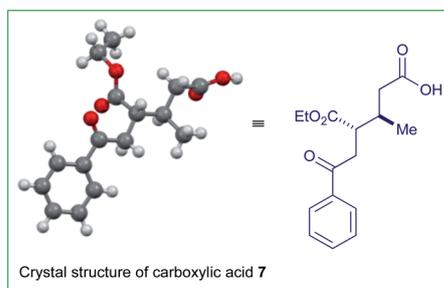
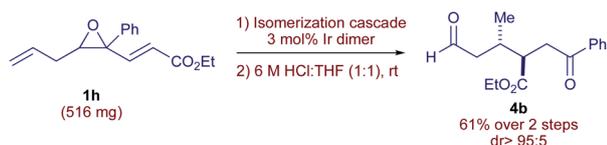




Scheme 3 Substrate scope for tandem iridium-catalyzed double alkene isomerization-Cope rearrangement of diallyl epoxides.



b, One-pot transformation on a larger scale



Scheme 4 Hydrolysis of oxepines and one-pot sequence.

CH₂OMe) smoothly underwent the double isomerization-Cope rearrangement cascade at 140 °C, furnishing oxepine **2i** with impressive yield and diastereoselectivity (Scheme 3). The use of alkene isomerization to form the reactive divinyl epoxide *in situ* avoids the isolation of the unstable divinyl epoxide, while controlling the stereochemistry of both double bonds, particularly not trivial to achieve using classical olefination reactions. Products **2m** and **2n** feature ester and silyl groups, highlighting the functional group tolerance of the catalytic system.

Our next objective was to hydrolyze the diastereomerically pure oxepines obtained through the rearrangement in a stereoretentive fashion, revealing the acyclic 1,6-dicarbonyl motif. Pleasingly, diversely substituted oxepines **2** underwent smooth hydrolysis either using 5 mol% of Pd(MeCN)₂Cl₂¹⁵ at 50 °C or an acidic aqueous solution to form 1,6-dicarbonyls **4** in diastereomerically pure form (Scheme 4).¹⁶ Dicarbonyl products featuring labile tertiary centers **4a** and **4b** are formed under these conditions with excellent diastereoselectivities and yields. Without surprise, oxepine **2f** (R² = R⁴ = R⁵ = H, R³ = Ph) furnished the keto-substituted product **4c** in good yield. The relative stereochemistry of **4b** was unambiguously confirmed by single crystal X-ray diffraction analysis of the corresponding carboxylic acid **7** (Scheme 4b).¹⁷ The reaction is scalable to 1/2 gram of substrate and could be performed in a single-pot operation without isolation of the intermediate oxepine (Scheme 4b). By using this approach, **1h** provides **4b** in 61% yield as a single diastereomer, underlining the synthetic potential and efficiency of this method.

Conclusions

In summary, we report a highly diastereoselective alkene isomerization-Cope rearrangement cascade, affording 3,4-dihydrooxepines bearing two contiguous stereocenters. These oxepines were hydrolyzed to obtain stereodefined acyclic 1,6-dicarbonyl compounds bearing two contiguous stereocenters, which are challenging to access through other means. Forming the key divinyl epoxides *in situ* through alkene isomerization allows excellent control over alkene stereochemistry, while sidestepping stability issues associated with divinyl epoxides.

Author contributions

RS and IM planned, conducted and analyzed the experiments. IM conceived and directed the project and wrote the manuscript with contribution of RS and IM. All authors contributed to discussions.

Conflicts of interest

There are no conflicts to declare.

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- 16 In some cases, during the Pd-catalyzed hydrolysis of oxepines, the intramolecular aldol products of **4** were observed, particularly when diketones were concerned. All data and complete analysis can be found in the ESI†
- 17 The relative stereochemistry of **7** was determined by X-ray structure analysis. CCDC 2074187 contains the supplementary crystallographic data for this paper†.

