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Co(II)-catalyzed isomerization of enals using hydrogen atom transfer†

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To develop a process for the synthesis of an enal acetate, the so called C5-acetate that is important in the industrial preparation of vitamin A, we show here that Co(II)-based hydrogen atom transfer catalysts under H₂ promote such isomerizations in high yield with low catalyst loading (0.1 mol%). D-labelling studies suggest the enal isomerization process and catalyst activation by H₂ to be reversible.

The catalytic isomerization of alkenes is a widely studied process.¹ Metal-catalyzed isomerization reactions are typically driven by the formation of more thermodynamically stable alkene products. In cases where alkene isomers may have similar stabilities, or the target product is less stable, high yielding processes are not readily achieved. However, recent methods have been developed for the catalytic isomerization of alkenes to less thermodynamically stable products, including terminal-selective,² strain-inducing,³ enantioselective,⁴ and Z-selective or E-selective isomerizations.⁵ Despite advances in catalytic alkene isomerization, some seemingly simple alkene isomerization reactions remain out of reach, including on substrates containing sensitive, reducible functional groups.

We sought a method for the isomerization of conjugated methylenic enals into the corresponding trisubstituted enal. Specifically, we aimed to prepare enal acetate **2** (C5-acetate), a valuable intermediate in the manufacturing of vitamin A⁶ from the readily available hydroformylation product **1**.⁷ While an array of protocols for the methylenic isomerization of ketones,⁸ esters,⁹ amides,¹⁰ and styrenes¹¹ have been reported, this type of isomerization with aldehyde substrates was unknown (Fig. 1).¹² This is presumably due to challenges associated with conducting metal hydride mediated isomerizations in the presence of a reducible aldehyde unit and the lack of strong

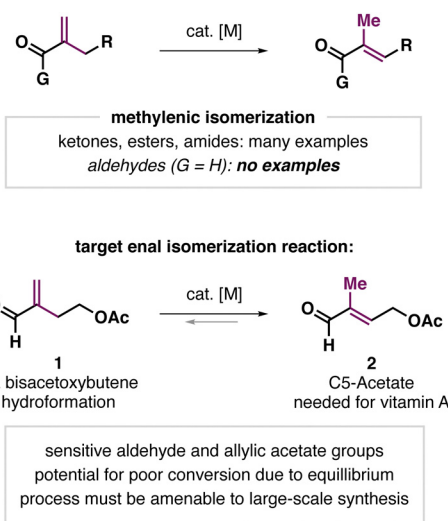


Fig. 1 Overview of conjugated methylenic isomerizations and challenges of enal isomerization.

thermodynamic driving force to favour the product. Our computational estimates suggest the energy difference between enal **1** and **2** is only $\sim 1 \text{ kJ mol}^{-1}$ in MeCN (see the ESI,† for details). Given the utility of enals as synthetic intermediates, the discovery of a general, efficient process to isomerize easily synthesized methylenic enals into more highly substituted products would be valuable. Here we show that Co(dmg)₂-type catalysts promote such enal isomerizations under H₂ to give trisubstituted products in yields > 80%, at low catalyst loadings (0.1 mol%), and with minimal alkene or aldehyde reduction.

Comprehensive reaction screening and mechanistic studies showed the classical isomerization catalyst RhCl₃ was a reasonable candidate to promote the desired enal isomerization.¹³ In buffered ethanol/dioxane the isomerization of enal **1** to target **2** in $\sim 50\%$ yield was observed (Fig. 2a).¹⁴ Further improvements could not be achieved because the enals were found to be in equilibrium and were unstable under the optimized conditions. Reactions under more forcing conditions led to enal hydrogenation, while

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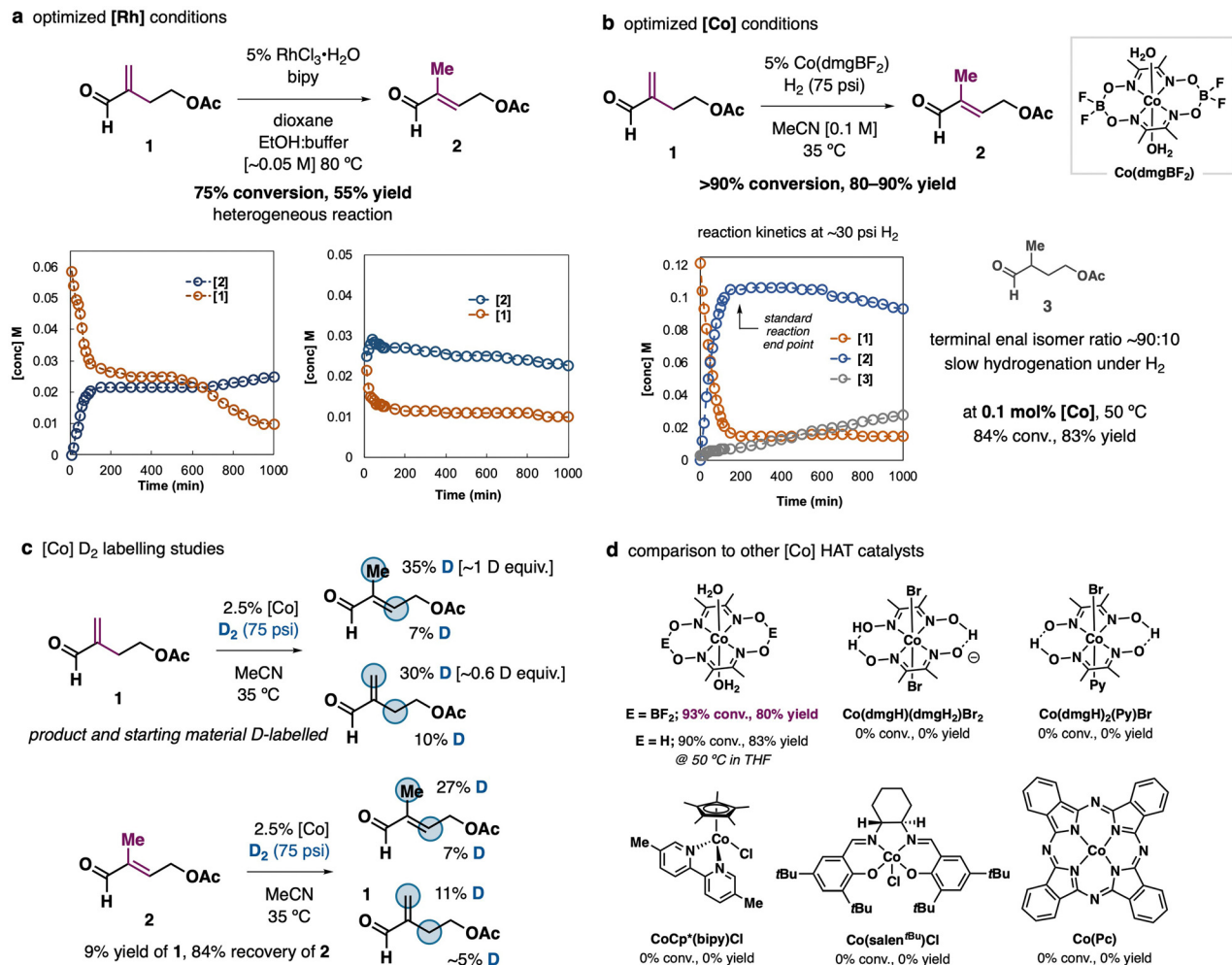


Fig. 2 Reaction development and mechanistic studies for the isomerization of enal **1**. (A) RhCl₃ catalyzed reactions and kinetics. (B) Co(dmgBF₂)₂ catalyzed reactions and kinetics. (C) Labelling studies for the Co-catalyzed enal isomerization using D₂. (D) Comparison to related Co-HAT catalysts. ^a THF as solvent, 50 °C, 5 h.

reactions conducted with a 1:1 mixture of **1** and **2** quickly showed ratios of **1**:**2** = 33:67 suggesting the reaction under RhCl₃ catalysis is not truly at equilibrium. These studies show the challenges associated with developing high yielding isomerizations of sensitive enals like **1** (see the ESI,[†] for additional screening data). It was not until a hydrogen atom transfer (HAT) approach using Co(dmg)₂-type catalysts^{15,16} was taken that trisubstituted enal **2** could be obtained in good yield (Fig. 2b). Reactions with Co(dmgBF₂)₂(H₂O)₂ proceed quickly to ~90% conversion and 80% yield of **2** under 75 psi H₂. Alkene hydrogenation is slow and saturated aldehyde **3** is only observed in >10% well after the isomerization is complete. Reactions could be conducted at 0.1 mol% of Co(II)-catalyst and still gave good yields (83%). The use of other H-atom donors resulted in lower yields (2-propanol: 8% yield; Ph₂SiH₂: 25% yield).

Isotope-labeling studies conducted with D₂ are consistent with a reaction that is reversible to some extent (Fig. 2c). Under the standard conditions at ~75 psi, the use of D₂ results in the formation of D-**2** in 72% yield with one equivalent of D at the

newly formed methyl position and 7% D at the alkenyl position. Recovered substrate (7%) is D-labeled to approximately the same extent on the same carbon atoms. The amount of labeling in both **1** and **2** increases even after isomerization to **2** reaches the maximum yield. When the enal product **2** is subjected to the standard isomerization conditions under D₂, 9% of **1** is formed with partial D-incorporation. Recovered **2** is labelled at both the methyl and alkenyl positions. The extent of labeling suggests a rate of isomerization that is bracketed by the rate of Co-DAT catalyst formation by reaction with D₂ and “Co-D” (the exact structure of the reactive hydride species generated from Co(dmg) catalysts is not resolved¹⁷) is generated reversibly. If the active Co-DAT catalyst was generated only in an initial reaction with D₂, product and starting material would be labelled in ~2.5% (*i.e.* the catalyst loading), while if the “Co-D” was in rapid equilibrium with Co $\frac{1}{2}$ D₂, the extent of labelling in product and substrate would converge and both would become completely labelled at the alkenyl and allylic positions. Thus, the lower extent of deuteration of the internal double bond reflects its less preferential reaction with “Co-D”.

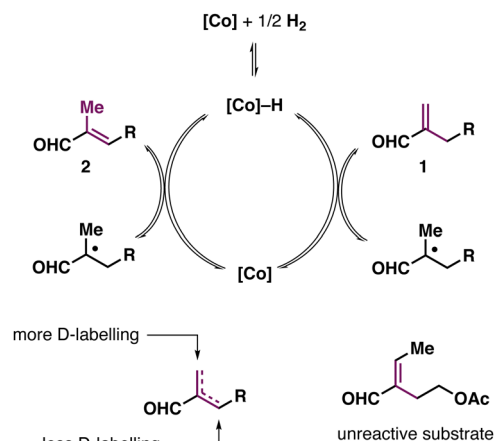


Fig. 3 Mechanistic proposal.

Use of the appropriate HAT catalyst was essential to observe productive reactivity. Co(II)-based (dmgbF₂) and (dmgH₂) complexes could be used as catalysts for enal isomerization, although Co(dmgbF₂)₂(H₂O)₂ performed better at reduced catalyst loadings (see the ESI,[†] for details). Other Co-based complexes established for HAT reactivity failed completely, including related Co(III)dmg type catalysts,^{2a} Cp*Co(II)(bipy)Cl, and Co(III)(salen)Cl complexes,^{9b} further highlighting the unique challenge of enal isomerization (Fig. 2d).

Fig. 3 provides a mechanistic proposal where Co–H mediated HAT generates a tertiary radical from enal **1**. This intermediate can undergo H-atom abstraction by Co to generate the isomerized product. Given an estimate of between 0–2 kJ mol^{−1} (*i.e.* 1 ± 1 kJ mol^{−1}) difference in energy between

the enals, the isomer distribution may be fully under thermodynamic control, however given the higher degree of D-labelling observed at the methyl/exo-methylene carbon, we suspect the catalyst exhibits some kinetic selectivity for addition to the more sterically accessible alkene in **1** vs. that in **2**. The poor reactivity of non-methylene aldehydes supports this assumption.¹⁸

We were interested in studying the scope of enal isomerization reactions catalyzed by Co(dmgbF₂)₂(H₂O)₂/H₂ with other methylenic substrates (Fig. 4). Norton and co-workers have previously reported Co(dmgbF₂)₂/H₂ catalyzed isomerization reactions with arylalkenes and α,β-unsaturated esters.¹⁵ Enal isomerization of ester and ether containing substrates were successful (OAc, OBn, and OMe; **1**, **4**, **5**), as was a substrate with a free alcohol group (**6**). Substrates containing potentially sensitive functional groups like enolizable ketones (**7**), alkyl chlorides (**8**), terminal (**9**) or trisubstituted alkenes (**10**), or aryl groups (**11**) were isomerized to the target products in ~90% yield. Di- and trisubstituted ketones (**12**, **13**) and lactone **14** underwent isomerization in good to moderate yield. Reactions with functionalized arylalkenes proceeded with moderate yields (**16**–**18**), as did itaconic acid derivative **19**. Notably, the majority of enal or arylalkene substrates gave poor conversions and yields when using RhCl₃-based conditions, suggesting the general benefit of an HAT approach in comparison to a metal-hydride based reactivity.

In summary, we have found using Co(dmgbF₂)₂-based HAT catalyst systems to be a solution for the high yielding isomerization of methylenic enals and other recalcitrant alkene substrates. This approach allows for an attractive new route to the industrially important C5-acetate in vitamin A synthesis. Our

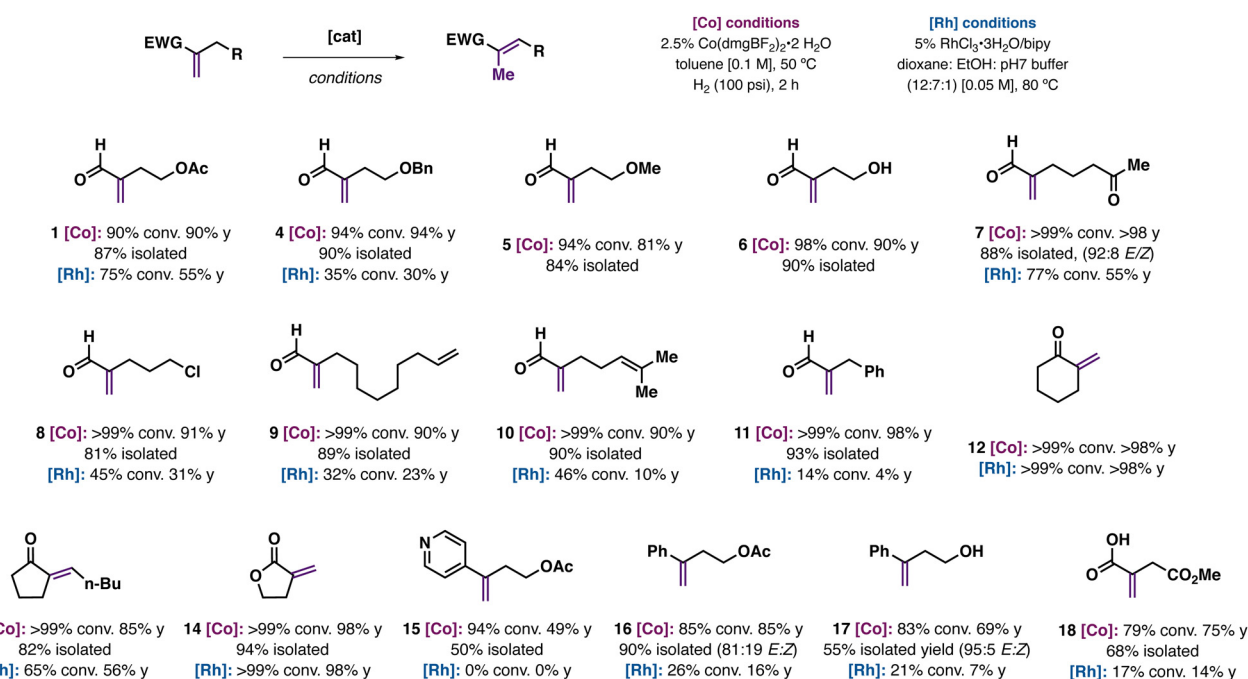
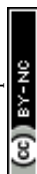


Fig. 4 Reaction scope and limitations of the Co(dmgbF₂)₂-catalyzed isomerization of enals and other alkenes along with select comparisons to conditions using RhCl₃.



work shows that HAT mechanisms can circumvent problems of substrate reduction and unfavourable equilibrium between isomers while operating under mild reaction conditions.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

BASF and the University of Alberta have filed a patent application on the reported technology.

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