Co(II)-Catalyzed Isomerization of Enals using Hydrogen Atom Transfer

Qiqige Qiqige,[1] Edward Richmond,[2]* Rocco Paciello,[2] Mathias Schelwies,[2] Rylan J. Lundgren[1]*

1. Department of Chemistry, University of Alberta, Edmonton, Alberta T6G 2G2, Canada
2. BASF SE, Synthesis & Homogeneous Catalysis, Carl-Bosch-Strasse 38, 67056 Ludwigshafen am Rhein, Germany

*Corresponding authors; email: edward.richmond@basf.com; rylan.lundgren@ualberta.ca

Abstract The catalytic isomerization of alkenes is a well-studied and valuable process in synthesis. Despite the development of numerous metal-catalyzed isomerization catalysts, methods for the selective isomerization of methylenic enal substrates have not been established. 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 H_2 promote such isomerizations in high yield (often ≥90%) with low catalyst loading (0.1 mol%). D-labelling studies suggest both the enal isomerization process and catalyst activation by H_2 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 A[6] 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 styrenes[11] 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 thermodynamic driving force to favour the product. Our computational estimates suggest the energy difference between enal **1** and **2** is only ~1 kJ/mol in MeCN (see the SI 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 H_2 to give trisubstituted products in yields >80%, at low catalyst loadings (0.1 mol%), and with minimal alkene or aldehyde reduction.

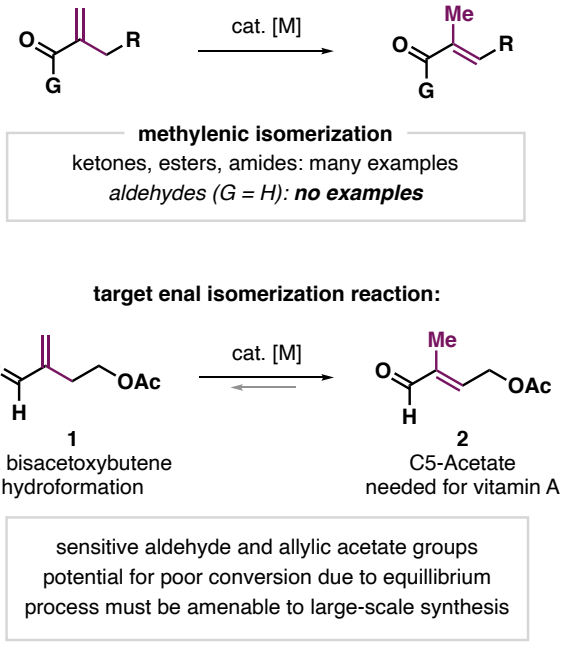

Fig 1. Overview of conjugated methylenic isomerizations and challenges of enal isomerization.

Comprehensive reaction screening and mechanistic studies showed the classical isomerization catalyst $RhCl_3$ was a reasonable candidate to promote the desired enal isomerization.[13] In buffered ethanol/dioxane catalyzed the isomerization of enal **1** to target **2** in ~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 reactions conducted with a 1:1 mixture of **1** and **2** quickly showed ratios of **1**:**2** = 33:67. These studies show the challenges associated with developing high yielding isomerizations of sensitive enals like **1** (see the SI 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 $Co(dmgBF_2)_2(H_2O)_2$ proceed quickly to ~90% conversion and 80% yield of **2** under 75 psi H_2. 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%).

Isotope-labeling studies conducted with D_2 are consistent with an equilibrium reaction (Fig 2c). Under the standard conditions at ~30 psi, the use of D_2 results in the formation of D-**2** with one equivalent of D at the newly formed methyl position and 7% D at the alkenyl position. Recovered substrate 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 D_2, 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 D_2 and "Co–D" (the exact structure of the reactive hydride species generated from Co(dmg) catalysts is not resolved) is generated reversibly. If the active Co-DAT catalyst was generated only in an initial reaction with D_2, 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 ½ D_2, the product and substrate would converge and 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".

Use of the appropriate HAT catalyst was essential to observe productive reactivity. Co(II)-based ($dmgBF_2$) and ($dmgH_2$) complexes could be used as catalysts for enal isomerization, although $Co(dmgBF_2)_2(H_2O)_2$ performed better at reduced catalyst loadings (see the SI 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).

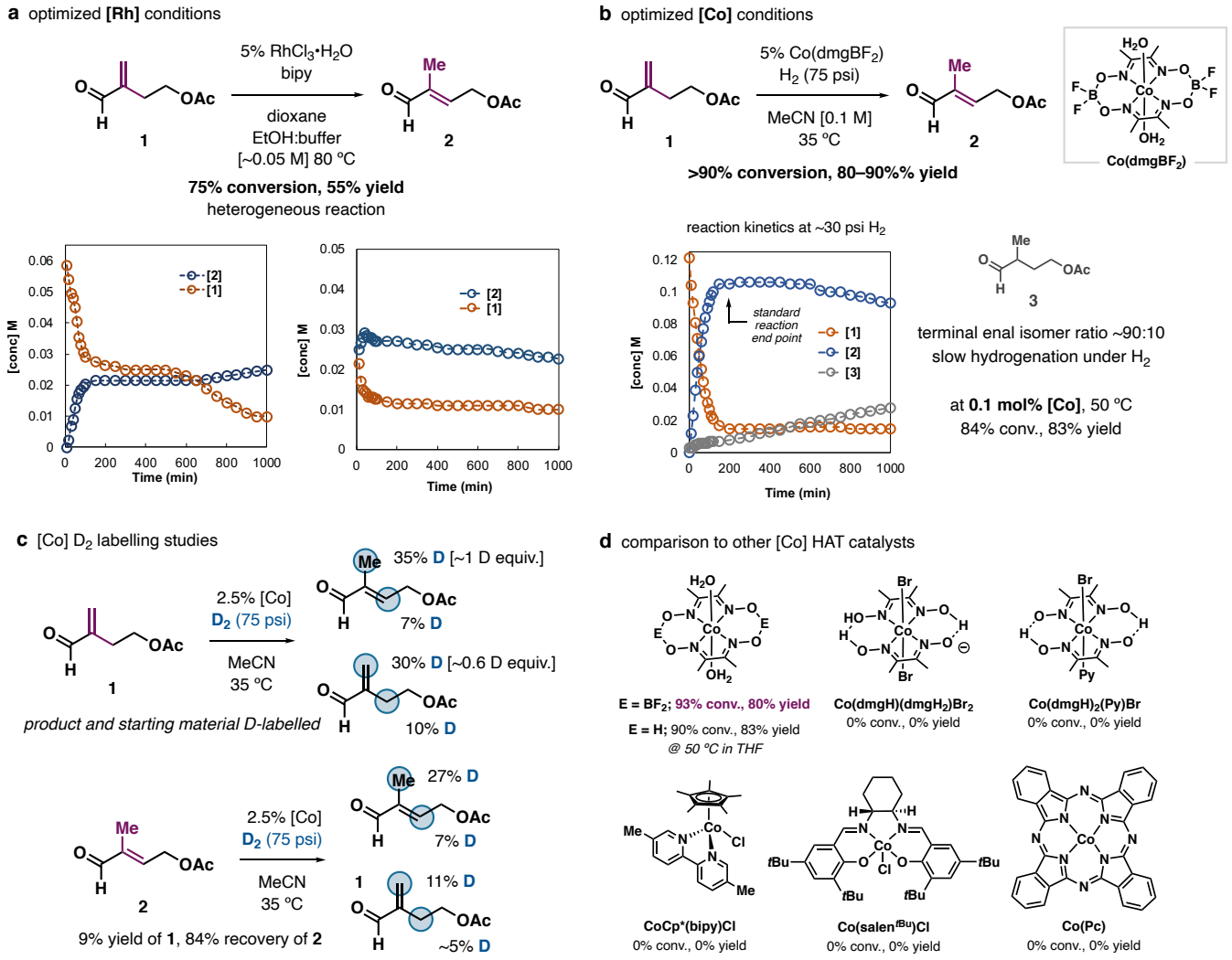

Fig 2. Reaction development and mechanistic studies for the isomerization of enal **1**. **A** $RhCl_3$ catalyzed reactions and kinetics. **B** $Co(dmgBF_2)_2$ catalyzed reactions and kinetics. **C** Labelling studies for the Co-catalyzed enal isomerization using D_2. **D** Comparison to related Co-HAT catalysts. [a]THF as solvent, 50 °C, 5 h.

We were interested in studying the scope of enal isomerization reactions catalyzed by $Co(dmgBF_2)_2(H_2O)_2/H_2$ along with further methylenic substrates (Fig 3). Norton and co-workers have previously reported $Co(dmgBF_2)_2/H_2$ 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 $RhCl_3$-based conditions, suggesting the general benefit of an HAT approach in comparison to a metal-hydride based reactivity.

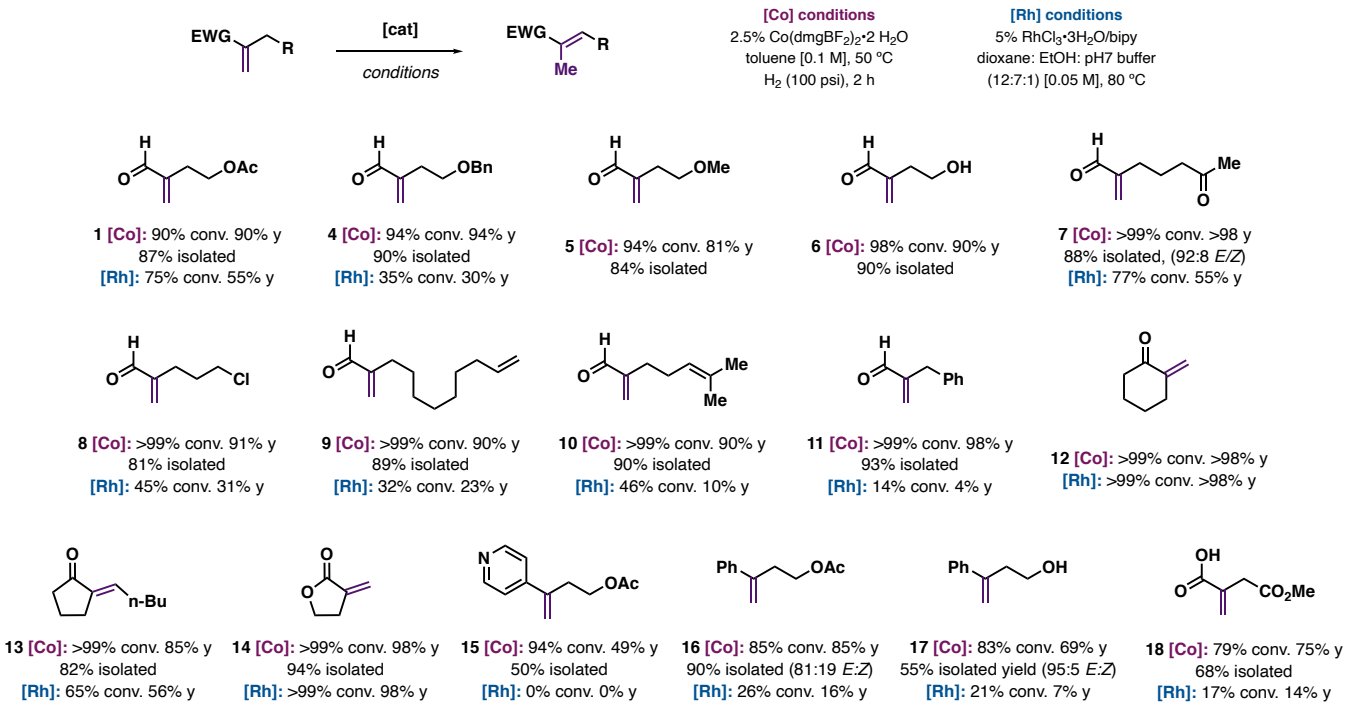

Fig. 3 Reaction scope and limitations of the Co(dmgBF$_2$)$_2$-catalyzed isomerization of enals and other alkenes along with select comparisons to conditions using $RhCl_3$.

In summary, we have found using Co(dmgBF$_2$)$_2$-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 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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Competing Interest: BASF and the University of Alberta have filed a patent application on the reported technology.

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