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Teaching Aldehydes New Tricks Using Rhodium- and Cobalt-Hydride Catalysis

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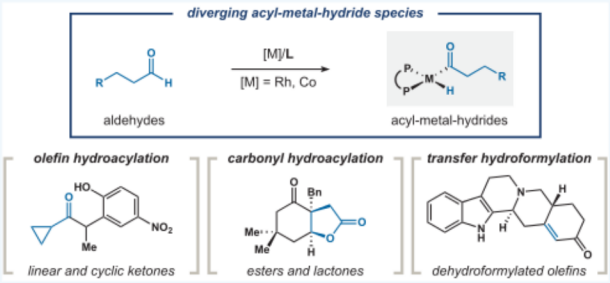
CONSPECTUS: By using transition metal catalysts, chemists have altered the "logic of chemical synthesis" by enabling the functionalization of carbon−hydrogen bonds, which have traditionally been considered inert. Within this framework, our laboratory has been fascinated by the potential for aldehyde C−H bond activation. Our approach focused on generating acyl-metal-hydrides by oxidative addition of the formyl C−H bond, which is an elementary step first validated by Tsuji in 1965. In this Account, we review our efforts to overcome limitations in hydroacylation. Initial studies resulted in new variants of hydroacylation and ultimately spurred the development of related transformations (e.g., carboacylation, cycloisomerization, and transfer hydroformylation).



Sakai and co-workers demonstrated the first hydroacylation of olefins when they reported that 4-pentenals cyclized to cyclopentanones, using stoichiometric amounts of Wilkinson's catalyst. This discovery sparked significant interest in hydroacylation, especially for the enantioselective and catalytic construction of cyclopentanones. Our research focused on expanding the asymmetric variants to access medium-sized rings (e.g., seven- and eight-membered rings). In addition, we achieved selective intermolecular couplings by incorporating directing groups onto the olefin partner. Along the way, we identified Rh and Co catalysts that transform dienyl aldehydes into a variety of unique carbocycles, such as cyclopentanones, bicyclic ketones, cyclohexenyl aldehydes, and cyclobutanones. Building on the insights gained from olefin hydroacylation, we demonstrated the first highly enantioselective hydroacylation of carbonyls. For example, we demonstrated that ketoaldehydes can cyclize to form lactones with high regio- and enantioselectivity. Following these reports, we reported the first intermolecular example that occurs with high stereocontrol. Ketoamides undergo intermolecular carbonyl hydroacylation to furnish α-acyloxyamides that contain a depsipeptide linkage.

Finally, we describe how the key acyl-metal-hydride species can be diverted to achieve a C−C bond-cleaving process. Transfer hydroformylation enables the preparation of olefins from aldehydes by a dehomologation mechanism. Release of ring strain in the olefin acceptor offers a driving force for the isodesmic transfer of CO and H_2. Mechanistic studies suggest that the counterion serves as a proton-shuttle to enable transfer hydroformylation. Collectively, our studies showcase how transition metal catalysis can transform a common functional group, in this case aldehydes, into structurally distinct motifs. Fine-tuning the coordination sphere of an acyl-metal-hydride species can promote C−C and C−O bond-forming reactions, as well as C−C bond-cleaving processes.

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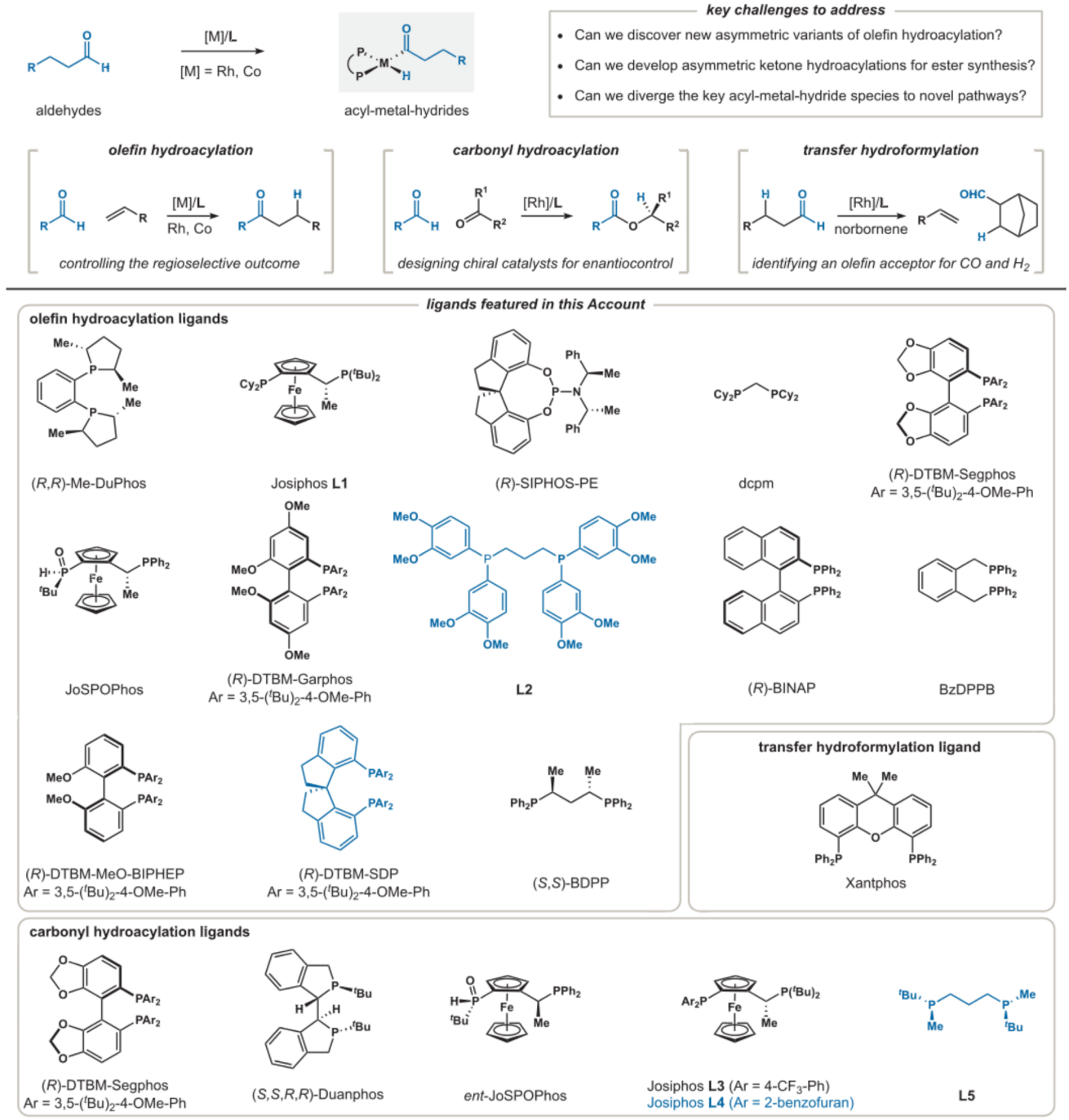

Figure 1. Overview of divergent transformations triggered by formyl C−H bond activation and ligands featured in this Account as they appear in chronological order (black, commercially available; blue, ligands our lab designed and synthesized).

hydroacylation; ketoaldehydes cyclize to the corresponding lactones under Rh catalysis.

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1. INTRODUCTION

One of the largest applications of homogeneous catalysis by volume is the Rh-catalyzed hydroformylation of olefins to generate aldehydes.[5] We reasoned that metal-catalyzed transformations similar in design to hydroformylation would have the same potential for broad use. Hydroformylation involves an acyl-Rh-hydride species that undergoes reductive elimination to generate the formyl C−H bond. Over the past decade, our laboratory has been interested in the reverse elementary step: activation of the aldehyde C−H bond to generate an acyl-metal-hydride species (Figure 1). By tuning the coordination sphere of

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this acyl-metal-hydride species, we have discovered C−C and C−O bond-forming reactions, as well as C−C bond-cleaving methods. In this Account, we present a personal report of our studies on Rh- and Co-catalyzed olefin hydroacylation and ketone hydroacylation, and the related carboacylation and transfer hydroformylation. We share how some discoveries were serendipitous, while others were guided by mechanistic insights. We identified the appropriate ligand by examining representative ligands from different families, searching for trends, and then fine-tuning the most promising scaffolds. In each case, however, the choice of ligand plays a key role in promoting reactivity and selectivity (see Figure 1 for an overview of the ligands featured in this Account).

2. ALDEHYDE C−H BOND FUNCTIONALIZATION

In 1965, Tsuji reported that aldehyde C−H bonds undergo oxidative addition to generate an acyl-metal-hydride species during his studies on decarbonylation.[6] Future efforts focused on diverting aldehyde reactivity away from decarbonylation. In 1972, Sakai and co-workers found that a series of 4-pentenals cyclized to the corresponding cyclopentanones when using stoichiometric Wilkinson's complex.[7] This study spurred developments in catalytic hydroacylation, which is defined as the addition of a hydrogen atom and acyl group across an alkene, alkyne, or carbonyl. To date, a range of transition metals (Rh, Ru, Ni, Co) and organic molecules (NHC's), catalyze intramolecular and intermolecular olefin hydroacylation.[8] The most efficient hydroacylation catalysts are designed around cationic Rh(I) centers, which were originally shown to be effective catalysts by Bosnich and co-workers.[9] Figure 2A depicts the well-accepted mechanism for Rh-catalyzed olefin hydroacylation. Oxidative addition of **I** to a formyl C−H bond generates acyl-Rh(III)-hydride **II**. Subsequent olefin coordination (**IV**), followed by migratory insertion, affords either linear or branched acyl-Rh(III)-alkyl species **V** or **VI**, respectively. Reductive elimination of **V** or **VI** releases the corresponding ketone product and regenerates catalyst **I**. The propensity for the acyl-Rh(III)-hydride species **II** to undergo an off-cycle reductive decarbonylation (i.e., Tsuji-Wilkinson decarbonylation) via Rh-carbonyl **III** presents a problem.[6]

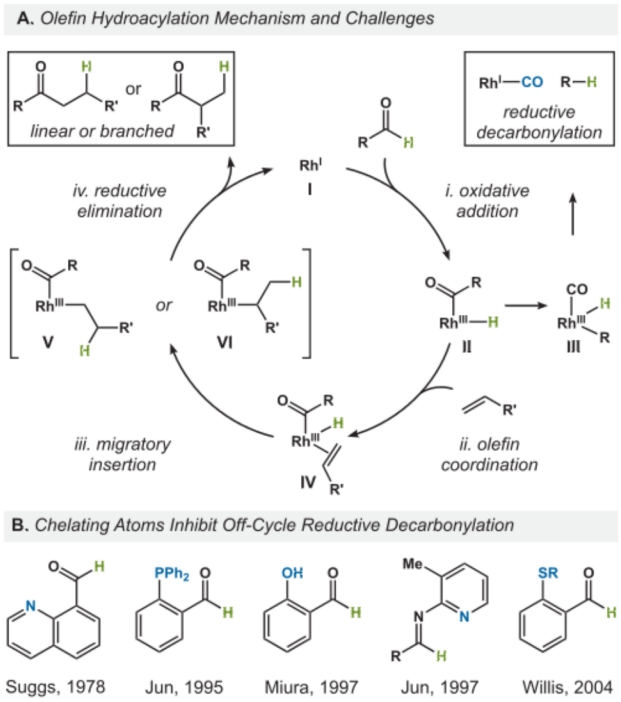

Figure 2. (A) Olefin hydroacylation mechanism and (B) strategy for suppressing decarbonylation.

Advances in Rh-catalyzed hydroacylation focus on inhibiting reductive decarbonylation. One successful strategy uses aldehyde partners that possess proximal coordinating atoms (Figure 2B). The coordination of an additional ligand to 16-electron Rh species **II** results in a fully saturated organometallic species. Following initial reports of intramolecular olefin hydroacylation, Suggs showed that quinoline aldehydes do not undergo decarbonylation but, instead, couple to olefins by intermolecular hydroacylation.[10] Next, Jun and co-workers discovered that 2-(diphenylphosphino)benzaldehyde couples to a range of olefins.[11] Miura and Willis expanded the scope of the aldehyde partner to include proximal coordinating groups, such as alcohols, sulfides, and amines.[12] An alternative strategy uses catalytic scaffolding groups to achieve similar levels of reactivity and selectivity. Jun and co-workers demonstrated that 2-amino-3-picoline acts as a cocatalyst for intermolecular hydroacylation by forming a chelating picolyl imine.[13] After hydroacylation, the resulting imine product undergoes hydrolysis to afford the corresponding ketone and regenerate the amine catalyst.

An overview of progress in hydroacylation can be found in a *Chemical Review*[8c] by Willis and an *Organic Reactions* chapter[8f] by our laboratory. For a recent review on asymmetric hydroacylation, we direct the reader to a *Chemical Communications* viewpoint from our group.[14] The majority of studies in the field of asymmetric hydroacylation focused on the cyclization of 4-pentenals, which bear different substitution patterns to afford cyclopentanones.[8,14] For intermolecular couplings, using chelating aldehydes has allowed for the enantioselective synthesis of ketones.[8,14] A rare example of intermolecular olefin hydroacylation with simple aldehydes was reported by Tanaka.[15] In this example, the authors demonstrated that acrylamides are suitable olefin partners and hypothesize that the proximal amide coordinates to the Rh center during catalysis to stabilize the acyl-Rh(III)-hydride intermediate. With this background in mind, our research team focused on three main questions:

(1) Can we expand asymmetric variants by incorporating directing groups on the olefin component?
(2) Can we develop an analogous transformation where ketones could be used in place of olefins to generate the corresponding esters and lactones?
(3) Can we diverge the key acyl-Rh(III)-hydride intermediate to other pathways, including those that involve C−C bond cleavage?

2.1. Olefin Hydroacylation with Chelating Substrates

Our work in the area of olefin hydroacylation with chelating substrates centers around four themes, which are summarized in Figure 3. Our contributions include (1) developing the enantio- and regioselective synthesis of medium-sized heterocyclic ketones, (2) using ring-strain to drive intermolecular hydroacylation, (3) incorporating an additional directing group on the olefin partner to control regioselectivity for intermolecular couplings, and (4) identifying a catalyst that allows for the intermolecular hydroacylation of unactivated olefins (e.g., α-olefins).

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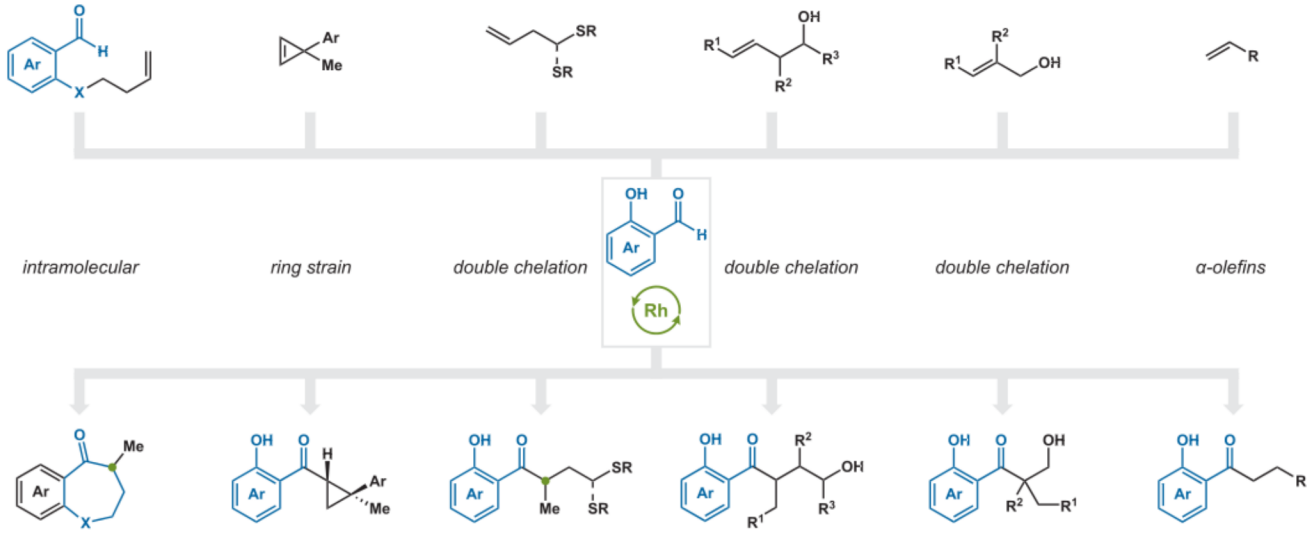

Figure 3. Overview of the developed olefin hydroacylations with chelating substrates.

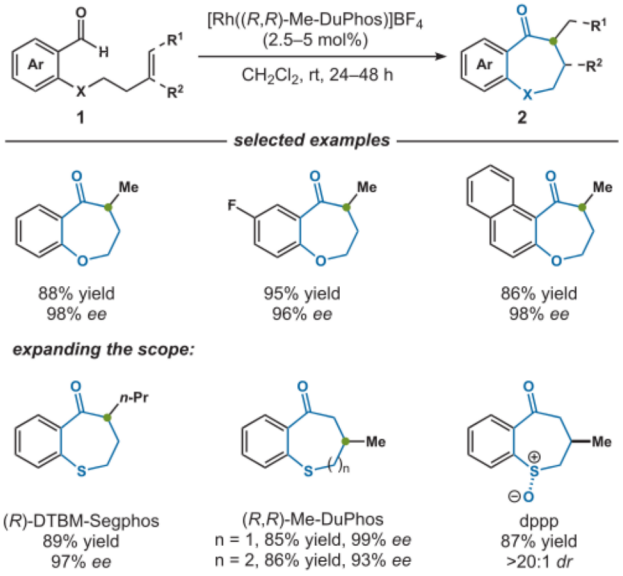

Figure 4. Enantioselective intramolecular hydroacylation for the synthesis of seven- and eight-membered heterocycles.

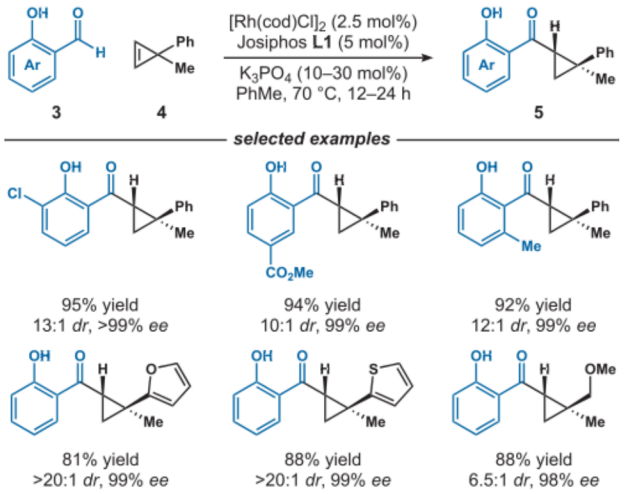

Figure 5. Enantioselective desymmetrization of cyclopropenes by intermolecular hydroacylation.

In 2009, we reported an enantioselective intramolecular olefin hydroacylation to afford seven- and eight-membered heterocycles (Figure 4).[16] The heteroatom (X) in the carbon framework of **1** promotes desired reactivity over decarbonylation. Starting with aldehyde **1**, a cationic Rh catalyst modified by (*R*,*R*)-Me-DuPHOS allows for the enantioselective preparation of seven- and eight-membered heterocyclic ketones **2**. Matching the ancillary ligand with the aldehyde substrate enabled high reactivity and stereoselectivity.

Preventing unwanted decarbonylation becomes more challenging with the intermolecular variant of olefin hydroacylation. To create a driving force for desired reactivity, we selected highly strained cyclopropenes **4** as the olefin partner (Figure 5).[17] Josiphos ligands promoted the desymmetrization of cyclopropenes to set vicinal stereocenters in **5**. High levels of diastereoselectivity (up to >20:1 *dr*) and enantioselectivity (up to >99% *ee*) were obtained. This method complemented the limited reports for synthesizing enantioenriched cyclopropanes bearing a quaternary stereocenter at the time. However, the optimal conditions were not applicable to linear olefins.

To control for branched selectivity in olefin hydroacylations, we used distal directing groups on the olefin partner (Figure 6). Transition metal-catalyzed reactions involving directing groups tethered to olefins have seen large success.[18a] However, this approach was rarely used for enantio- and regioselective intermolecular olefin hydroacylation. Two examples were reported in 2009 at the time of our initial studies: Tanaka demonstrated that acrylamides are suitable chelating olefins,[15] and Suemene reported that 1,5-hexadienes promote branched selectivity.[18b] Building on this strategy, we used homoallylic sulfides **6** as the olefin partner because we had previously demonstrated that intramolecular olefin hydroacylation occurs in the presence of a sulfide tether (Figure 6A).[19] Various salicylaldehydes **3** undergo the coupling reaction to afford aryl ketones **7** bearing α-stereocenters. Moreover, a multitude of aryl homoallylic sulfides **6** are compatible. Decarbonylation is mitigated by combining low reaction temperatures, an appropriate ligand, and the presence of directing groups on both reactants. To investigate the regioselective outcome, we

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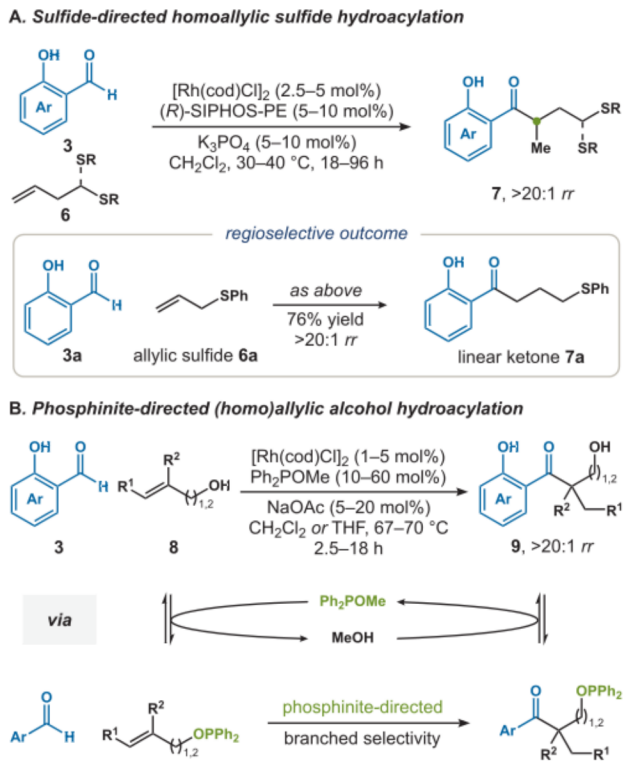

Figure 6. (A) Regio- and enantioselective coupling of salicylaldehydes and homoallylic sulfides. (B) Analogous regioselective hydroacylations of allylic and homoallylic alcohols.

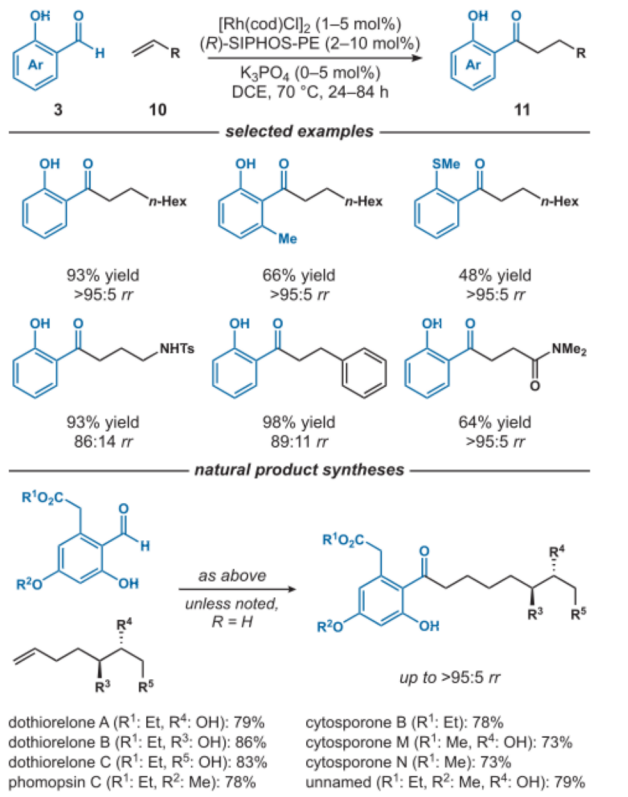

Figure 7. Rh-catalyzed hydroacylation of unactivated olefins and octaketide natural product synthesis.

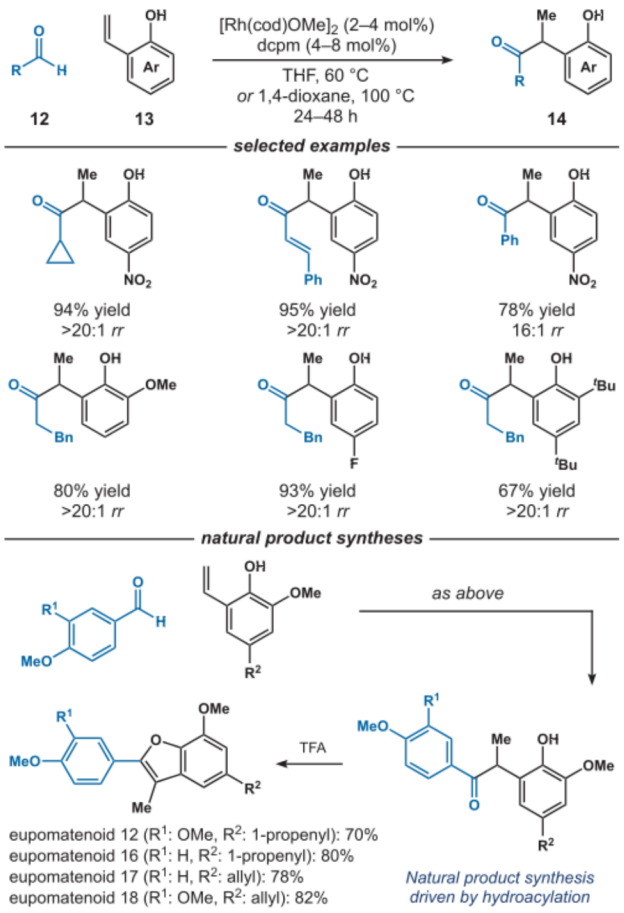

Figure 8. Olefin-directed hydroacylation with nonchelating aldehydes.

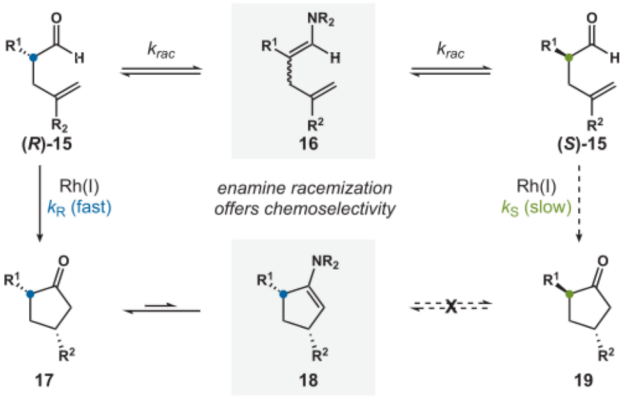

Figure 9. Design and strategy for the intramolecular DKR hydroacylation of racemic 4-pentenals.

subjected allylic sulfide **6a** to the standard reaction conditions and observed linear ketone **7a**. This result suggests that a five-membered rhodacycle intermediate influences the branched versus linear regioselectivity.

Toward branch-selective hydroacylation, we developed a tandem catalytic cycle that converts allylic and homoallylic alcohols **8** to (homo)aldol motifs **9** (Figure 6B).[20] The design leverages the reversible alcoholysis of phosphinites. Methyl diphenylphosphinite undergoes exchange with an equivalent of alcohol **8** to afford an allylic phosphinite, which is a competent directing group for Rh-catalyzed hydroacylation. A variety of

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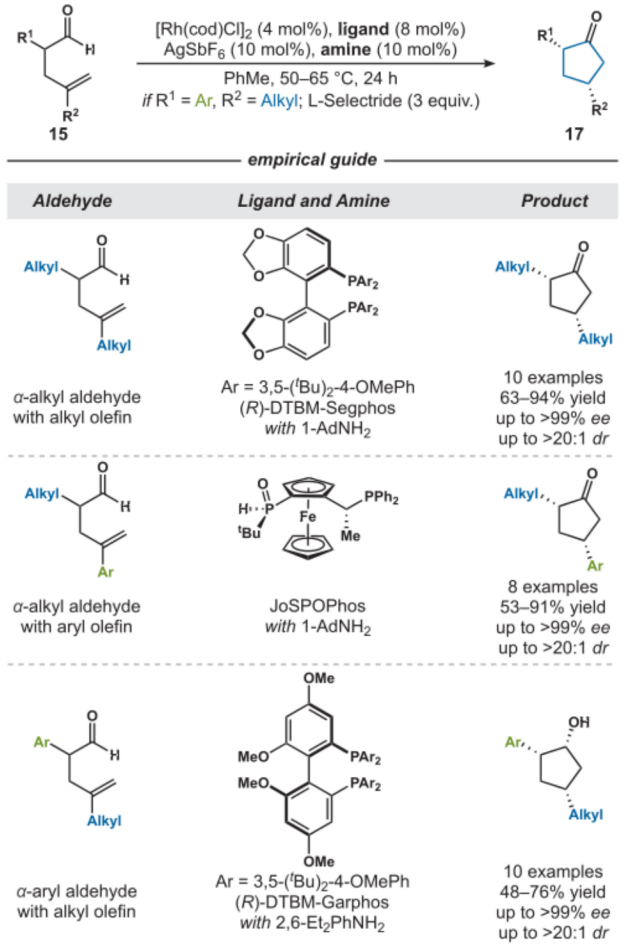

Figure 10. Optimal ligands for the enantioselective DKR hydroacylation.

salicylaldehydes **3** and (homo)allylic alcohols **8** couple to form hydroxy ketones **9**. Reactivity depends on the ability of the hydroxyl group to form a phosphinite; the analogous methyl ether of **8** shows no reactivity under these standard conditions.

We then discovered a Rh catalyst that allows for the regioselective preparation of linear ketones **11** (Figure 7).[1] The combination of a phosphoramidite ligand (*R*-SIPHOS-PE) and a heterogeneous base are critical for reactivity and regioselectivity. We proposed that (*R*)-SIPHOS-PE aids in inhibiting decarbonylation by lowering the barrier for reductive elimination of the acyl-Rh(III)-alkyl species. In agreement with this proposal, mechanistic findings suggest that hydrorhodation to form a branched acyl-Rh(III)-alkyl species is reversible, whereas linear hydrorhodation is irreversible. We prepared eight biologically active octaketide natural products (i.e., dothiorelones, cytosporones, and phomopsin C). In a related study, we synthesized 12 analogs of the cytosporone family and ultimately found an increase in cytotoxicity with a densely fluorinated acyl carbogenic chain.[21]

We aimed for hydroacylations with simple, nonfunctionalized aldehyde partners by using olefins bearing directing groups (Figure 8).[22] Vinylphenols **13** undergo Rh-catalyzed hydroacylation with a broad scope of aldehydes **12**, including aryl, alkenyl, and alkyl aldehydes—none of which contained a coordinating functional group.[22a] Benzylic ketones **14** can then undergo an acid-mediated dehydrative cyclization to afford the

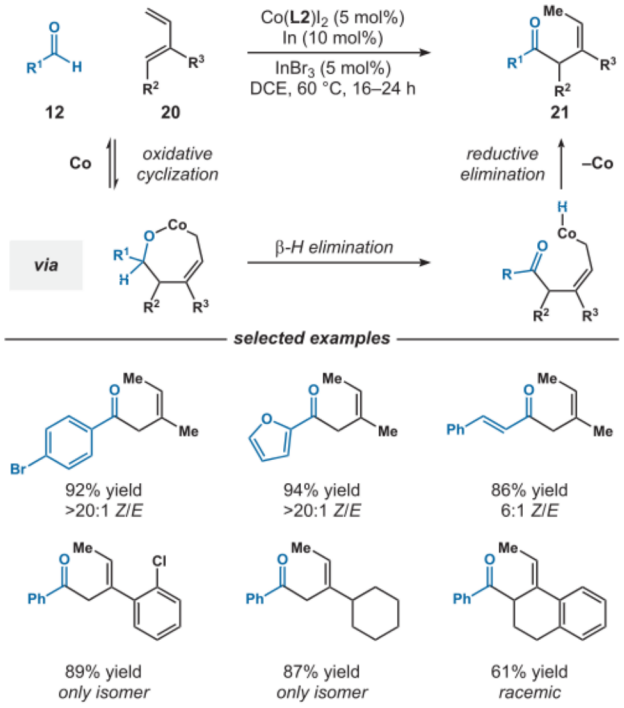

Figure 11. Co-catalyzed hydroacylation of 1,3-dienes.

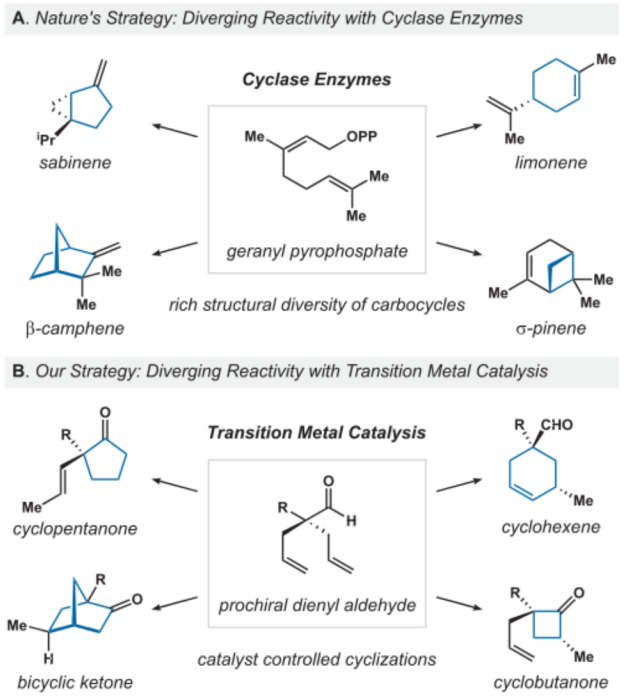

Figure 12. (A) Enzyme-directed cyclizations of geranyl pyrophosphate. (B) Transition metal-catalyzed hydroacylation to afford various carbocyclic frameworks.

corresponding benzofurans. This sequence leads to four natural products: eupomatenoids 12, 16−18. The kinetic profile shows saturation kinetics for the vinylphenol partner.[22b] Chelation of the vinylphenol aids in favoring hydroacylation over decarbonylation. Moreover, the small bite-angle ligand (dcpm) lowers the

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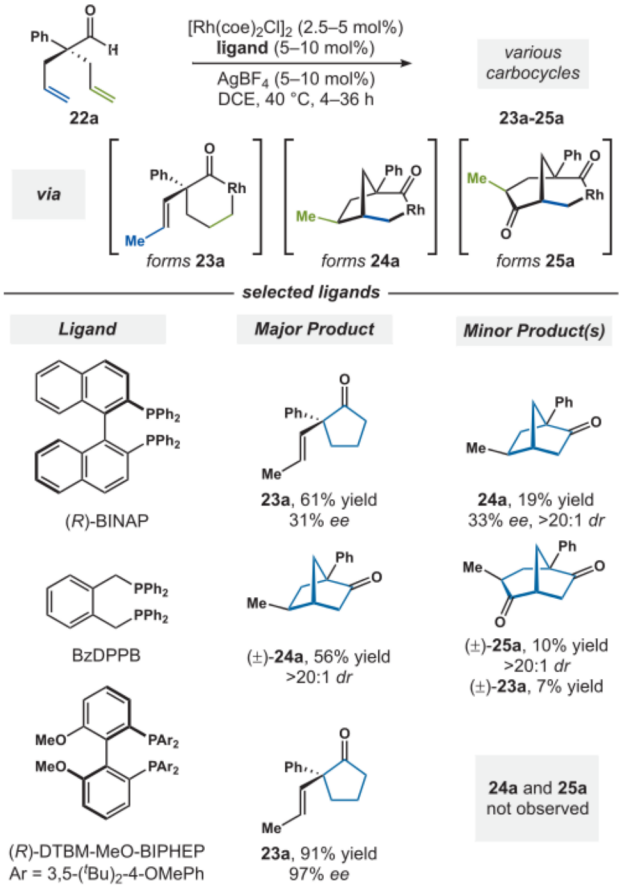

Figure 13. Divergent cyclizations of a dienyl aldehyde **22a** based on ligand choice.

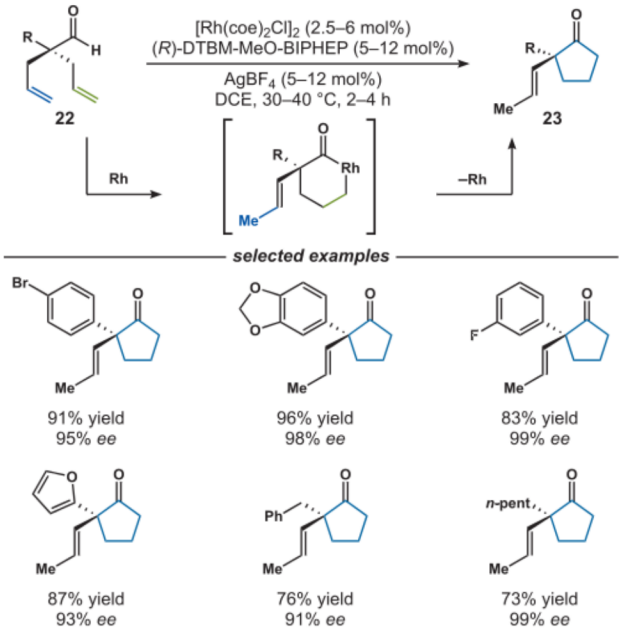

Figure 14. Rh-catalyzed desymmetrization of quaternary centers by hydroacylation.

barrier of oxidative addition of the Rh catalyst to the formyl C–H bond, which we determined to be the turnover-limiting step.

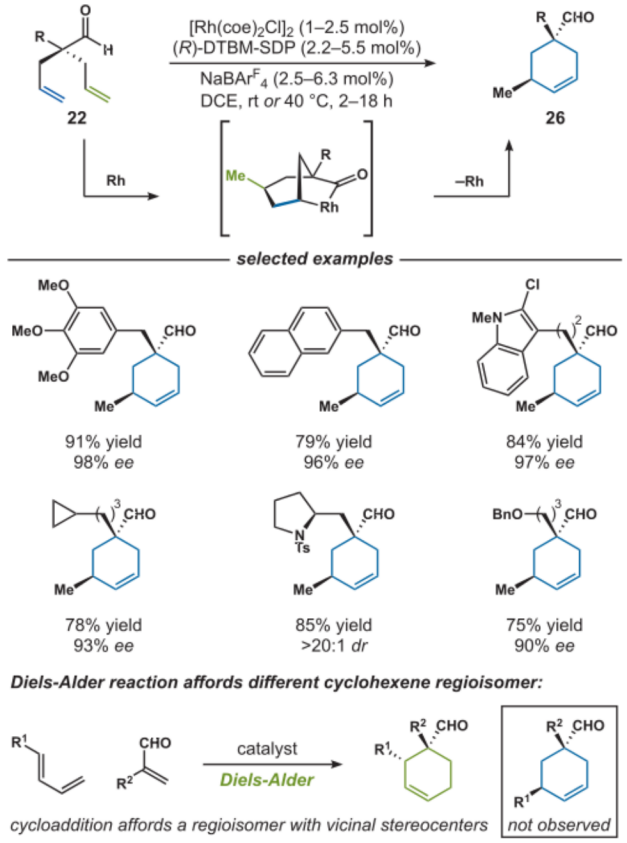

Figure 15. Asymmetric cycloisomerization to access cyclohexenes.

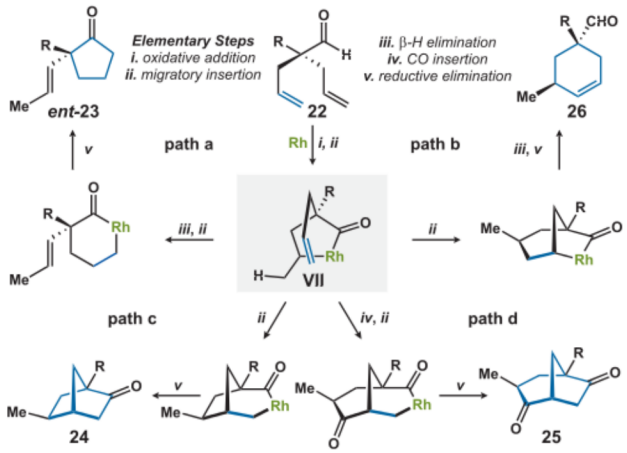

Figure 16. Mechanistic pathways for the Rh-catalyzed cyclizations of dienyl aldehydes.

2.2. Other Strategies and Metals for Olefin Hydroacylation

James and Young reported the first enantioselective intramolecular olefin hydroacylation, a kinetic resolution of racemic 4-pentenals.[23] While this was a groundbreaking result, the cyclization was limited to a theoretical yield of 50%. Nearly four decades later, we set out to achieve a related variant using dynamic kinetic resolution (DKR).[24] However, examples of C–C bond-forming DKR processes are rare.[25] Our strategy relies on a cocatalyst (a bulky primary amine) to selectively racemize the aldehyde starting material **15**, by means of enamine **16**, and not the cyclopentanone product **17** (Figure 9).[26] This selective

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Acc. Chem. Res. 2021, 54, 1236–1250

racemization exploits the electrophilicity of these different carbonyls. If the amine cocatalyst condenses onto enantioenriched ketone **17**, the formation of the less-substituted enamine **18** is preferred. Therefore, avoiding allylic strain prevents product epimerization to **19**.

Similar to other intramolecular olefin hydroacylations, we observe a strong ligand dependence for the DKR hydroacylation of homoallylic aldehydes **15** (Figure 10).[26] The cyclization depends on matching the ligand with the substituents on both the α-carbon atom and pendant olefin. We identified three combinations of substrate, ligand, and amine cocatalyst that allow access to various alkyl- and aryl-substituted cyclopentanones **17**. In the case of α-aryl cyclopentanones, Houminer demonstrated that this motif undergoes oxidative decomposition.[27] Therefore, to inhibit product decomposition and epimerization, we performed a reductive workup with L-selectride to furnish cyclopentanols. Preliminary mechanistic findings suggest that reductive elimination is the turnover-limiting step. This DKR enables access to α,γ-disubstituted cyclopentanones that are difficult to access otherwise.[28]

Our laboratory,[2,29] Yoshikai,[30] and Vinogradov[31] have found that the more earth abundant, Co-derived catalysts, can also promote olefin hydroacylation. By using Co catalysis, we accessed allylic ketones **21** with 1,3 dienes **20** acting as the olefin partner (Figure 11).[29] The mechanism differs from the typical Rh-catalyzed olefin hydroacylation mechanism. In the initial step, oxidative cyclization of the two substrates and Co catalyst forges the new C−C bond. Subsequently, an endocyclic β-H elimination of the seven-membered cobaltacycle affords a Co−H species. Reductive elimination completes the cycle to afford ketone **21**. We applied this method to aryl, alkenyl, and alkyl aldehydes, forming ketones **21** in high yield with excellent regioselectivity. This method contributes to the emerging hydroacylation strategies that exploit nonprecious metal catalysis.[8]

2.3. Divergent Synthesis of Carbocycles

Cyclase enzymes convert geranyl pyrophosphate to a variety of structurally unique carbocycles (Figure 12A). Inspired by Nature, we hypothesized that a common dienyl aldehyde could undergo a variety of metal-catalyzed bond formations, which would all be triggered by C−H bond activation (Figure 12B). Our investigations began with a chiral Rh catalyst and symmetric dienyl aldehyde **22a** (Figure 13).[32] We found that changing the ancillary ligand yields different mixtures of cyclopentanone **23a**, bicyclic ketone **24a**, and bicyclic diketone **25a**. When using (*R*)-BINAP, we observe cyclopentanone **23a** as the major product alongside bicyclic ketone **24a**; both ketones **23a** and **24a** are formed with low levels of enantioinduction. However, when using BzDPPB the product ratio favors bicyclic ketone **24a**, which arises from a novel carboacylation pathway that is triggered by C−H bond activation.[33] Lastly, the use of (*R*)-DTBM-MeO-BIPHEP solely affords cyclopentanone **23a** with high levels of enantioselectivity. Interested by the array of products formed from **22a**, we sought to develop the divergent carbocyclization chemistry and unearth the mechanistic pathways.

Our initial study focused on expanding the substrate scope of the enantioselective cyclopentanone synthesis (Figure 14).[32] Desymmetrization of dienyl aldehydes **22** proceeds with high enantiocontrol. In the presence of lower catalyst loadings than our initial lead (see Figure 12), an array of α-aryl and α-alkyl aldehydes **22** transform to carbocycles **23**. This method allows

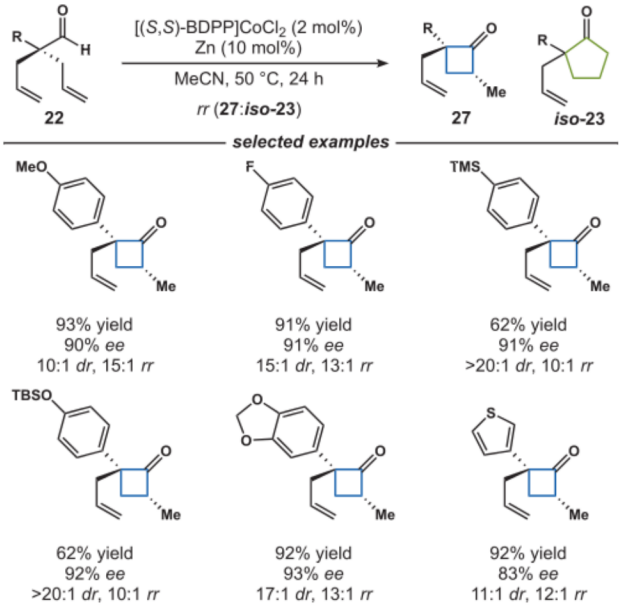

Figure 17. Co-catalyzed hydroacylation affords enantioenriched cyclobutanones.

for the synthesis of cyclopentanones bearing a stereodefined quaternary center. Mechanistic findings support an irreversible and enantioselective olefin isomerization followed by hydroacylation of the remaining terminal olefin (vide infra). We proposed that the α-vinyl group, which is initially formed by olefin isomerization, not only directs hydroacylation to the remaining terminal olefin but also coordinates to the Rh center to slow decarbonylation.

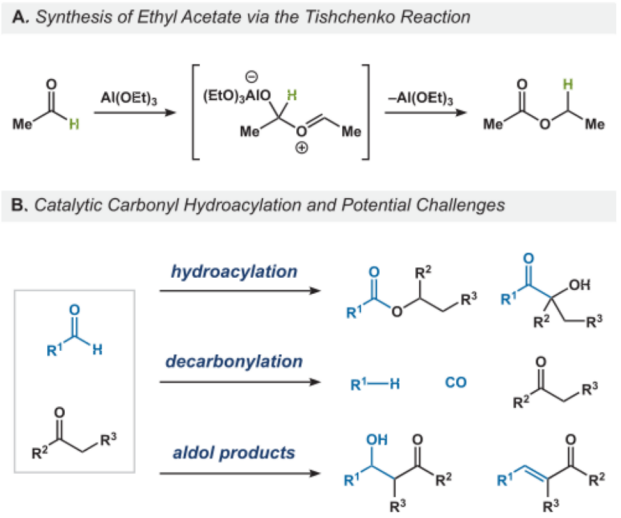

Figure 18. (A) Inspiration for carbonyl hydroacylation and (B) challenges to overcome.

After observing olefin isomerization in the synthesis of cyclopentanones **23**, we were interested in intercepting a related acyl-Rh-hydride intermediate (Figure 15).[34] Changing the chiral ligand to a spirobiindane (SDP) backbone and the salt additive to $NaBAr^F_4$ diverted the reactivity of **22** to cyclohexenyl aldehydes **26**. The scope of this cycloisomerization compares favorably to the previous olefin hydroacylation to afford

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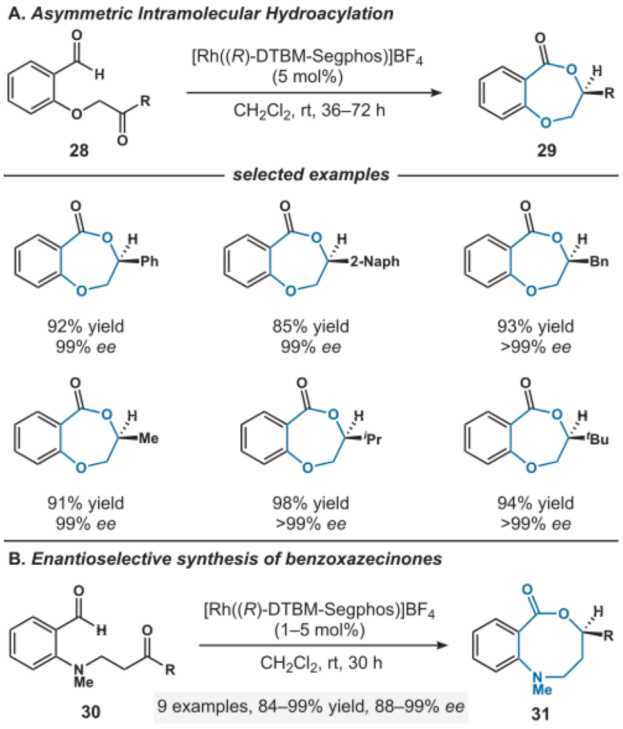

Figure 19. Rh-catalyzed carbonyl hydroacylations furnishes medium-sized heterocyclic lactones.

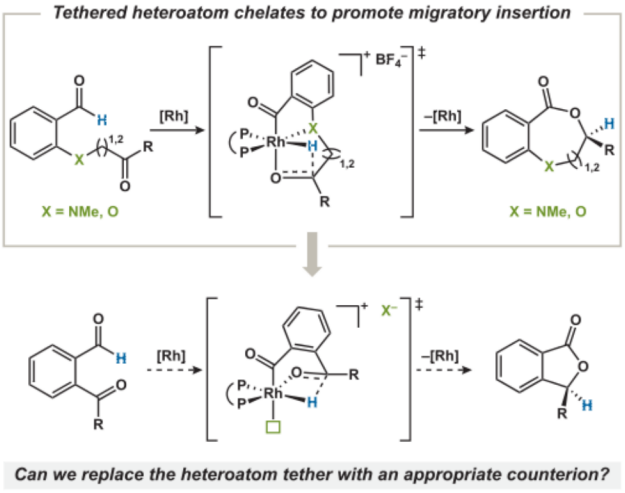

Figure 20. Design of a strategy uses coordinating counterions to expand the scope to nonchelating aldehydes.

cyclopentanones **23**. This method sets a quaternary stereocenter, as well as a distal tertiary stereocenter, with high levels of stereocontrol. Moreover, cyclohexenes **26** are complementary to the regioisomers formed from a Diels–Alder reaction between terminal dienes and α,β-unsaturated aldehydes.[35] The cycloisomerization proceeds by formyl C–H bond activation, regioselective carbometalation, and then endocyclic β-H elimination (vide infra).

On the basis of literature precedent and our own mechanistic findings, we propose that a key intermediate can diverge into the four distinct products **23**–**26** (Figure 16).[8,32,34] Initial oxidative addition of the Rh catalyst to the aldehyde C–H bond affords an acyl-Rh(III)-hydride intermediate. Stereoselective hydrorhodation of one olefin then affords five-membered rhodacycle **VII**, which is the common denominator between all four products we observe in our studies. Collectively, these findings showcase that fine-tuning the Rh catalyst can diverge the reactivity of a common aldehyde into unique carbocycles. However, at no point in our studies did we observe reductive elimination of **VII** to furnish a cyclobutanone product. Interested by the possibility of forming densely substituted cyclobutanones, we decided to explore Co catalysis.

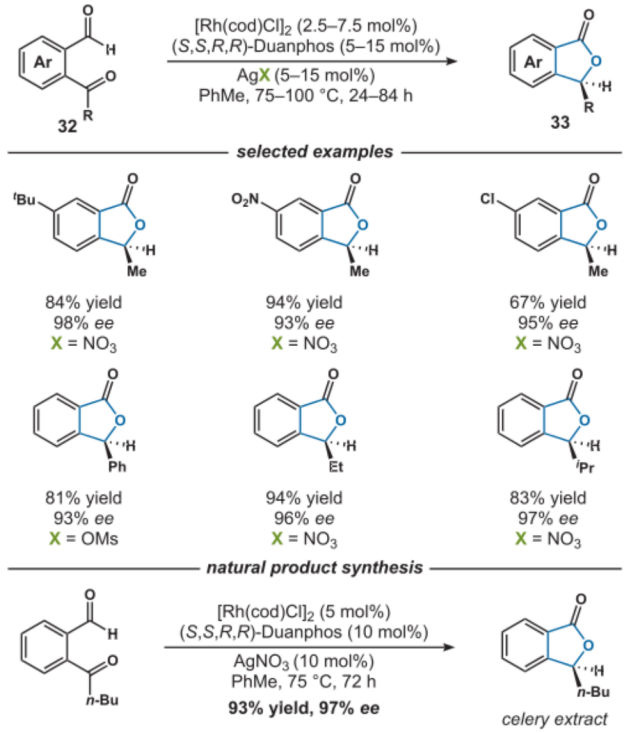

Figure 21. Enantioselective preparation of phthalides by Rh-catalyzed carbonyl hydroacylation.

Bergman and co-workers characterized a five-membered cobaltacycle that undergoes oxidatively induced reductive elimination to form cyclobutanones.[36] In addition, Vinogradov showed that paramagnetic Co(0)-complexes catalyze intramolecular hydroacylation of 4-pentenal to afford cyclopentanone.[31] This precedent, paired with our previous success in Co catalysis,[29] led us to investigate hydroacylation to form cyclobutanones. We identified that a Co catalyst, modified by (*S*,*S*)-BDPP, and substoichiometric amounts of Zn reductant formed cyclobutanones **27** with high selectivity (Figure 17).[2] A variety of α-aryl bisallyl aldehydes **22** undergo the transformation to favor cyclobutanones **27** over cyclopentanones *iso*-**23** ($\geq$10:1 *rr*). This study features enantioselective construction of cyclobutanones **27** by hydroacylation and complements previous methods that rely upon parallel kinetic resolutions.[23b,c] Mechanistic findings support a canonical hydroacylation mechanism that involves reductive elimination of a five-membered cobaltacycle to afford **27**.

3. CARBONYL HYDROACYLATION

In comparison to olefin hydroacylation, the corresponding carbonyl hydroacylation for asymmetric ester synthesis remains much less explored.[37] Bosnich reported the first example of ketone hydroacylation.[38] In this study, 1,4-ketoaldehydes cyclize

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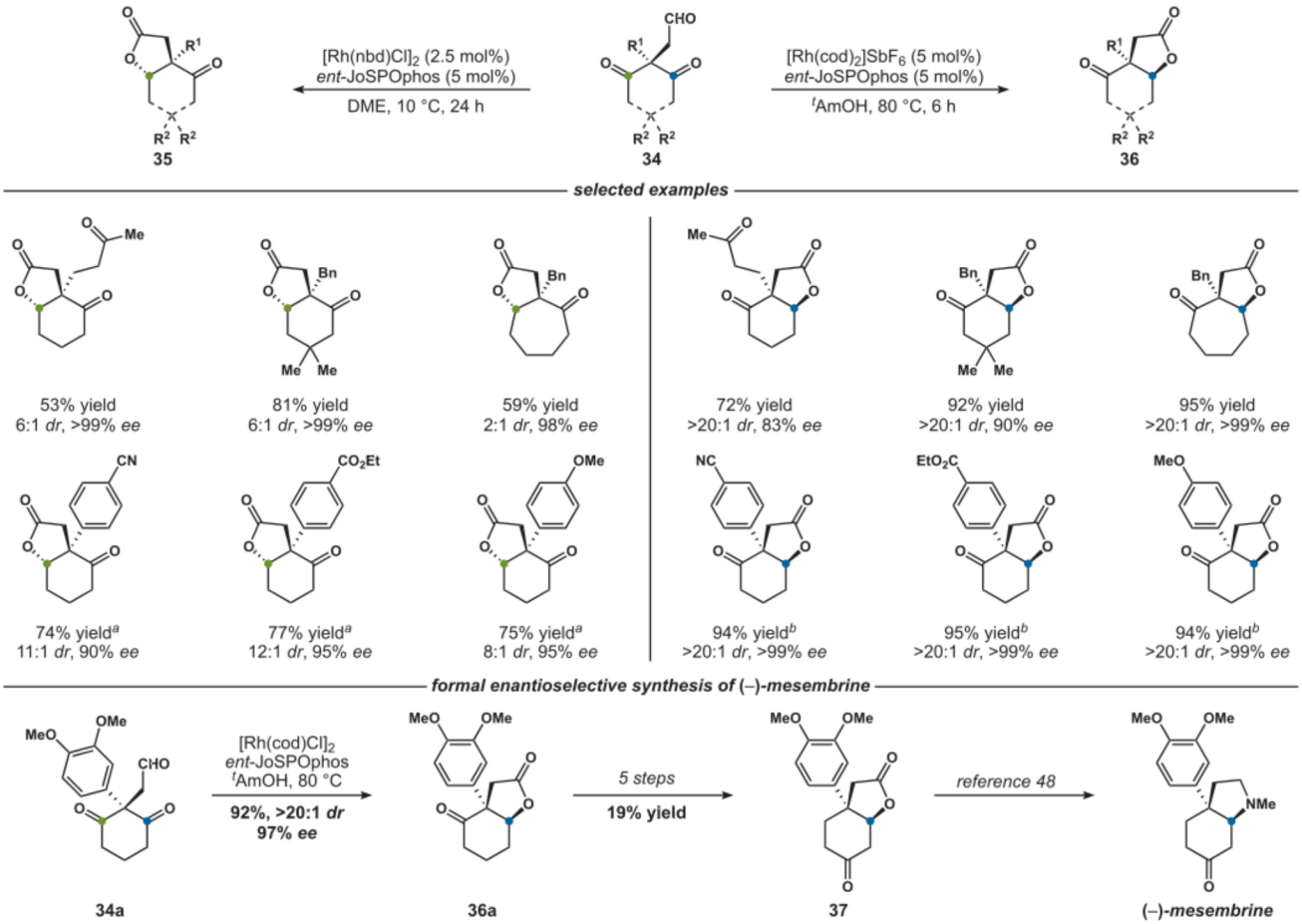

Figure 22. Diastereodivergent construction of bicyclic lactones by enantioselective carbonyl hydroacylation.

to racemic γ-lactones under Rh catalysis. While distinct in mechanism, hydroacylation to generate esters bears similarities to the Tishchenko reaction,[39] which is a process catalyzed by base. For example, the industrial synthesis of ethyl acetate involves a Tishchenko reaction of acetaldehyde with an alkoxide catalyst (Figure 18A).[40] While industrially relevant, enantioselective variants of the Tishchenko reaction were rare at the time we began our studies.[41] We imagined that functionalization of aldehyde C−H bonds would represent an attractive and unified approach to making both ketones and esters. Preventing reductive decarbonylation and controlling regioselectivity (Tishchenko-like versus Benzoin-like products) are main obstacles shared between carbonyl and olefin hydroacylation (Figure 18B). However, an additional challenge arises when attempting to couple two carbonyl starting materials. The aldol and aldol condensation reactions represent well-established pathways that compete with carbonyl hydroacylation.

3.1. Intramolecular Carbonyl Hydroacylation

We started investigations with the intramolecular cyclization of ketoaldehydes **28**, which contain an oxygen atom in the tether (Figure 19A).[3] Despite all possible products, we identified a Rh catalyst that affords the Tishchenko-type ester **29**, with only minor amounts of decarbonylation. A variety of ketoaldehydes **28** undergo the desired cyclization to afford seven-membered heterocyclic lactones **29**, with high reactivity and selectivity. In a related study, we expanded the scope of the ketoaldehydes to include nitrogen atom tethers that cyclize to afford benzoxazecinones **31** (Figure 19B).[42] Therefore, both oxygen and nitrogen atoms bind to Rh to inhibit decarbonylation and lower the entropic cost for medium ring formation. While limited in scope, this breakthrough afforded an enantioselective preparation of medium-sized rings and provided an opportunity to study the mechanism of ketone hydroacylation.

While the mechanism was assumed to mirror olefin hydroacylation, experiments were necessary to confirm. Kinetic isotope effects and Hammett plot studies suggest that ketone insertion into the Rh−H bond is the turnover-limiting step.[43] Moreover, the absence of crossover products supports an intramolecular hydrorhodation of the ketone. This elementary step affords an acyl-Rh-alkoxide species, which then undergoes reductive elimination to afford heterocyclic lactones **29** and **31**. Density functional theory (DFT) studies support our experimental observations.

While we successfully identified a chiral Rh catalyst for enantioselective carbonyl hydroacylation, only medium-sized lactones could be accessed. Therefore, to identify a catalyst for small-membered ring construction we focused on substrates without a coordinating atom in the tether (Figure 20). We hypothesized that tuning the counterion for the Rh catalyst would expand the scope of intramolecular carbonyl hydroacylation. For this study, we chose the intramolecular hydroacylation of ketoaldehyde **32** to afford phthalides **33** (Figure 21).[44] Fine-tuning of a silver salt resulted in inhibiting decomposition pathways. Specifically, the coordinating ability of the anion (depicted as X) needed to be matched with the

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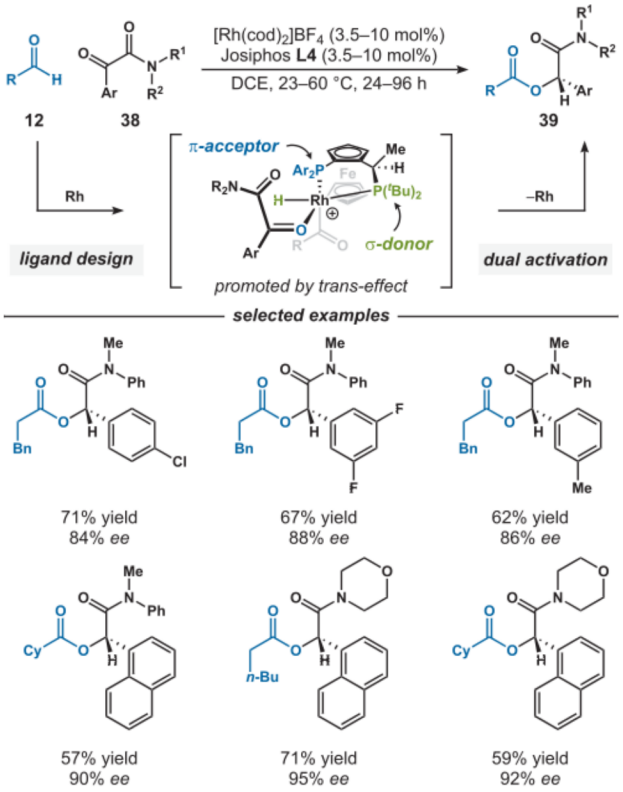

Figure 23. Enantioselective coupling of aldehydes and ketoamides.

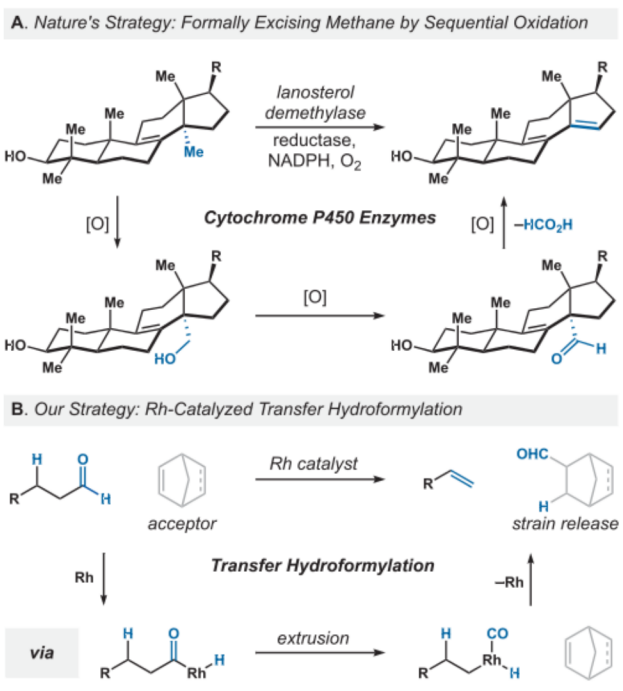

Figure 24. (A) Nature's approach to dehydroformylation. (B) Rh-catalyzed transfer hydroformylation.

ketone substituent (depicted as R). Empirical studies revealed a nitrate anion is optimal for alkyl-substituted ketones, whereas aryl-substituted ketones require a mesylate counterion. In general, stronger coordinating counterions can help prevent decarbonylation. However, the resulting catalysts are often more sluggish. As a result, the counterion remains a valuable parameter for tuning both reactivity and selectivity. Currently, the substrate scope is limited to aryl-substituted ketoaldehydes **32**. Careful selection of the bisphosphine ligand alongside the counterion resulted in high reactivity and enantioselectivity. With this method, we prepared (*S*)-3-*n*-butylphthalide in 93% yield and 97% *ee*. This natural product imparts the flavor of celery and its racemate reached phase-III clinical trials for treating strokes.[45]

In a subsequent study, we focused on desymmetrization of bisketoaldehydes **34** for the enantioselective preparation of bicyclic lactones **35** and **36** (Figure 22).[46] Choosing the appropriate Rh source, solvent, and temperature allowed for the diastereodivergent synthesis of *anti*- and *syn*-bicyclic lactones (**35** and **36**, respectively). With dimeric $[Rh(nbd)Cl]_2$, an ethereal solvent, and a lower reaction temperature, we observed selective formation of the *anti*-lactone **35**. Changing to cationic $[Rh(cod)_2]SbF_6$, an alcoholic solvent, and increasing the temperature furnished *syn*-fused lactones **36**. Both transformations progress with high levels of reactivity and selectivity. We propose that the use of polar, coordinating solvents (i.e., DME and ^{t}AmOH) inhibits decarbonylation. This strategy enables an enantioselective formal synthesis of (−)-mesembrine.[47] Starting with bisketoaldehyde **34a**, carbonyl hydroacylation affords *syn*-fused lactone **36a**. Redox manipulations and an allylic alcohol transposition affords lactone **37** and completes the formal synthesis.[48]

3.2. Intermolecular Carbonyl Hydroacylation

Like Rh-catalyzed olefin hydroacylation, intermolecular carbonyl hydroacylation poses more challenges compared to the intramolecular counterpart. We hypothesized that a directing group on the carbonyl partner could address these challenges. We selected ketoamides **38** as the carbonyl partner and identified a Rh catalyst that could afford the corresponding α-acyloxyamides **39** with high regio- and enantiocontrol (Figure 23).[49] Key to the success of this coupling was the design and synthesis of a new Josiphos ligand (**L4**) that possessed both a π-accepting diarylphosphine and a σ-donating dialkyl phosphine substituent. We propose that the π-accepting phosphine substituent is positioned *trans* to the carbonyl partner, making it more prone to migratory insertion. Likewise, the σ-donating dialkyl phosphine is positioned *trans* to the hydride ligand therefore increasing hydricity. This dual activation explains why the Josiphos ligand class was uniquely effective for the transformation. In a follow-up study, we prepared a novel dcpp-inspired bisphosphine ligand (**L5**) that contains two *P*-stereogenic centers.[50] This bidentate ligand for Rh expands the scope to include isatins and linear α-ketoamides with aliphatic aldehydes.

4. TRANSFER HYDROFORMYLATION

Nature uses cytochrome P450 enzymes to oxidize C−H bonds in a highly selective manner.[51] Within this family of enzymes, the demethylases excise methyl groups in the biosynthesis of sterols (Figure 24A).[52] In this cascade, an aldehyde intermediate undergoes dehydroformylation to access the olefin product. Inspired by this biosynthetic sequence, we envisaged developing a dehydroformylation of aldehydes as a complementary tool for organic synthesis (Figure 24B). Notably this transformation would occur via the cleavage of one C−C bond to generate olefins. This approach stands in stark contrast to staple olefinations where aldehydes transform to olefins via C−C

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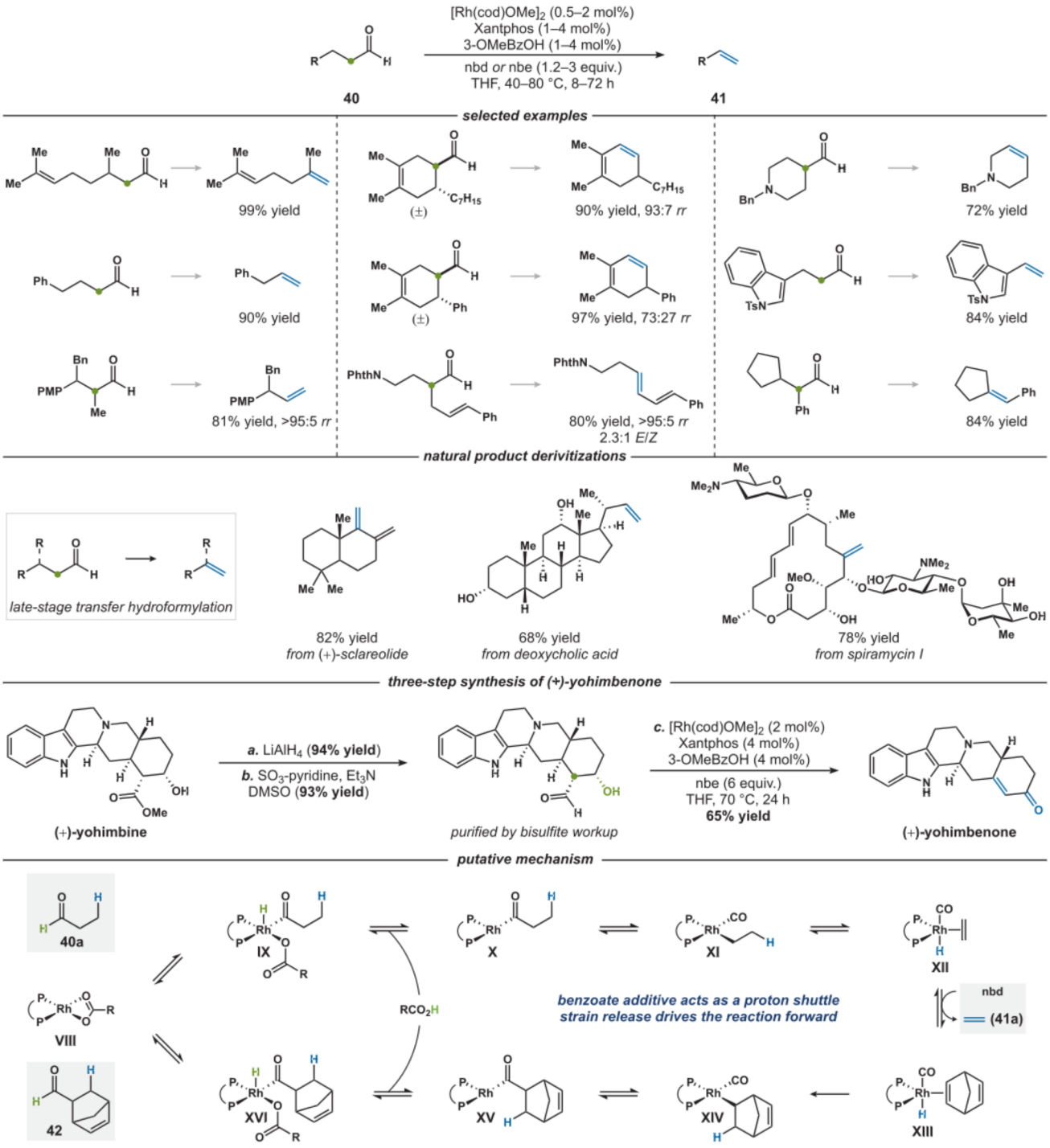

Figure 25. Rh-catalyzed C−C bond cleavage by transfer hydroformylation.

bond formations, such as the Wittig, Julia−Lythgoe, and Horner−Wadsworth−Emmons reactions.[53]

Our proposal relied on triggering C−C bond cleavage by chemoselective activation of formyl C−H bonds using Rh catalysis. This process requires trapping the acyl-Rh(III)-hydride species in a pathway that outcompetes known hydroacylation and decarbonylation. Olefins generated by dehydroformylation have been observed in reactions that use stoichiometric catalysts or require elevated reaction temperatures (160−300 °C).[54] We imagined that a Rh catalyst could work in tandem with a sacrificial strained olefin acceptor to transfer a hydrogen atom and formyl group from the aldehyde substrate. We postulated that the release of substantial ring strain in the olefin acceptor could offer a driving force for the isodesmic reaction[55] and allow for selective access to the desired olefin product. Notably, this process would avoid the intermediacy of CO gas, which could potentially act as a catalyst poison. If successful, this strategy could pave the way for future transfer hydroformylations that use alcohols and alkanes as substrates with an oxidizing agent.

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A Rh catalyst promotes selective transfer hydroformylation of a variety of aldehydes **40** (Figure 25).[4] Crucial to the success of this process was the appropriate counterion (i.e., 3-methoxybenzoate) and strained olefin acceptor (nbd = norbornadiene or nbe = norbornene). An array of aldehydes **40** transform to terminal and internal olefins, conjugated dienes, as well as cyclic and trisubstituted olefins (**41**). The transformation tolerates a range of functional groups. We demonstrated a late-stage transfer hydroformylation of natural product derivatives. Specifically, we prepared indole alkaloid (+)-yohimbenone in three-steps from the inexpensive, commercially available precursor (+)-yohimbine. Our synthesis starts with reduction of the exocyclic ester to afford the corresponding aldehyde. Subjecting this aldehyde to the transfer hydroformylation conditions affords (+)-yohimbenone in 65% yield. The cascade initially forms the corresponding allylic alcohol, but after a prolonged reaction time, a transfer hydrogenation event occurs to afford the enone functionality in (+)-yohimbenone.

We sought to understand the mechanistic underpinnings of transfer hydroformylation. Deuterium labeling studies and characterization of organometallic intermediates support the catalytic cycle shown in Figure 25. Oxidative addition of Rh(benzoate) species **VIII** to aldehyde **40a** affords acyl-Rh-hydride **IX**. Reductive elimination of **IX** releases an equivalent of 3-OMeBzOH and affords coordinatively unsaturated complex **X**. Species **X** then undergoes CO-migratory extrusion followed by β-hydride elimination to yield olefin complex **XII**. Ligand exchange with the strained olefin partner releases olefin **41a**. Migratory insertion of the olefin into the Rh−H bond of **XIII** yields **XIV**. CO-insertion, oxidative addition to 3-OMeBzOH, and finally, reductive elimination furnishes the acceptor byproduct **42** and regenerates the active catalyst **VIII**.

The proposed transfer hydroformylation mechanism highlights why the judicious choice of counterion and olefin acceptor facilitate productive chemistry. The counterion effectively acts as a proton-shuttle between the two distinct acyl-Rh-hydride species **IX** and **XVI**. Therefore, fine-tuning the basicity of this chemical species is paramount. Moreover, the olefin acceptor needs to be sufficiently strained to drive the reaction in the forward direction. Following our study, Morandi and co-workers have unlocked an array of exciting transformations that bear similar design features, which they refer to as shuttle catalysis.[56] Also, the Nozaki laboratory has reported an Ir-catalyzed dehydroformylation of aldehydes that directly expels CO gas instead of transferring it to a strained acceptor.[57] Recently, Sorenson and co-workers have developed a Co catalyst that works in tandem with photoredox catalysis to transform aldehydes to olefins by dehydroformylation.[58] Our laboratory has also developed a cascade that enables the conversion of alcohols to dehomologated olefins via the intermediacy of an aldehyde.[59]

5. OUTLOOK

Discovered in the late 1700s and coined in 1835, the aldehyde represents one of the most fundamental functional groups in organic synthesis.[60] Aside from oxidations and reductions, aldehydes act as both nucleophiles and electrophiles. In addition, they engage in atom economical transformations with olefins (e.g., the Paternò−Büchi reaction) and umpolung chemistry (e.g., the Stetter reaction and Benzoin condensation).[35] Chemists today continue to develop strategies to both synthesize and transform aldehydes. This Account summarizes our efforts in diverting the reactivity of an organometallic intermediate that arises from aldehyde C−H bond activation to prepare novel motifs. The resulting methodologies allow for the rapid construction of C−C and C−O bonds and also C−C bond cleavage. The idea of taking common functional groups and discovering new ways to couple them with other partners is an emerging area of theoretical and experimental research.[61]

Our efforts have aided in the development of (1) intramolecular hydroacylations to afford carbocycles other than five-membered systems and (2) regio- and enantioselective intermolecular hydroacylations. There remains significant opportunities to (1) expand the substrate scope of directed hydroacylations and (2) identify more earth-abundant catalysts. The use of earth-abundant catalysts that promote formal hydroacylation via distinct mechanisms represents an emerging area of research.[62] We hope these insights will guide the use of transition metal catalysis to enable divergent reaction pathways for aldehydes and other common functional groups.

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The authors declare no competing financial interest.

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