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Rh-Catalyzed C–C Bond Cleavage by Transfer Hydroformylation

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Abstract

The dehydroformylation of aldehydes to generate olefins occurs during the biosynthesis of various sterols, including cholesterol in humans. Here, we implement a synthetic version that features the transfer of a formyl group and hydride from an aldehyde substrate to a strained olefin acceptor. A Rh(Xantphos)(benzoate) catalyst activates aldehyde C–H bonds with high chemoselectivity to trigger C–C bond cleavage and generate olefins at low loadings (0.3 to 2 mol%) and temperatures (22 to 80 °C). This mild protocol can be applied to various natural products and was used to achieve a three step synthesis of (+)-yohimbenone. A study of the mechanism reveals that the benzoate counterion acts as a proton-shuttle to enable transfer hydroformylation.

The cytochrome P450 enzymes have captured the imagination of chemists who seek to emulate their reactivity. For example, monooxygenases motivated the design of catalysts that epoxidize olefins and oxidize C–H bonds (1–4). This enzyme superfamily also includes various demethylases that break C–C bonds (5). In particular, lanosterol demethylase converts aldehydes to olefins by dehydroformylation during the biosynthesis of sterols in bacteria, algae, fungi, plants, and animals (6) (Figure 1A). Inspired by this step in biosynthesis, we sought a transition-metal catalyst for dehydroformylations in organic synthesis.

To this end, we aimed to trigger C–C bond cleavage (7–11) by chemoselective activation of aldehyde C–H bonds using Rh-catalysis (Figure 1B). Over the past fifty years, activating aldehyde C–H bonds with Rh has been thoroughly investigated (12); however, the resulting acyl–Rh^{III}–hydrides have been trapped mainly by hydroacylation (13) and/or decarbonylation (14,15). This common intermediate is also implicated in hydroformylation, which is practiced on an industrial scale using syngas (16). Thus, we needed a strategy for diverting the acyl–Rh^{III}–hydride towards dehydroformylation. To date, olefins generated by dehydroformylation have been observed in low-quantities during decarbonylations (15,17,18). One report describes the use of stoichiometric Ru for dehydroformylation of butyraldehyde (19), while another uses heterogeneous Rh or Pd catalysts for transforming steroidal aldehydes at 160–300 °C (20). In contrast, an Fe-peroxo complex cleaves aldehyde

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Supplementary Materials:
Materials and Methods
Data
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C–C bonds at room temperature, but this complex must be used in stoichiometric amounts and can lead to olefin epoxidation (21,22).

Given this challenge, we designed a strategy where dehydroformylation of an aldehyde substrate is driven by the concomitant hydroformylation of a strained olefin acceptor (Figure 1C) (23,24). This transfer hydroformylation avoids the accumulation of CO gas, which acts as a catalyst poison in related aldehyde dehomologations. Thus, formyl group transfer should proceed under mild conditions. Brookhart's study on the linear-to-branched isomerization of aldehydes with Rh-catalysis supports the feasibility of this approach (25). Moreover, Morimoto developed hydroformylations of mono-substituted olefins using formaldehyde as a source of CO and H_2 (26). Here, we report a Rh-catalyst for transfer hydroformylation that operates in the 22 to 80 °C temperature range, with loadings as low as 0.3 mol%. This mild protocol for dehydroformylation can be applied to a wide range of aldehydes, including those derived from alkaloid, terpene, steroid, and macrolide natural products.

During initial studies, we obtained promising results by investigating non-traditional counterions for Rh(Xantphos) complexes (Figure 2). The Xantphos ligand was chosen given its success in related hydroacylations, hydroformylations, and decarbonylations (13,16). Using citronellal (**1a**) and norbornadiene (**5a**) as the model substrate and acceptor, respectively, we observed that typical counterions such as BF_4^- and Cl^- yielded trace decarbonylation products, whereas a softer counterion, I^-, led to mixed dehydroformylation and decarbonylation reactivity. An increase in reactivity and selectivity was obtained by switching to organic counterions such as phenolates and sulfonamidates. The use of a benzoate counterion provided a breakthrough in efficiency. Against expectations, further tuning of the counterion revealed few trends related to pK_a, Hammett parameters, or coordinating ability. This observation suggests that the counterion plays a critical role in the mechanism (*vide infra*). 3-Methoxybenzoate provided a five-fold increase in initial rate compared to benzoate. We also identified 5-norbornene-2-carboxaldehyde (**6a**) as a stoichiometric product in each of these reactions indicating that a transfer hydroformylation mechanism operates.

The choice of olefin acceptor influences both catalyst loading and reaction temperature (Figure 2). Because norbornadiene (**5a**) gave selectivity greater than 99:1 **2a:3a**, the catalyst loading could be lowered to 0.3 mol% at 80 °C or 1 mol% at 60 °C using this acceptor. The reaction temperature could be further reduced by using olefin acceptors that cannot chelate to Rh. For instance, norbornene (**5b**) displayed excellent reactivity at 40 °C, while a slightly more strained acceptor, benzonorbornadiene (**5c**), provided reactivity at ambient temperature. To examine the scope of this strategy, we chose norbornadiene (**5a**) as the acceptor because it afforded the highest chemoselectivity with the lowest catalyst loadings.

This transfer hydroformylation protocol enables access to olefins from a wide range of aldehyde precursors. The Diels-Alder cycloaddition was used to easily generate cyclohexene-4-carboxaldehdye substrates **1b** through **1d**. The *trans* adduct **1b** underwent dehydroformylation to yield the conjugated 1,3-diene, whereas **1c** gave a mixture of 1,3- and 1,4-dienes. The *cis* Diels-Alder adduct **1d** yielded the 1,3-diene exclusively, most likely as a

result of a *syn*-selective β-hydride elimination. We reason that the observed regioselectivities are controlled by kinetics because 4-phenylbutanal (**1e**) yields the terminal olefin (**2e**) without any isomerization to the styrene derivative. In general, Lewis basic functionality, such as ethers, esters, amines, phthalimides, and indoles, were tolerated (**1f**–**1i, 1l**). A vinylindole was derived by dehydroformylation of **1g**, which was ultimately prepared from commercial indole and acrolein. Although 4-pentenals are prototypical substrates for intramolecular olefin hydroacylation, the α-allylated aldehyde **1h** underwent chemoselective dehydroformylation to yield the conjugated diene. Disubstituted olefins enriched in the *E*-stereoisomer (>20:1 *E*/*Z*) were accessed from the corresponding α-arylated aldehydes (**1i**). Substrates that do not form conjugated products upon dehydroformylation were transformed with modest regioselectivities (**1j** and **1k**); however, steric congestion favored terminal olefins over tri-substituted products (**1l**). Nonetheless, tri-substituted olefins were generated from substrates containing a single *syn*-β-hydrogen such as **1m**.

Next, we applied this protocol to generate structurally complex olefins from natural products (Figure 3C). By dehydroformylation of a (+)-sclareolide derivative, we accessed a carbon-based scaffold **2n** containing an exocyclic diene adjacent to a quaternary center. This product is a key intermediate in the synthesis of several terpenes. Furthermore, (+)-sclareolide is an inexpensive and readily available precursor, whereas typical precursors such as (+)-manool and (−)-polygodial have either been discontinued by commercial suppliers or are available only in milligram quantities (27).

To study the chemoselectivity of dehydroformylation, we examined steroid and macrolide substrates (Figure 3C). Deoxycholic acid derivative **2o** was prepared without protection of the hydroxyl groups, despite the potential for alcohol oxidation under Rh-catalysis (28,29). Thus, activation of the aldehyde C–H bond occurred with high chemoselectivity to initiate C–C bond cleavage. Smooth dehydroformylation of the antibiotic spiramycin I to generate macrolide **2p** highlights the tolerance of this method to many functional groups, including dienes, amines, ethers, esters, and acetals. In this case, dehydroformylation introduced an exocyclic olefin that dramatically altered the topology of the macrolide.

The yohimbinoid family of indole alkaloids has often served as a testing ground for methodology (30). Padwa reported the *de novo* synthesis of racemic yohimbenone in eleven steps from methyl 3-indolylacetate (31). By using dehydroformylation as a key step, we prepared (+)-yohimbenone in three steps from commercially available and inexpensive (+)-yohimbine. Conversion of ester **7a** to β-hydroxy aldehyde **7b** was achieved in 87% yield by $LiAlH_4$ reduction followed by Parikh-Doering oxidation, and the resulting aldehyde was purified by a simple workup with sodium bisulfite. This aldehyde contains both a *syn*- and an *anti*-β-hydrogen. *Syn*-selective dehydroformylation established the trisubstituted olefin at the ring-junction. To our surprise, however, the resulting allylic alcohol underwent transfer dehydrogenation in the same pot to yield (+)-yohimbenone in 65% yield. Because dehydroformylation is faster that the allylic alcohol oxidation, either the allylic alcohol or enone product could be selectively formed by controlling the reaction temperature and stoichiometry of the strained olefin acceptor (32).

Through experiments designed to probe the mechanism, we obtained insight into why the counterion and strained acceptor are critical in diverting the acyl-Rh^{III}-hydride intermediate along a unique pathway. Isotopic labeling studies revealed that the deuterium label of aldehyde ***d*-1q** is incorporated into the formyl group of the product ***d*-6c**. However, statistical scrambling occurred when protio-**1q** was subjected to transfer hydroformylation in the presence of deuterated methanol (Figure 4A). Together, these results suggest that the aldehyde proton is transferred to the product via the intermediacy of 3-methoxybenzoic acid, which can undergo proton-exchange with methanol. Experiments using stoichiometric Rh support this mechanistic scenario (Figure 4B). Combining the Rh-source, 3-methoxybenzoic acid, and phosphine ligand resulted in an equilibrium mixture of Rh-complexes **8a** and **8a′**, each with 3-methoxybenzoate counterions. Upon treatment of this mixture with hydrocinnamaldehyde (**1q**), we observed styrene (**2q**) in high yields along with the regeneration of the benzoic acid derivative (33). Subsequent addition of PPh_3 enabled us to identify the organometallic product, Rh-hydrido-carbonyl **9**, which is a catalyst for traditional hydroformylations (34). Although stoichiometric dehydroformylation takes place in the absence of the strained acceptor, our studies on the catalytic process revealed a correlation between the ring strain of the acceptor and the selectivity for dehydroformylation versus decarbonylation. Therefore, we propose that stoichiometric dehydroformylation in the absence of acceptor is thermodynamically downhill and reversible, but norbornadiene can irreversibly trap the Rh-hydrido-carbonyl intermediate to prevent decarbonylation and turn over the catalyst.

A proposed catalytic cycle for transfer hydroformylation is depicted in Figure 4C. The neutral Rh-complex **8a** activates the aldehyde C–H bond to generate acyl-Rh^{III}-hydride **8b**. The 3-methoxybenzoate counterion can then undergo reductive elimination with the hydride ligand to generate acyl-Rh^{I} **8c** and 3-methoxybenzoic acid (35). In contrast, most hydroacylations and decarbonylations typically employ innocent counterions such as Cl^- and BF_4^-. De-insertion of CO and subsequent β-hydride elimination forges Rh-hydrido-carbonyl **8e**. Exchange of the olefin product with nbd (**5a**) generates **8f**, which irreversibly leads to the transfer hydroformylation product **6a** through similar mechanistic steps in reverse order (Figure 4C). Thus, the ring-strain of the olefin acceptor and the ability of the counterion to act as a proton-shuttle by reversible redox processes afford high reactivity and selectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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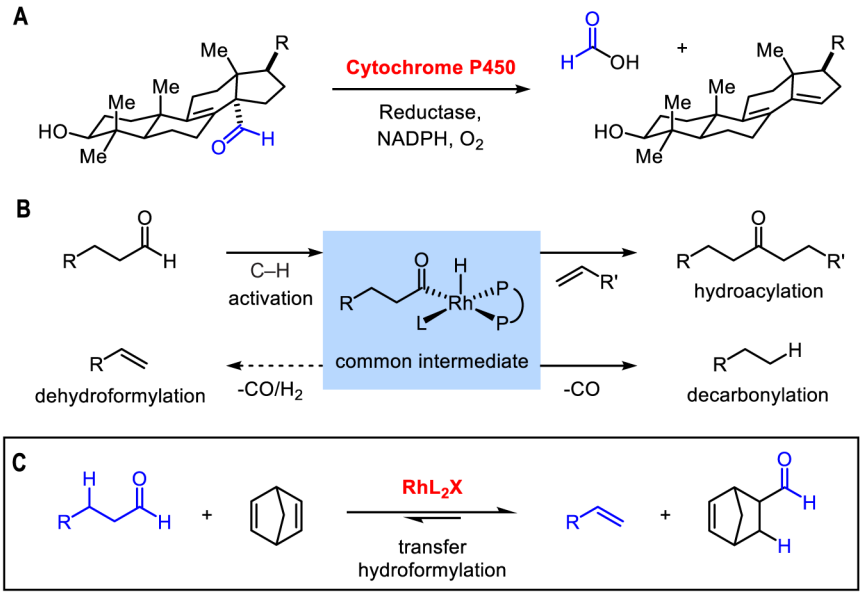

Fig. 1. Dehydroformylation in nature and organic synthesis. (A) Dehydroformylation during sterol biosynthesis. **(B)** Reactivity of acyl-Rh^{III}-hydrides. **(C)** Proposed transfer hydroformylation.

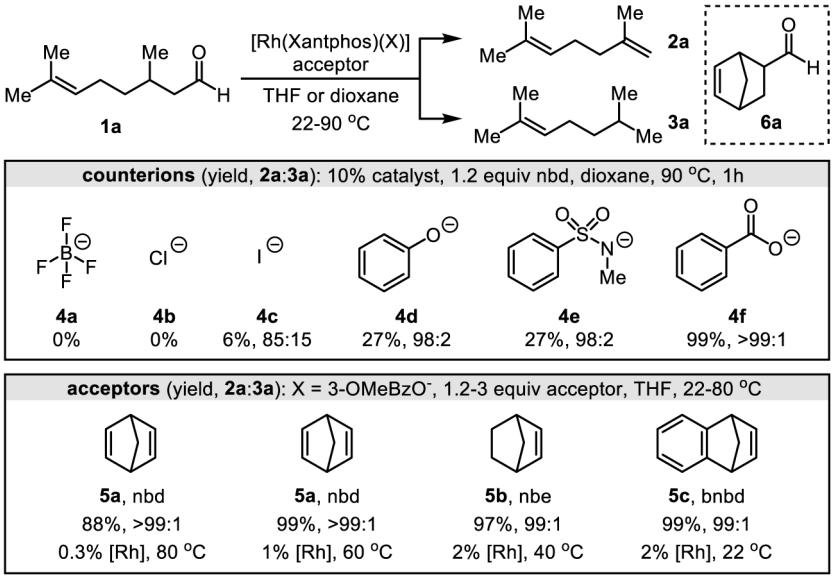

Fig. 2. Effects of counterion structure and ring strain

nbd = 1,5-norbornadiene, nbe = norbornene, bnbd = benzonorbornadiene; yields were determined by GC-FID analysis of the reaction mixtures using durene as an internal standard.

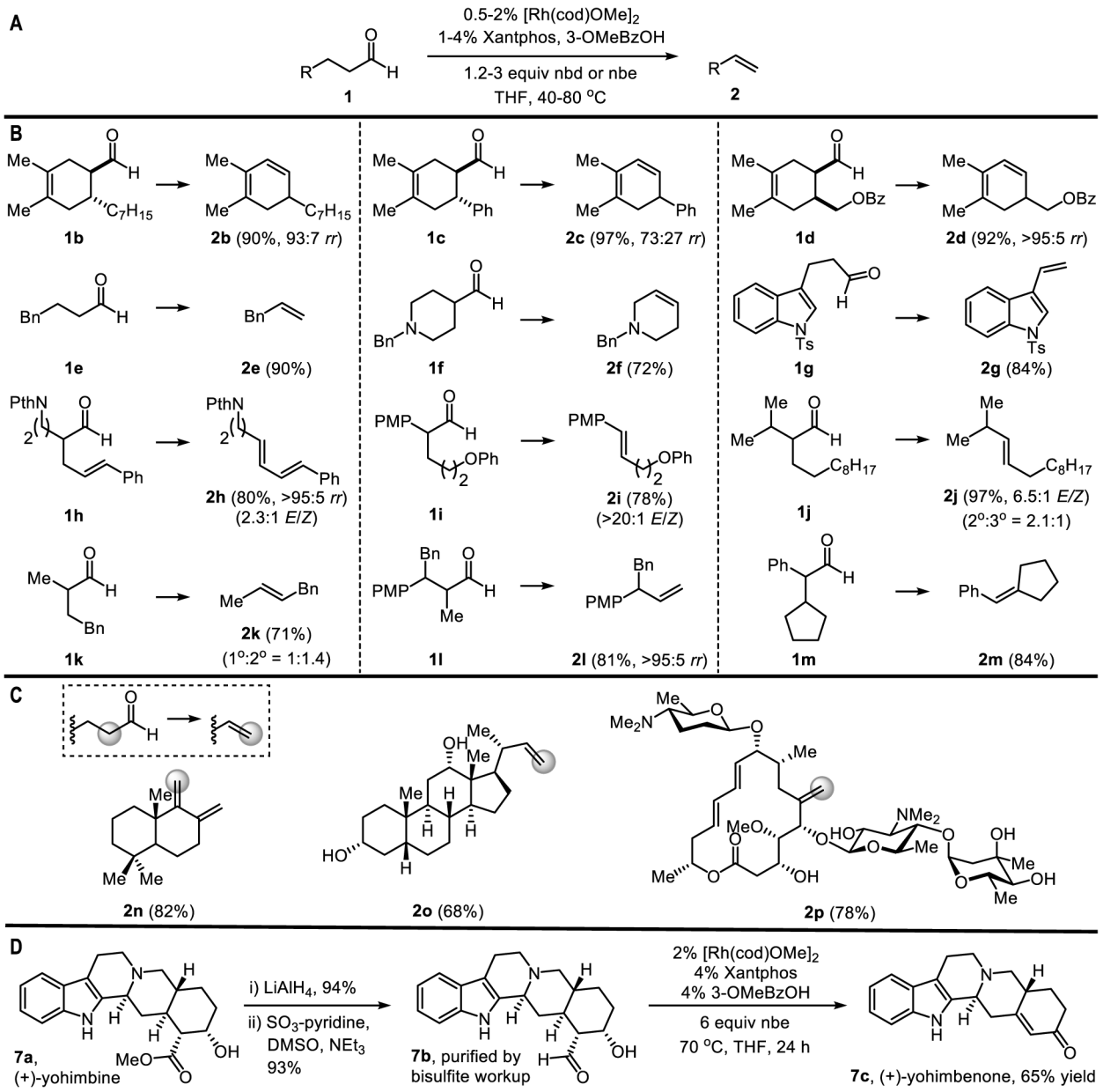

Fig. 3. Applications of dehydformylation

(A) General conditions for transfer hydroformylation. **(B)** Substrate scope. **(C)** Natural product derivatization. **(D)** Three step synthesis of (+)-yohimbenone. Yields are of isolated materials and mixtures of regioisomers where indicated; *rr* = regioisomeric ratio; *rr* values were determined by ^{1}H NMR analysis of the reaction mixtures; the yields of **2e** and **2k** were determined by ^{1}H NMR analysis of the reaction mixtures using durene as an internal standard; see the supplementary materials for details.

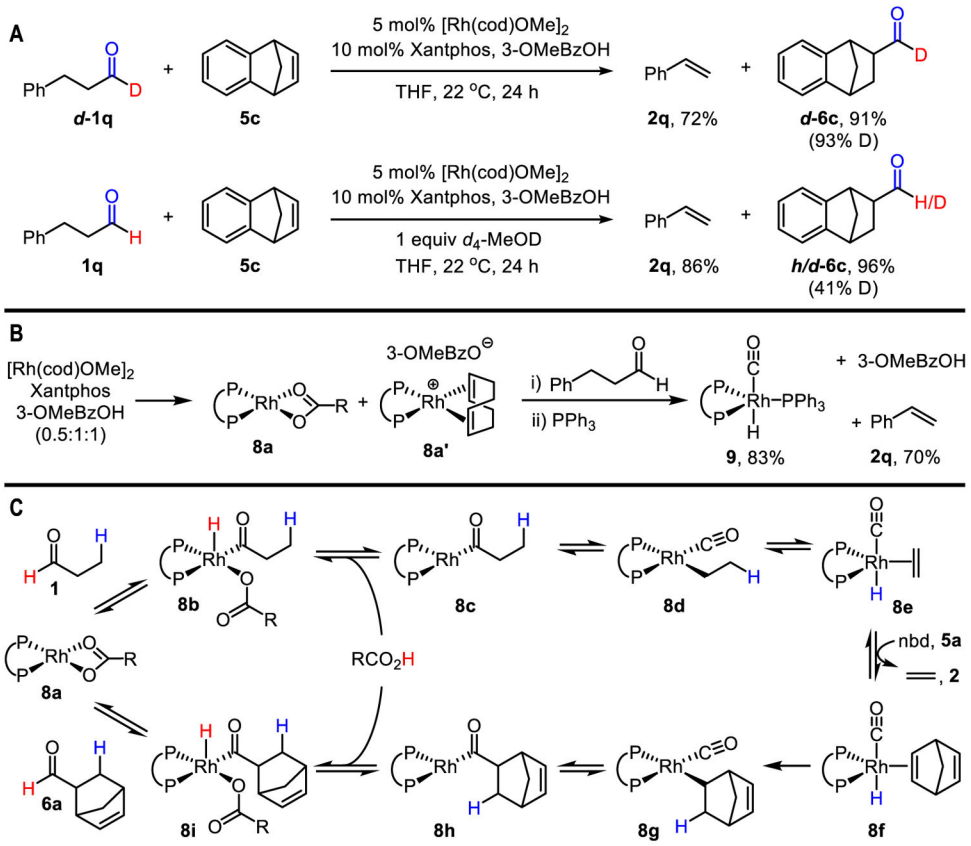

Fig. 4. Mechanistic studies

(A) Deuterium labelling studies. **(B)** Isolation of organometallic intermediates. **(C)** Proposed catalytic cycle.