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Direct conversion of esters to imines/enamines and applications to polyester waste upcycling†

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Semi-reductive transformations of esters remain an underdeveloped but valuable class of functional group interconversions. Here, we describe the development of a highly selective method for the interconversion of esters to imines, enamines, aldehydes or amines through an amine-intercepted zirconocene hydride (ZrH)-catalyzed reduction. This protocol employs an inexpensive zirconium catalyst in combination with hydrosilanes and simple unprotected amines. A variety of aryl, benzylic, and aliphatic esters are directly transformed to imines and enamines in up to 99% yield or aldehydes in up to 84% yield, with little-to-no reduction to the corresponding alcohols. The utility of this method for the direct catalytic chemical upcycling of polyester plastic waste is demonstrated through multiple unprecedented depolymerization transformations. Further, the efficient preparation of nitrogen-containing products is also presented, including single-flask multicomponent reactions and the reductive amination of esters.

The direct conversion of esters to imines and enamines remains an elusive functional group interconversion, despite the apparent simplicity of such a transformation. Yet, semi-reductive imination or enamination of esters would serve as a step- and redox-economical alternative to prevailing synthetic strategies necessitating sequential reduction and condensation steps (Scheme 1a).¹ Likewise, the continued reduction of these intermediates to amines would provide an unconventional disconnection to traditional reductive aminations using aldehydes, a frequently employed transformation for medicinal and process chemists alike.² The enhanced stability and wide commercial availability of esters provides further impetus for such a transformation.

Moreover, the partial reduction of esters to aldehydes is a widely desired transformation in organic synthesis. Despite efforts to develop protocols for the direct conversion of esters to aldehydes, chemists still seek safe and reliable procedures for this transformation that do not result in concomitant over-reduction to the corresponding alcohol (Scheme 1a, path 1).^{3–5} For example, organic chemists most frequently rely on diisobutylaluminum hydride (DIBAL-H) to achieve this semi-reduction.^{4g} However, large scale use of this reductant requires careful handling due to associated pyrophoricity and continuous maintenance of cryogenic reaction temperatures. For these reasons, chemists may instead rely on alternative routes altogether (*i.e.*, utilization of Weinreb amides,⁶ Rosenmund

reduction,⁷ Fukuyama reduction⁸) to obtain aldehyde products from precursors at higher oxidation states (Scheme 1a, path 2).

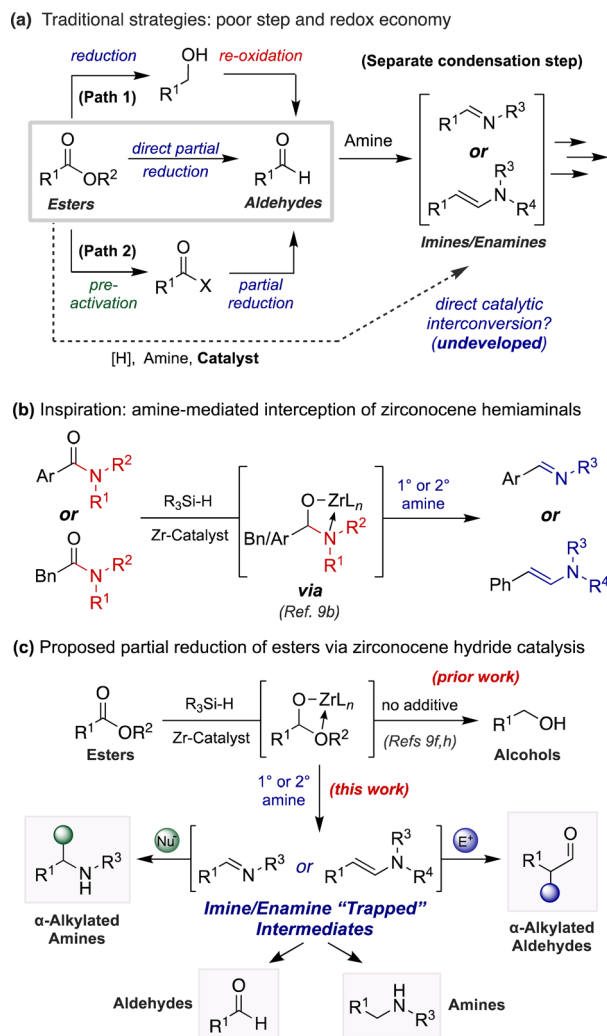
Recently, a renewed interest in zirconocene hydride (ZrH) catalysis has prompted the exploration of new methodologies concerning the functional group interconversion of carbonyl-containing molecules.⁹ Until now, manifolds employing ZrH reagents in either stoichiometric or catalytic quantities have exclusively resulted in the complete reduction of esters to alcohols.^{9f,h,j,10,11} Our initial work regarding the ZrH-catalyzed reduction of carbonyls using hydrosilanes showcased this selectivity,^{9h} as did a later report by Cantat and coworkers using an analogous strategy but employing Schwartz's reagent (Cp₂-ZrHCl) directly.^{9f} In both studies aldehyde intermediates were not observed, even in trace quantities, as these intermediates are more susceptible to reduction than the starting materials themselves.

Among our work in this research area, we recently disclosed the transamination semi-reduction of tertiary amides to imines and enamines (Scheme 1b).^{9b} Key insights from accompanying mechanistic studies suggested the nucleophilic interception of zirconocene hemiaminal intermediates by an exogenous unprotected amine.^{9b,d} Gaining inspiration from these studies, we surmised that this platform could be extended to the partial reduction of esters through interception of zirconocene hemiacetal intermediates by an amine. This would instead promote formation of imines or enamines as a protective trap for the aldehyde oxidation level. This mechanistic distinction would likewise deliver a synthetic handle for the direct conversion of esters to nitrogen-containing products (Scheme 1c).

We began our studies by employing zirconocene dichloride (Cp₂ZrCl₂) as an inexpensive and stable pre-catalyst in combination with hydrosilanes as the reductant (Table 1). Initial

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Scheme 1 Strategies for the conversion of esters to aldehydes, imines, and enamines and inspiration for a ZrH-catalyzed direct strategy.

attempts to reduce aryl ester **1a** with diethoxy(methyl)silane (DEMS) in the absence of an amine either resulted in over-reduction to the alcohol or unreacted starting material (see Table SI-2†). We then carried out the reduction in the presence of *n*-butylamine (entry 1). Strikingly, product selectivity completely diverged, favoring the formation of imine **3a** in 82% yield. Conversion of **1a** was diminished when catalyst loading was decreased or when Cp_2ZrHCl was employed as the catalyst (entries 2 and 3). Replacing DEMS with polymethylhydrosiloxane (PMHS) likewise resulted in lower conversion and yield (entry 4). Finally, the yield of **3a** was improved upon simply increasing reaction time from 18 to 21 hours (entry 5). Notably, <5% of alcohol was observed throughout the course of these optimization studies.

After identifying the optimal reaction conditions for the semi-reductive imination of aryl esters, we turned our attention to aliphatic ester **2a**. We supposed that a secondary amine could be used instead to promote the formation of an enamine. Upon exploration of various amine additives (see Table SI-6†), piperidine proved to be the optimal amine, quantitatively furnishing

Table 1 Reaction optimization^a

| Entry | Catalyst (mol%) | Silane (equiv.) | % Yield ^b | % Conversion ^b |
|-------|----------------------------------|-----------------|----------------------|---------------------------|
| 1 | Cp_2ZrCl_2 (5) | DEMS (3 equiv.) | 82 | 85 |
| 2 | Cp_2ZrCl_2 (2.5) | DEMS (3 equiv.) | 34 | 39 |
| 3 | Cp_2ZrHCl (5) | DEMS (3 equiv.) | 42 | 52 |
| 4 | Cp_2ZrCl_2 (5) | PMHS (5 equiv.) | 23 | 39 |
| 5 | Cp_2ZrCl_2 (5) | DEMS (3 equiv.) | 91 | 91 ^c |

| Entry | Catalyst (mol%) | Silane (equiv.) | % Yield ^b | % Conversion ^b |
|-------|---------------------------------|-----------------|----------------------|---------------------------|
| 6 | Cp_2ZrCl_2 (10) | DEMS (3) | 99 | 100 |
| 7 | Cp_2ZrCl_2 (5) | DEMS (3) | 75 | 86 |
| 8 | Cp_2ZrCl_2 (10) | TMDS (5) | 7 | 28 |
| 9 | Cp_2ZrCl_2 (10) | PMHS (5) | 82 | 83 |
| 10 | Cp_2ZrHCl (10) | DEMS (3) | 93 | 93 |

^a Entries 1–4: reactions were carried out under a N_2 atmosphere using 0.2 mmol of **1a** and 1.7 equiv. *n*-butylamine in anhydrous PhMe (0.4 M) for a duration of 18 h. Entries 6–10: Reactions were carried out under a N_2 atmosphere using 0.2 mmol of **2a** and 1.5 equiv. piperidine in anhydrous PhMe (0.4 M) for a duration of 18–23 h.

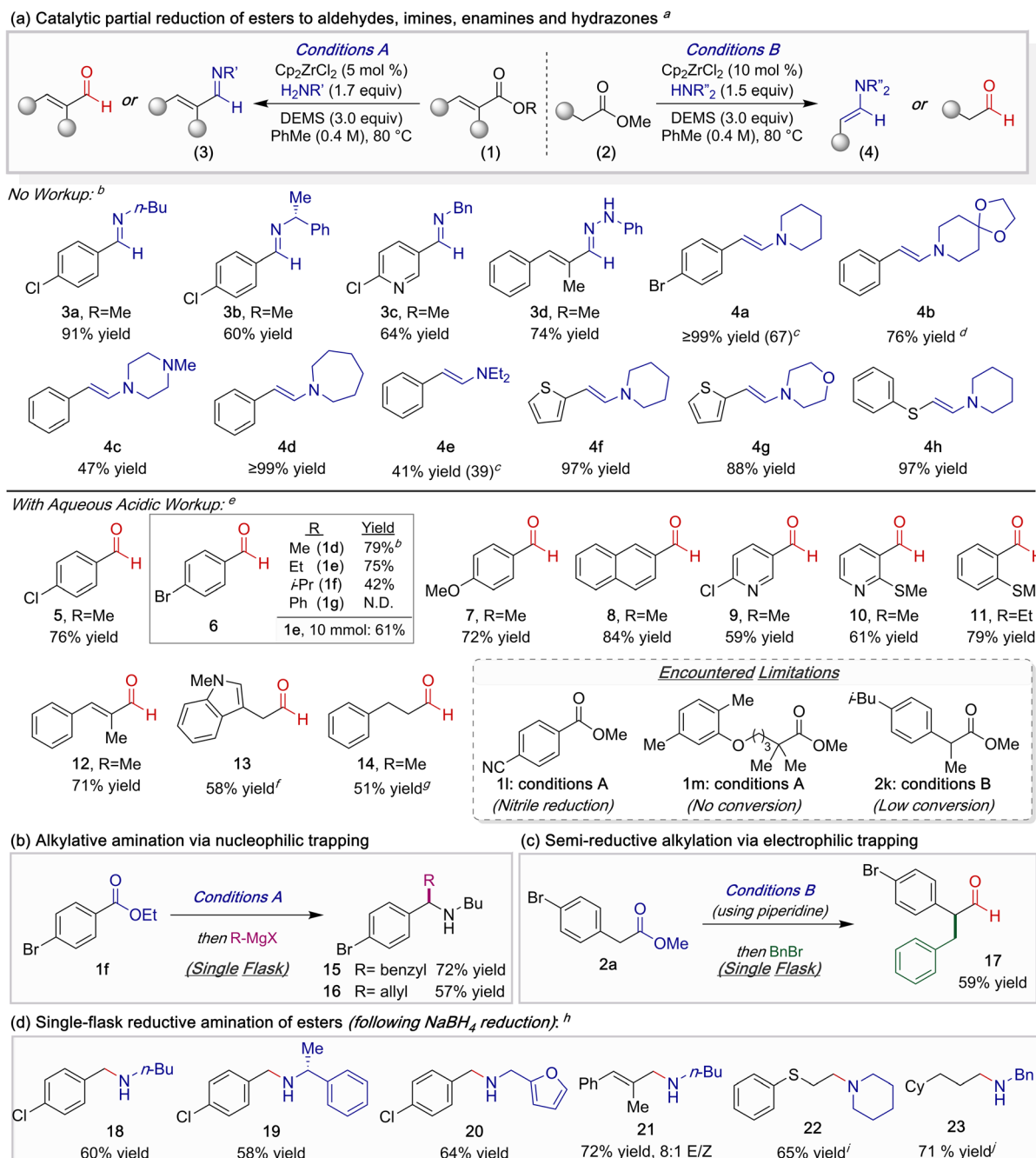
^b Yields were determined by ^1H NMR spectroscopy of the crude reaction mixture, using mesitylene as an internal standard. ^c Carried out using 1 mmol **1a** for 21 h instead.

enamine **4a** (entry 6). Decreasing the catalyst loading to 5 mol% provided the desired product in a synthetically useful, but lower yield (entry 7). Replacing DEMS with tetramethyldisiloxane (TMDS) proved ineffective; however, we were pleased to find that PMHS promoted the transformation of **2a**, albeit with a slightly lower yield of 82% (entries 8 and 9). This hydrosilane, a byproduct of the silicon industry, is an especially appealing reductant due to its low cost and safety profile.¹² Lastly, Cp_2ZrHCl facilitated the semi-reduction with similar efficiency as Cp_2ZrCl_2 (entry 10).

With optimized conditions defined, we first investigated the single-step catalytic semi-reductive imination (3) and enamination (4) of esters, a direct functional group interconversion that, to the best of our knowledge, remains unreported (Table 2a). Aryl esters were directly converted to imines using various primary amines (**3a–3c**), while a cinnamate was transformed into hydrazone **3d** when phenylhydrazine was employed as the nucleophile. The enamination of aliphatic esters could be carried out as well when using an assortment of cyclic amines (**4a–4d**). Notably, when diethylamine was employed instead, enamine **4e** was formed in moderate yield. Thiophene, morpholine, and sulfide functionality were all tolerated under these reaction conditions (**4f–4h**).

Next, we explored the ZrH-catalyzed semi-reduction of esters to aldehydes through the implementation of a hydrolytic workup. Methyl and ethyl benzoates (**1d**, **1e**) smoothly reacted



Table 2 Substrate scope of the ZrH-catalyzed semi-reduction of esters to aldehydes and extended applications^a

^a Reactions were carried out under an atmosphere of N_2 at 80 °C on a 0.2–1.0 mmol scale (unless indicated otherwise) using a primary amine (conditions A) or a secondary amine (conditions B) in anhydrous PhMe (0.4 M) for a duration of 18–48 h. ^b Yield was determined by ^1H NMR spectroscopy of the crude reaction mixture, using mesitylene as an internal standard. ^c Isolated yield on a 1.0 mmol scale. ^d Carried out using 2.0 equiv. amine instead. ^e Reactions were carried out using *n*-butylamine (conditions A) or piperidine (conditions B) and subsequently quenched with 1 N aq. HCl. Yields reflect isolated yields. N.D. = Not Detected. ^f Carried out using 5 equiv. PMHS instead. ^g Carried out using 4 equiv. *n*-butylamine and 6 equiv. DMMS instead. ^h Carried out on a 0.5–1 mmol scale using conditions A without acidic workup, followed by NaBH_4 (1.5–3 equiv.) reduction at 65 °C for 4–9 h. ⁱ Carried out using conditions B instead, followed by NaBH_4 (3 equiv.) reduction at 65 °C for 9 h. ^j Carried out using 3 equiv. *n*-butylamine and 6 equiv. DMMS instead.

to afford benzaldehydes in high yields, whereas more sterically encumbered esters either resulted in lower conversion of the starting material (**1f**) or amidation (**1g**). The partial reduction of **1e** proved to be scalable, furnishing greater than 1 gram of

aldehyde **6** on a 10 mmol scale. In general, various esters bearing ether, halide, N-heterocyclic, and sulfide functionality were amenable to the catalytic semi-reduction (**7–11**). Additionally, reduction of cinnamate **1c** provided enal **12** in 71%



yield, extending the utility of this protocol to the preparation of α,β -unsaturated aldehydes. Finally, aliphatic aldehydes **13** and **14** were obtained in moderate yields.

Throughout these studies, several notable limitations were observed. Though not detected in our prior studies, at elevated temperatures competitive nitrile reduction becomes problematic under this catalytic manifold. For example, substrate **11** underwent unselective reduction to afford terephthalaldehyde. In accord with our prior observations regarding the steric sensitivity of this catalytic system, esters bearing an α -quaternary or tertiary carbons (e.g. **1m** and **2k**) failed to undergo reduction.

The use of an amine to interrupt traditional metal hydride-mediated ester reduction enables concise entry to valuable reactive intermediates that can be directly telescoped through multi-step synthetic sequences, necessitating only a single purification step.^{13,14} For example, the interception of imine intermediates with nucleophiles delivers access to α -alkylated secondary amines (Table 2b, 15 and 16). Alternatively, the ester starting material can instead serve as the nucleophilic component through generation of an enamine. This latter strategy was displayed through the single-flask multicomponent synthesis of α -alkylated aldehyde **17** in 59% yield when benzyl bromide was added after enamine formation (Table 2c).

Finally, we sought to illustrate the potential of this catalytic manifold for the two-step single-flask reductive amination of esters when incorporating a NaBH_4 reduction prior to workup. An assortment of benzylic, allylic, and aliphatic amines were isolated in 60–72% yield (Table 2d, 18–23). The juxtaposition of imine **3a**, aldehyde **5**, and amine **18** best exemplify the controllable selectivity attainable through this catalytic manifold.

As a direct application toward the chemical recycling of accumulated plastic waste, we sought to leverage this catalytic protocol for new modes of polyester depolymerizations. The catalytic depolymerization of polyester plastics to access versatile chemical feedstocks at an oxidation state in-between that of their original carboxylic acid starting monomers and the fully reduced alcohol monomers would be a powerful and unprecedented form of plastic upcycling.¹⁵ Polyethylene terephthalate (PET), often found in plastic beverage bottles and containers, represents the most common polyester recyclable.¹⁶

For example, Scheme 2a demonstrates the conversion of an assortment of post-consumer PET wastes to terephthalaldehyde, a versatile building block used for the preparation of small molecules, polymers, and other porous and nonporous materials with wide-ranging uses (ligands, dyes, sensors, liquid crystals, thin films, re-healable thermosets, *etc.*).¹⁷ Utilizing modified semi-reduction conditions, PET plastic pieces obtained directly from a single use water bottle or a green beverage bottle afforded terephthalaldehyde (**24**) in 83% and 64% yields, respectively. We also chose to investigate the depolymerization of polyester fabric, the most widely produced fiber constituting >50% of total fiber production globally.^{16d} Whether using PET sourced from a 100% polyester t-shirt or dyed fibers belonging to packaging waste from a recent laptop purchase (fabric screen protector insert), the catalytic reduction produced dialdehyde **24** in reasonable quantities (91% and 48% yield respectively).



Scheme 2 Applications to polyester depolymerization. (^aReported values are based on the theoretical amount of repeating monomer unit).

The strength of this strategy, however, lies in the ability to directly convert polyester waste to nitrogen-containing building blocks, offering a unique strategy for the repurposing of this plastic. For example, when PET was subjected to the standard depolymerization conditions without hydrolytic workup, diimine **25** was isolated in high purity in 55% yield (Scheme 2b). Further, poly(ethylene) succinate, an aliphatic polyester, underwent a novel depolymerization-cyclization sequence under similar reaction conditions (Scheme 2c). When the catalytic protocol was carried out using benzylamine, depolymerization occurred with concomitant Paal–Knorr-type cyclization to furnish pyrrole **26** in 85% isolated yield.

The profound effect on product chemoselectivity imparted by a simple unprotected amine prompted us to investigate the mechanism of this interrupted ZrH-catalyzed ester reduction. Prior reports regarding the interconversion of esters to amides mediated by Lewis acidic zirconocenes suggested to us that a similar mechanistic pathway might be involved, the products of which would be amenable to ZrH-catalyzed partial reduction.¹⁸ Of note, varying quantities of amide byproducts were observed throughout the course of our studies. However, our



experimental mechanistic investigations suggest to us that this is unlikely the sole or major route of conversion.¹⁹

Instead, we hypothesize that the dominant mechanistic pathway leading to product formation could involve zirconocene hemiacetal **II** (Fig. 1a and b). This species may be directly intercepted by an exogenous amine, analogous to our prior observations with related hemiaminals (Fig. 1a).^{9b} Alternatively, upon β -alkoxy elimination, interception of the resulting aldehyde by the amine may simply outpace continued reduction to the alcohol (Fig. 1b) (e.g., **I** to **V'**).^{9f,10c} In either scenario, the resulting putative hydroxyzirconocene or alkoxyzirconocene species, **III**/**III'**, could regenerate active catalyst **I** through hydrosilane-mediated metathesis.²⁰

To gain further mechanistic insight, we performed a series of experiments with varying ZrH sources and loadings. Initial attempts to hydrozirconate **1a** using 1.0 equivalent of Cp_2ZrHCl in the presence of *n*-butylamine did not result in the formation of imine **3a**, even in trace quantities. Rather, within 30 minutes **1a** was iteratively reduced to produce a zirconocene alkoxide, **27** (see Scheme SI-3†). However, while studying the ester reduction at various catalyst loadings, we were perturbed by the distinct differences in reaction outcome (Fig. 1c). Reactions employing ≤ 25 mol% Cp_2ZrHCl exhibited pronounced selectivity for imine **3a**, while those employing ≥ 30 mol% Cp_2ZrHCl sharply favored full reduction to **27** and **28**. Conversely, this effect was not observed when carrying out an analogous study employing

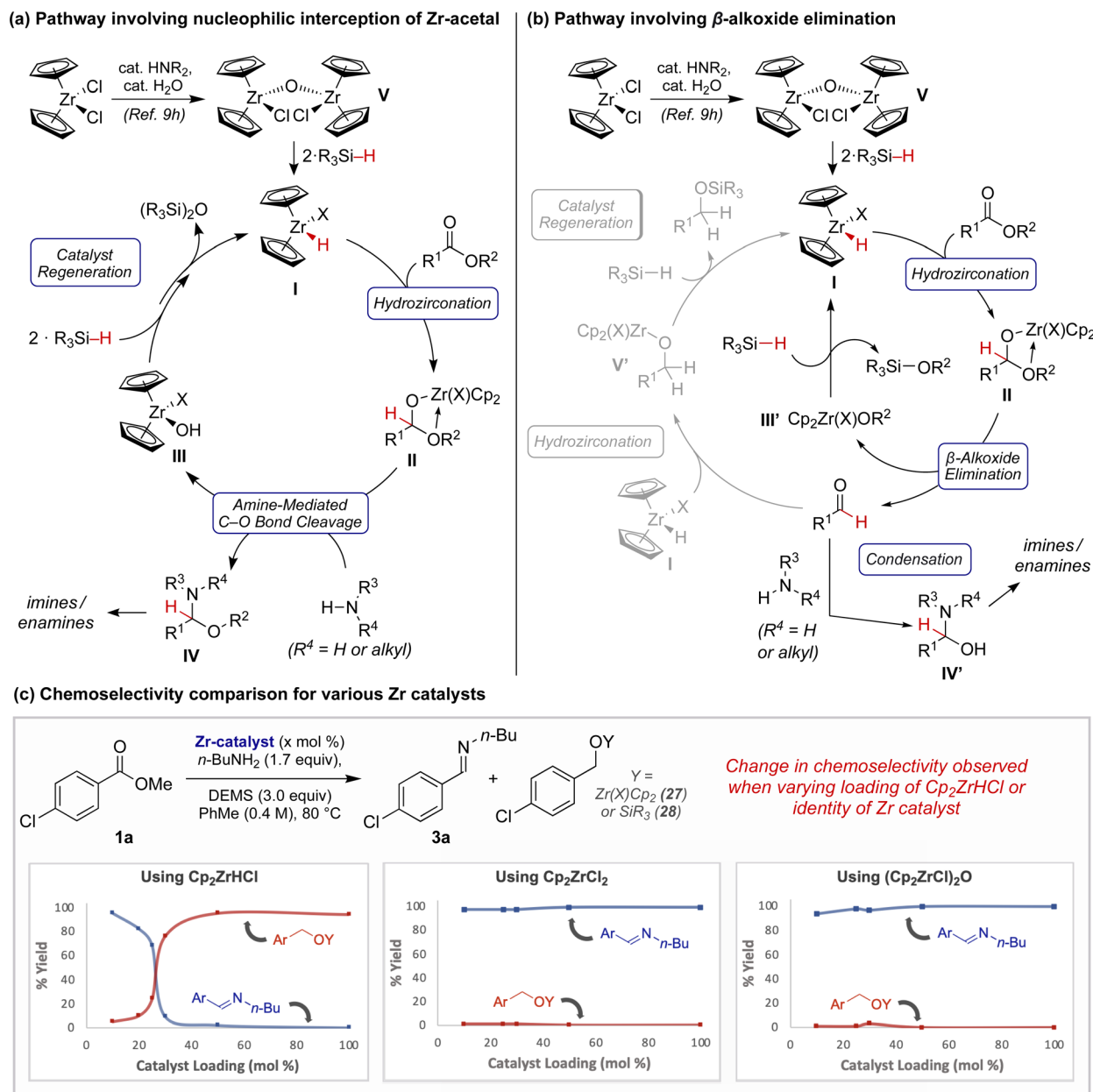


Fig. 1 Plausible mechanistic pathways and experimental mechanistic studies.

either Cp_2ZrCl_2 or $(\text{Cp}_2\text{ZrCl})_2\text{O}$ (V) pre-catalysts instead. In both studies, the major product observed at all catalyst loadings was imine **3a**. These findings suggest that the active catalyst for semi-reduction may involve a ZrH complex **I** where $\text{X} \neq \text{Cl}$.²¹ The contrasting product outcomes observed when employing ≥ 30 mol% of these zirconocene complexes suggests that the identity of the “X” ligand on zirconium may result in impeded rates of catalyst regeneration and/or hydrozirconation.²² Although mechanistic studies are ongoing, at this time we speculate that this “X” ligand could be an alkoxide or siloxide, or that the active catalyst could be dimeric in nature.²³

Conclusions

In conclusion, we have developed a series of highly selective and novel reductive transformations of esters enabled by ZrH catalysis. The interrupted catalytic reduction of esters *via* addition of simple unprotected amines results in the formation of imine and enamine “trapped” intermediates thereby preserving the intermediate oxidation level until workup. The exceptional selectivity of this catalytic strategy was demonstrated through seminal semi-reductive iminations and enaminations of esters in up to 99% yield. Analogously, either monomeric esters or polyester waste materials afforded aldehydes in high yields and with excellent chemoselectivity. α -Alkylated aldehydes and amines are also accessible through single-flask operations *via* electrophilic or nucleophilic interception of intermediates. Further, we established the reductive amination of esters using primary and secondary amines. Mechanistic studies reveal that the identity of the ZrH-complex has a profound impact on the outcome of these reactions. Additional studies to better understand the mechanism and identity of the active ZrH catalyst are currently underway.

Data availability

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

Author contributions

R. A. Kehner: conceptualization, data curation, investigation, methodology development, and writing the manuscript. W. Huang: data curation, investigation, methodology development, and editing the manuscript. L. Bayeh-Romero: conceptualization, data curation, funding acquisition, investigation, project administration, supervision, and writing the manuscript.

Conflicts of interest

There are no conflicts to declare.

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