ZrH-Catalyzed Semi-Reduction of Esters Enabled by an Imine/Enamine Trap

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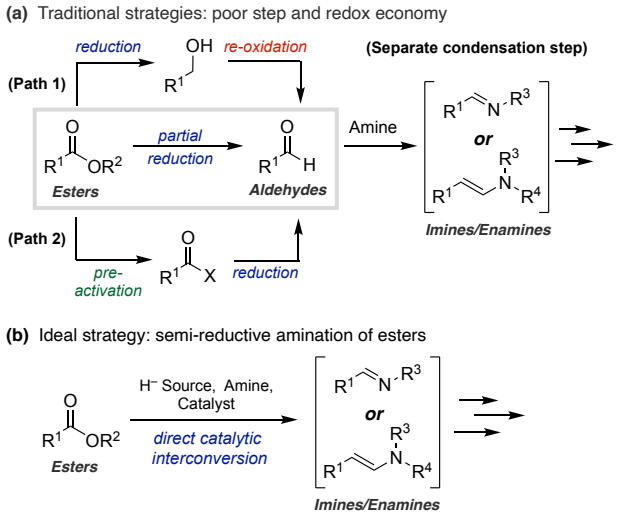
ABSTRACT: Semi-reductive transformations of esters remains an underdeveloped but valuable class of functional group interconversions. For example, few strategies exist for the catalytic partial reduction of esters to aldehydes, and the direct catalytic semi-reductive imination/enamination of esters is absent from synthetic strategy. 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 ZrH-catalyzed reduction. This protocol employs Cp_2ZrCl_2 as an inexpensive catalyst in combination with hydrosilanes and simple unprotected amines. The *in situ* formation of imines and enamines effectively preserves an aldehyde oxidation level throughout the course of the reaction. A variety of aryl 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 efficient preparation of nitrogen-containing products is also presented, including single-flask multicomponent reactions and the direct reductive amination of esters. These findings further demonstrate the utility of oxophilicity-driven ZrH catalysis for unconventional chemical transformations.

The direct conversion of esters to imines and enamines remains an elusive functional group interconversion. Yet, semi-reductive imination or enamination of esters would serve as a redox economical alternative to multi-step synthetic sequences necessitating sequential reduction and condensation steps (**Scheme 1**).[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.

Scheme 1. Strategies for the Conversion of Esters to Aldehydes, Imines and Enamines

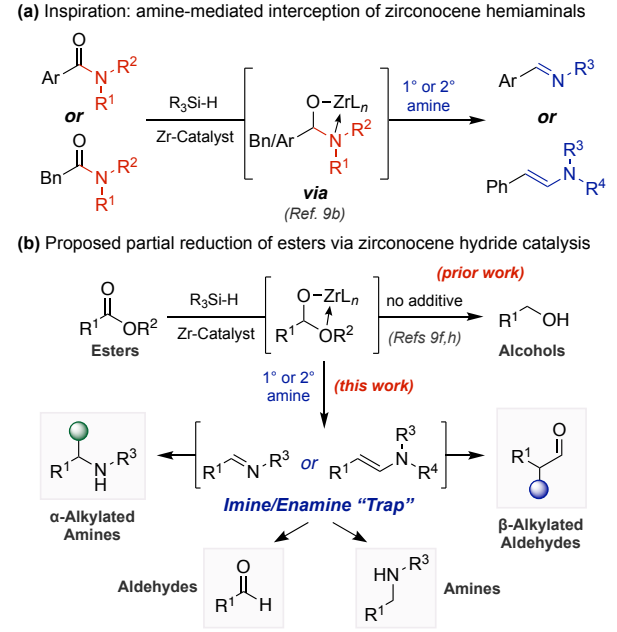


Moreover, the partial reduction of esters to aldehydes is a widely desired transformation in organic synthesis. Yet, few safe and reliable protocols exist for the direct conversion of esters to aldehydes without some degree of concomitant over-reduction to the corresponding alcohol (**Scheme 1a,** path 1).[3] These methods typically proceed through aluminum-bound[4] or silylated acetal[5] intermediates, which then undergo hydrolysis to furnish aldehydes upon workup. 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 reduction[8]) 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 seminal work regarding the ZrH-catalyzed reduction of carbonyls using hydrosilanes showcased this selectivity.[9h] Ensuing work by Cantat and coworkers used an analogous strategy but employing Schwartz's reagent (Cp_2ZrHCl) directly.[9f] In both studies, aldehyde intermediates or byproducts were not observed, even in trace quantities.

Among our work in this research area, we recently disclosed the transaminative semi-reduction of tertiary amides to imines and enamines (**Scheme 2a**).[9b] Key insights from accompanying mechanistic studies suggested the nucleophilic

Scheme 2. Inspiration for the Zirconocene Hydride-Catalyzed Reductive Diversification of Esters



interception of zirconocene hemiaminal intermediates by an exogenous unprotected amine.[9d] 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 2b**).

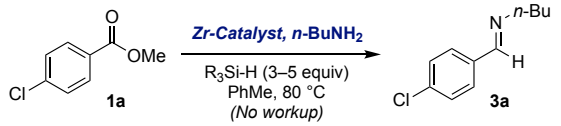
We began our studies by employing zirconocene dichloride (Cp_2ZrCl_2) as an inexpensive and stable pre-catalyst in combination with hydrosilanes as the reductant (**Table 1**). Initial attempts to reduce aryl ester **1a** with diethoxy(methyl)silane (DEMS) in the absence of an amine either resulted in 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 (**Table 1**, 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 (entries2 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 to 21 hours (entry 5). Of note, while <5% alcohol was observed throughout our optimization studies, varying quantities of *N*-butyl 4-chlorobenzamide formed.[12]

After identifying the optimal reaction conditions for the reduction of aryl esters, we turned our attention to the reduction of aliphatic ester **2a**. An initial attempt using *n*-butylamine to facilitate the reduction of **2a** resulted in full conversion of the ester, however only a diminutive amount of aldehyde **4a** was observed (entry 6). 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-5), piperidine proved to be the optimal amine, quantitatively furnishing enamine **4a** (entry 7). Decreasing the catalyst loading to 5 mol% provided the desired product in synthetically useful, but lower, yield, while replacing DEMS with tetramethyldisiloxane (TMDS) proved ineffective (entries 8 and 9). Unlike aryl ester **1a**, we were pleased to find that PMHS promoted this transformation, albeit with a slightly lower yield of 82% (entry 10). This hydrosilane is an especially appealing reductant due to its low cost and safety profile.[13]

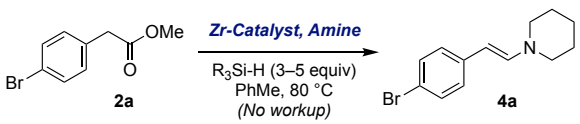
With optimized conditions defined, we first investigated the single-step catalytic semi-reductive imination (**3**) and enamination (**4**) of esters, a direct functional group interconversion that, to the best of our knowledge, remains unreported (**Table 2a**). Aryl esters were directly converted to imines using various primary amines (**3a–3c**), while acrylate **1c** was transformed into hydrazone **3d** when phenyhydrazine 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 to afford benzaldehydes in high yields, whereas sterically more encumbered substrates 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 (**7–12**). Finally, reduction of cinnamate **1d** provided enal **13** in 71% yield, extending

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]

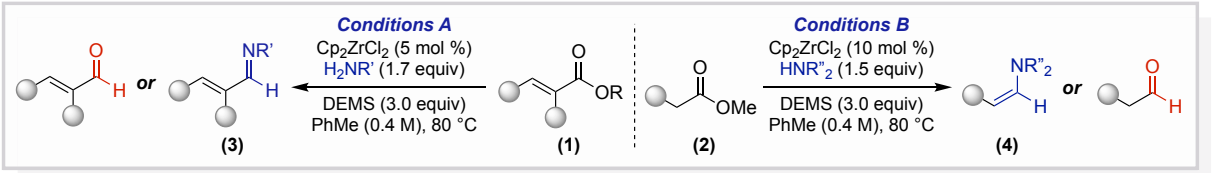


Entry	Catalyst (mol %)	Amine (equiv)	Silane (equiv)	% Yield (Conv.)[b]
6	Cp_2ZrCl_2 (10)	*n*-butylamine (1.7)	DEMS (3)	12 (100) [d]
7	**Cp_2ZrCl_2 (10)**	**piperidine (1.5)**	**DEMS (3)**	**99 (100)**
8	Cp_2ZrCl_2 (5)	piperidine (1.5)	DEMS (3)	75 (86)
9	Cp_2ZrCl_2 (10)	piperidine (1.5)	TMDS (5)	7 (28)
10	Cp_2ZrCl_2 (10)	piperidine (1.5)	PMHS (5)	82 (83)
11	Cp_2ZrHCl (10)	piperidine (1.5)	DEMS (3)	93 (93)

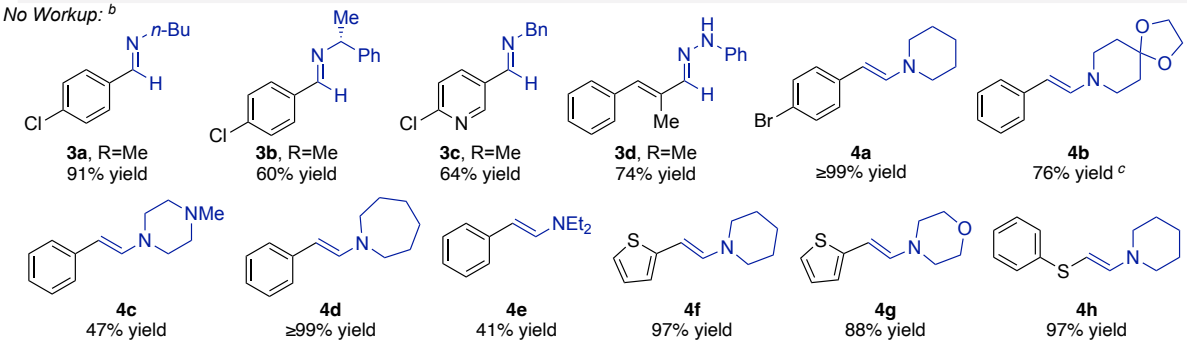
[a] ***Entries 1-4:*** Reactions were carried out under a N_2 atmosphere using 0.2 mmol of **1a** in anhydrous PhMe (0.4 M) for a duration of 18 h. ***Entries 6-11:*** Reactions were carried out under a N_2 atmosphere using 0.2 mmol of **2a** in anhydrous PhMe (0.4 M) for a duration of 18–23 h. [b] Yields were determined by ^1H NMR spectroscopy of the crude reaction mixture, using mesitylene as an internal standard. Parenthetical values reflect % conversion of the starting material. [c] Carried out using 1 mmol of **1a** for 21 h instead. [d] Reaction carried out at 0.2 M instead.

Table 2. Substrate Scope of the ZrH-Catalyzed Semi-Reduction of Esters to Aldehydes and Extended Applications

(a) Catalytic partial reduction of esters to aldehydes, imines, enamines and hydrazones [a]

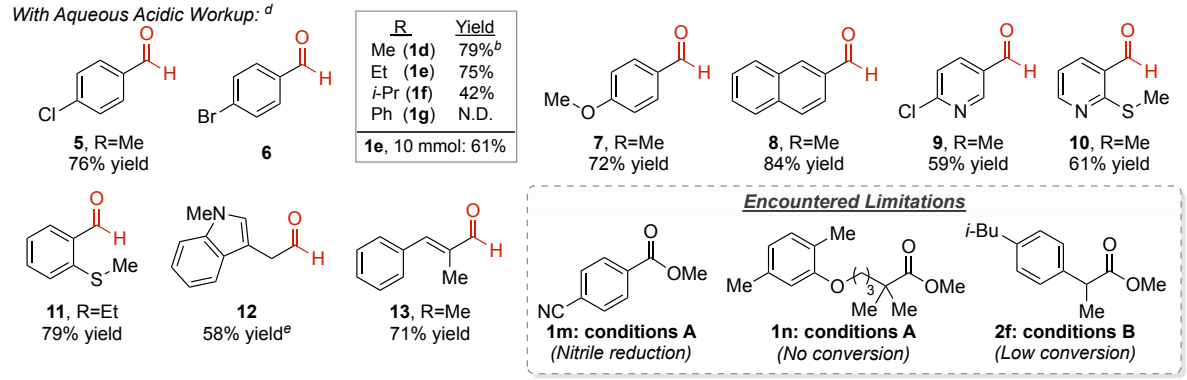


No Workup: [b]



3a, R=Me, 91% yield; **3b**, R=Me, 60% yield; **3c**, R=Me, 64% yield; **3d**, R=Me, 74% yield; **4a** ≥99% yield; **4b** 76% yield [c]; **4c** 47% yield; **4d** ≥99% yield; **4e** 41% yield; **4f** 97% yield; **4g** 88% yield; **4h** 97% yield

With Aqueous Acidic Workup: [d]



5, R=Me, 76% yield; **6**

R	Yield
Me (**1d**)	79%[b]
Et (**1e**)	75%
i-Pr (**1f**)	42%
Ph (**1g**)	N.D.

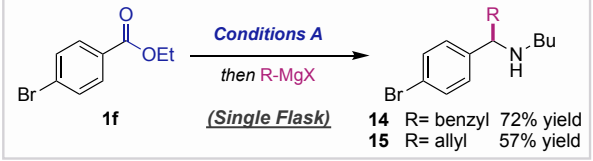
1e, 10 mmol: 61%

7, R=Me, 72% yield; **8**, R=Me, 84% yield; **9**, R=Me, 59% yield; **10**, R=Me, 61% yield; **11**, R=Et, 79% yield; **12** 58% yield[e]; **13**, R=Me, 71% yield

Encountered Limitations

1m: conditions A *(Nitrile reduction)*; **1n: conditions A** *(No conversion)*; **2f: conditions B** *(Low conversion)*

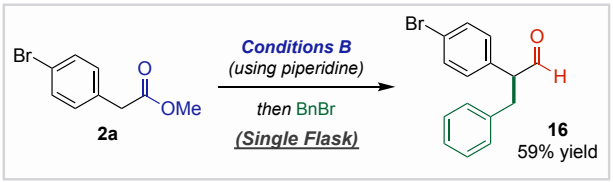
(b) Alkylative Amination via Nucleophilic Trapping



1f

14 R= benzyl 72% yield
15 R= allyl 57% yield

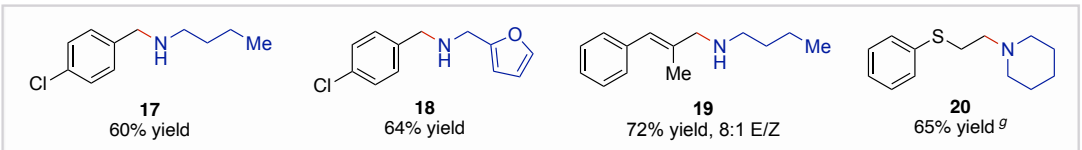
(c) Semi-Reductive Alkylation via Electrophilic Trapping



2a

16 59% yield

(d) Single-flask reductive amination of esters *(following $NaBH_4$ reduction)*: [f]



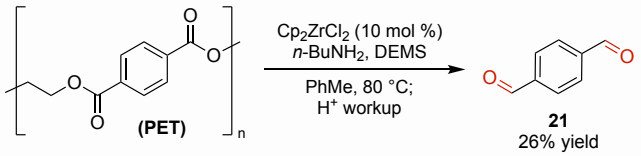
17 60% yield; **18** 64% yield; **19** 72% yield, 8:1 E/Z; **20** 65% yield [g]

(e) Application to the depolymerization of PET

Polyester-Based Waste:

- Found in beverage bottles, food containers, fabrics, etc.
- The most recycled waste (via hydrolysis & transesterification)
- Chemical upcycling to aldehyde monomers – unreported

Starting Material (Empty water bottle)



21 26% yield

[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 *n*-butylamine (Conditions A) or piperidine (Conditions B) in anhydrous toluene (0.4 M) for a duration of 18–48 h. [b] Yield was determined by ^{1}H NMR spectroscopy of the crude reaction mixture, using mesitylene as an internal standard. [c] Carried out using 2.0 equiv amine instead. [d] Reactions were quenched with 1N aq. HCl. Yields reflect isolated yields. N.D. = Not Detected. [e] Carried out using 5 equiv PMHS instead. [f] 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 h. [g] Carried out using conditions B instead, followed by $NaBH_4$ (3 equiv) reduction at 65 °C for 9 h.

the utility of this protocol to the preparation of α,β-unsaturated aldehydes.

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 **1m** underwent unselective reduction to afford terephthaladehyde. In accord with our prior observations regarding the steric sensitivity of this catalytic system, esters bearing an α-tertiary or quaternary carbons (e.g. **1n** and **2f**) failed to undergo reduction.

The use of an amine to interrupt traditional metal hydride-mediated ester reduction enables concise entry to valuable reactive intermediates.[14] For example, the interception of imine intermediates with nucleophiles delivers access to α-alkylated secondary amines (**Table 2b**, **14** and **15**). Alternatively, the ester starting material can instead serve as the nucleophilic component through generation of an enamine.[15] This latter strategy was displayed through the single-flask multicomponent synthesis of α-alkylated aldehyde **16** in 58% 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 to yield amines via $NaBH_4$ reduction (**Table 2d**, **17**–**20**). The juxtaposition of imine **3a**, aldehyde **5**, and amine **17** best exemplify the flexibility attainable through this catalytic manifold.

As a direct application to the chemical recycling of accumulated plastic waste, we were able to extend this catalytic protocol toward the partial reduction of polyethylene terephthalate (PET), the most common commercial polyester recyclable (**Table 2e**).[16] The catalytic depolymerization of polyester plastics to

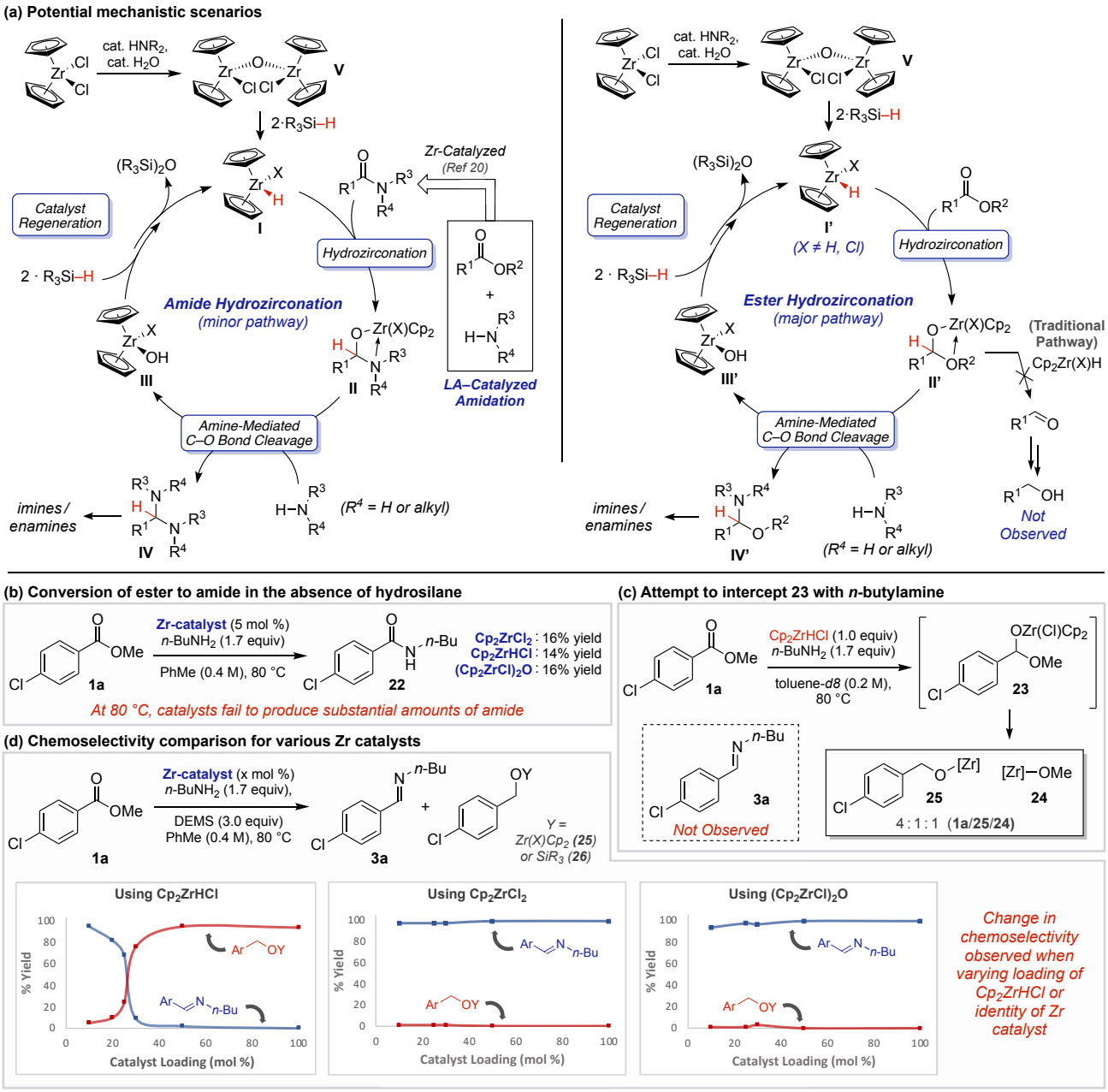


Figure 1. Plausible mechanistic pathways and experimental mechanistic studies.

access value-added 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.[17] Utilizing the developed semi-reduction conditions, terephthalaldehyde **21** was isolated in 26% yield using PET plastic pieces obtained directly from a single-use water bottle.

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. We envisioned two mechanistic scenarios that could lead to the observed products (**Figure 1a**). Prior examples regarding the interconversion of esters to amides mediated by Lewis acidic zirconocenes suggested to us that a similar mechanistic pathway might be involved in the Zr-catalyzed partial reduction of esters.[18] We considered that a plausible pathway leading to product formation could be i) Lewis acid activation of an ester to generate an amide, followed by ii) partial reduction of the amide (**II**) to yield imine or enamine products that would be stable under the reaction conditions until workup (**Figure 1a**, left). Alternatively, we also considered a separate mechanistic pathway wherein the ester directly inserts into **I'** forming a transient zirconocene hemiacetal (**II'**) that is intercepted by amine (**Figure 1a**, right). In either scenario, the resulting putative hydroxyzirconocene species, **III/III'**, could regenerate active catalysts **I/I'** through hydrosilane-meditate metatheses.

Thus, we first tested the ability of several Zr-complexes to catalyze amidation under the optimized reaction conditions but in the absence of hydrosilane (**Figure 1b**). Though ester **1a** was converted to amide **22** in up to 16 % yield, the majority of the starting material remained unreacted after 24 hours. While Lewis acid-mediated amide formation is a viable route contributing to product formation, these results suggest to us that it may not be the sole or major route of conversion.

Instead, we hypothesize that the dominant mechanistic pathway involves the formation of **II'** and its amine-mediated interception, an analogous mechanism to our prior observations.[9b] Previous studies reveal that zirconocene hemiacetals (e.g., **23**) derived from Cp_2ZrHCl readily eliminate to aldehydes, which rapidly undergo a second reduction (**Figure 1c**).[9f,10c] This is in stark contrast to analogous zirconocene hemi*aminals* which are comparatively stable.[9b] 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**. Rather, within 30 minutes **1a** was iteratively reduced to yield a mixture of species, putatively zirconcenes **24** and **25**.

However, while studying the ester reduction at various catalyst loadings, we were perturbed by the distinct differences in reaction outcome (**Figure 1d**). Reactions employing ≤ 25 mol% Cp_2ZrHCl exhibited pronounced selectivity for imine **3a**, while those employing ≥ 30 mol% Cp_2ZrHCl sharply favored full reduction to **25** and **26**. Conversely, a similar effect was not observed when carrying out an analogous study employing the dichloride and μ-oxo (**V**) pre-catalysts instead. In both studies, the major product observed at all catalyst loadings was imine **3a**. These results allude to a change in mechanism wherein the fate of hemiacetal **II'** may diverge in favor of the traditional reduction pathway at higher concentrations of Schwartz's reagent. More significantly, these findings also indicate that the active catalyst for semi-reduction may involve a ZrH complex **I'** where X≠Cl.[19] Although mechanistic studies are ongoing, at this time we speculate that this X-type ligand could be an alkoxide or siloxide, or that the active catalyst could be dimeric in nature.[20]

In conclusion, we have developed a series of highly selective and novel ZrH-catalyzed reductive transformations of esters. The interrupted catalytic reduction of esters via addition of simple unprotected amines enables the formation of imine and enamine "trapped" intermediates as a means to conserve the higher 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, aldehydes were obtained in up to 84% yield 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 direct 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 exact identity of the active ZrH catalyst are currently underway.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.

General procedural information, mechanistic studies, characterization data and spectra (PDF)

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Notes

The authors declare no competing interests.

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