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# Reduction of Secondary Amides to Imines Catalysed by Schwartz's Reagent

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## Abstract

The partial reduction of amides is a challenging transformation that must overcome the intrinsic stability of the amide bond, a ubiquitous motif in organic chemistry, and exhibit high chemoselective control. To address this challenge, we describe a zirconium-catalysed synthesis of imines by the reductive deoxygenation of secondary amides. This reaction exploits the excellent chemoselectivity of Schwartz's reagent ( $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ ) to avoid overreduction to amine products and utilises  $(\text{EtO})_3\text{SiH}$  as a mild stoichiometric reductant to enable catalyst turnover. The reaction generally proceeds with high yields (13 examples, 70 to 95% yield) and tolerates a variety of functional groups (alkene, ether, nitro, etc.). Stoichiometric mechanistic investigations suggest the regeneration of the active  $[\text{Zr}]-\text{H}$  catalyst is achieved through the  $\sigma$ -bond metathesis of  $\text{Si}-\text{H}$  and  $\text{Zr}-\text{OR}$ .

## Introduction

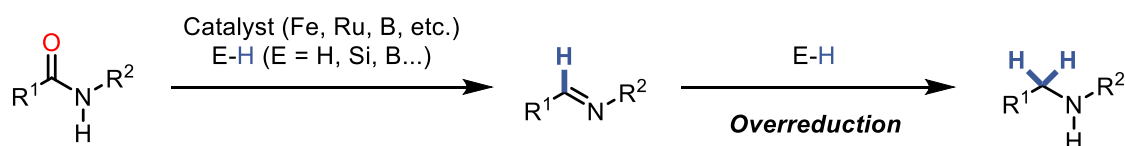
Organic amides are prevalent in pharmaceutical, agrochemical and natural products as well as a variety of functional polymer materials. Therefore, methods to selectively reduce these functional groups could open new opportunities for late-stage functionalisation and post-polymerisation modification to access products that are difficult to synthesise by classical methods.<sup>1-3</sup> However, the carboxamide bond is relatively inert to hydride addition requiring forcing conditions using strongly reducing stoichiometric reagents, such as  $\text{LiAlH}_4$ , leading to narrow functional group tolerance. Several catalytic protocols with a variety of catalysts (Fe, Ru, La, B, etc.) have been developed to enable the use of milder reducing agents (such as  $\text{H}_2$ , hydrosilanes and hydroboranes) with the aim of improving the chemoselectivity of these transformations (Scheme 1A). However, upon reduction of the amide the corresponding imine derivative is initially formed and, because the imine derivative is more electrophilic than the amide, further reduction to the amine is observed for the majority of these protocols.<sup>1, 4-5</sup> The development of catalytic methodologies that avoid overreduction to the amine product and instead allow selective formation of the imine product, an important electrophilic synthon in organic chemistry, are highly valuable and can complement traditional methods for imine synthesis.

Charette and co-workers reported the direct conversion of secondary amides to imine derivatives using  $\text{Tf}_2\text{O}$  as an activator and  $\text{Et}_3\text{SiH}$  as the reductant.<sup>6-7</sup> This powerful

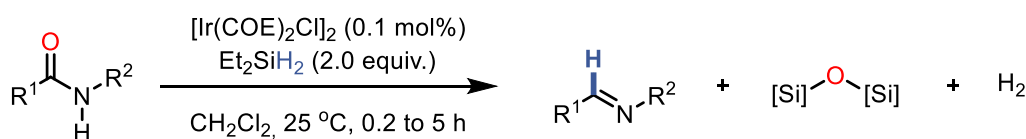
transformation offered exceptional functional group tolerance (e.g., nitrile, ester, aldehyde) and generally proceeded with high yields. However, the reaction requires the use of cryogenic temperatures and stoichiometric quantities of the air-sensitive and corrosive  $\text{TiF}_4$ . Brookhart and co-workers reported the Ir-catalysed deoxygenation of secondary amides to imines or amines, depending on the equivalents of  $\text{Et}_2\text{SiH}_2$  present in the reaction, using an Ir(I) catalyst  $[\text{Ir}(\text{COE})_2\text{Cl}]_2$  (COE = cyclooctene) (Scheme 1A).<sup>8</sup> A similar protocol using Vaska's complex ( $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$ ) for the formation of enamines from tertiary amides bearing monosubstituted  $\beta$ -carbon atoms was reported by Nagashima and co-workers.<sup>9</sup> Several groups have since expanded on these seminal reports to develop methods for the reductive functionalization of secondary and tertiary amides by addition of a variety of nucleophiles to the transiently formed imine derivatives.<sup>10-14</sup>

#### A) Current Methods for the Catalytic Reduction of Secondary Amides

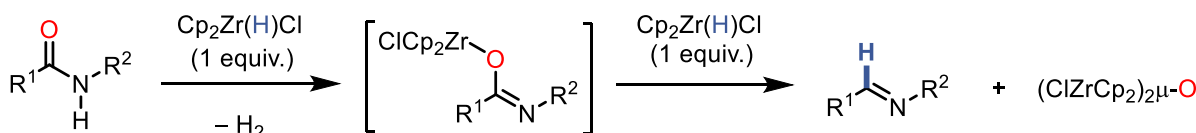
*Overreduction to amine:*



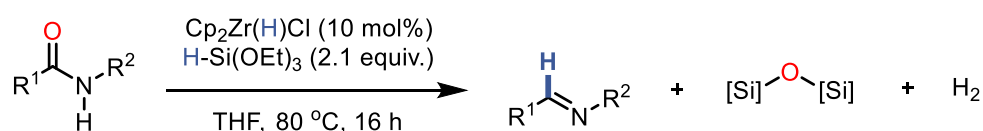
*Brookhart et al, 2012:*



#### B) Stoichiometric Reduction of Secondary Amides using Zirconium



#### C) This work: Catalytic Reduction of Secondary Amides using Zirconium



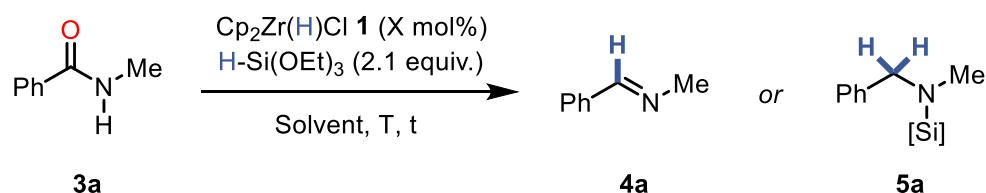
Scheme 1. The challenge of chemoselectivity in the catalytic reduction of amides to amines or imines.

Although these Ir(I) complexes are competent catalysts for the deoxygenation of amides, there is a desire to replace catalysts based on noble metals with more earth abundant metals. Ganem and Georg showed that the commercially available Schwartz

reagent ( $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ ) (**1**) can reduce secondary amides to imines stoichiometrically with liberation of  $(\text{ClZrCp}_2)_2\text{O}$  (**2**) as a byproduct (Scheme 1B).<sup>15-18</sup> Very recently, Wu and coworkers reported the hydroboration of amides catalyzed by  $\text{Cp}_2\text{ZrH}_2$ , however, the final product is the corresponding amine rather than the imine.<sup>19</sup> Complex **1** was shown to be an active, albeit sluggish, catalyst for this reaction. This result confirms the ability to regenerate Zr-H from Zr-OR using main group hydrides and enable catalyst turnover. Inspired by this work, we envisaged that hydrosilanes would be well poised to act as milder reductants to control the chemoselectivity of the amide reduction and stop at the imine product,<sup>20</sup> in a similar fashion to our previous work on the reduction of ureas to formamidines.<sup>21</sup> Herein, we report a practical and efficient protocol for the deoxygenation of secondary amides to imines using catalyst **1** and hydrosilanes (Scheme 1C). We also describe our preliminary studies aimed at elucidating the reaction mechanism.

## Results & Discussion

Initial conditions using catalyst **1** (10 mol%) in  $\text{C}_6\text{D}_6$  at 60 °C for 16 h were applied to a screen of hydrosilanes (2.1 equiv.) for the reduction of *N*-methylbenzamide **3a** (ESI). The aryl- and alkylsilanes  $\text{Ph}_2\text{SiH}_2$ ,  $\text{Ph}_3\text{SiH}$ ,  $\text{Et}_3\text{SiH}$  and  $\text{Et}_2\text{SiH}_2$  only provided trace conversion to the imine product **4a**. The alkoxysilanes  $\text{Me}(\text{EtO})_2\text{SiH}$  and  $(\text{EtO})_3\text{SiH}$  provided the imine as the major product (82% and 86%) and the overreduced amine as the minor product (10% and 7%). However, polymethylhydrosiloxane (PMHS) only provided trace yield of imine and tetramethyldisiloxane (TMDS) gave 14% conversion of the amide with an 11% yield of imine.

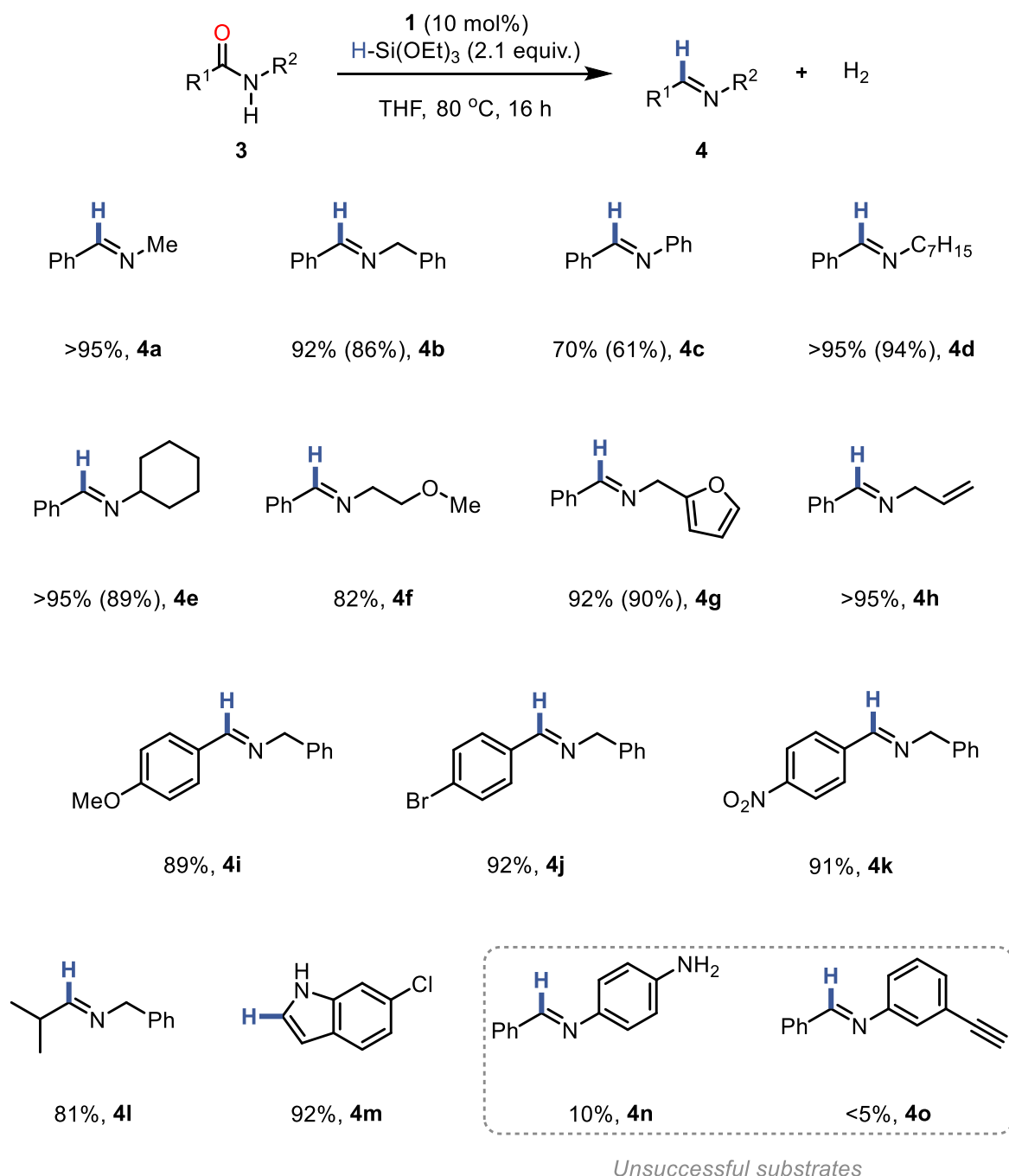


Entry	X	Solvent	T(°C)/t(h)	Conversion	Yield <sup>a</sup> ( <b>4a/5a</b> )
1	10	$\text{C}_6\text{D}_6$	80/8	>95%	84%/10%
2	10	THF- $\text{d}_8$	80/8	90%	86%/0%
3	10	$\text{CD}_2\text{Cl}_2$	80/16	52%	39%/13%
4	10	THF- $\text{d}_8$	60/16	68%	68%/0%
5	5	THF- $\text{d}_8$	80/16	88%	85%/6%
6	10	THF- $\text{d}_8$	80/16	>95%	91%/4%
7 <sup>b</sup>	10	THF- $\text{d}_8$	80/16	>95%	>95%/0%
8	0	THF- $\text{d}_8$	80/16	0%	0%/0%

Table 1. Optimisation of reaction conditions for the reduction of **3a** to **4a**. <sup>a</sup>Yield measured by  $^1\text{H}$  NMR against mesitylene as an internal standard. <sup>b</sup>Order of addition: add [Zr] before silane instead of adding [Zr] last.

Further optimisation of this reaction was conducted using (EtO)<sub>3</sub>SiH as the silane (Table 1). Switching solvents from C<sub>6</sub>D<sub>6</sub> to THF-d<sub>8</sub> and increasing the temperature to 80 °C gave higher chemoselectivity for the imine **3** product over the corresponding amine **4** (Entries 1 and 2), however, the reaction in CD<sub>2</sub>Cl<sub>2</sub> gave reduced yields and chemoselectivity (Entry 3). Running the reaction at 60 °C gave a poorer yield even after an extended reaction time of 48 h (Entry 4). Reducing the catalyst loading to 5 mol% also resulted in poorer yields and reduced chemoselectivity (Entry 5). Optimised conditions were established with 10 mol% of the catalyst at 80 °C for 16 h and changing the order of addition from adding the catalyst to adding the silane last appears to increase the chemoselectivity (Entries 6 and 7). The reaction does not proceed in the absence of **1** and only gives <5% yield in the absence of silane (Entry 8).

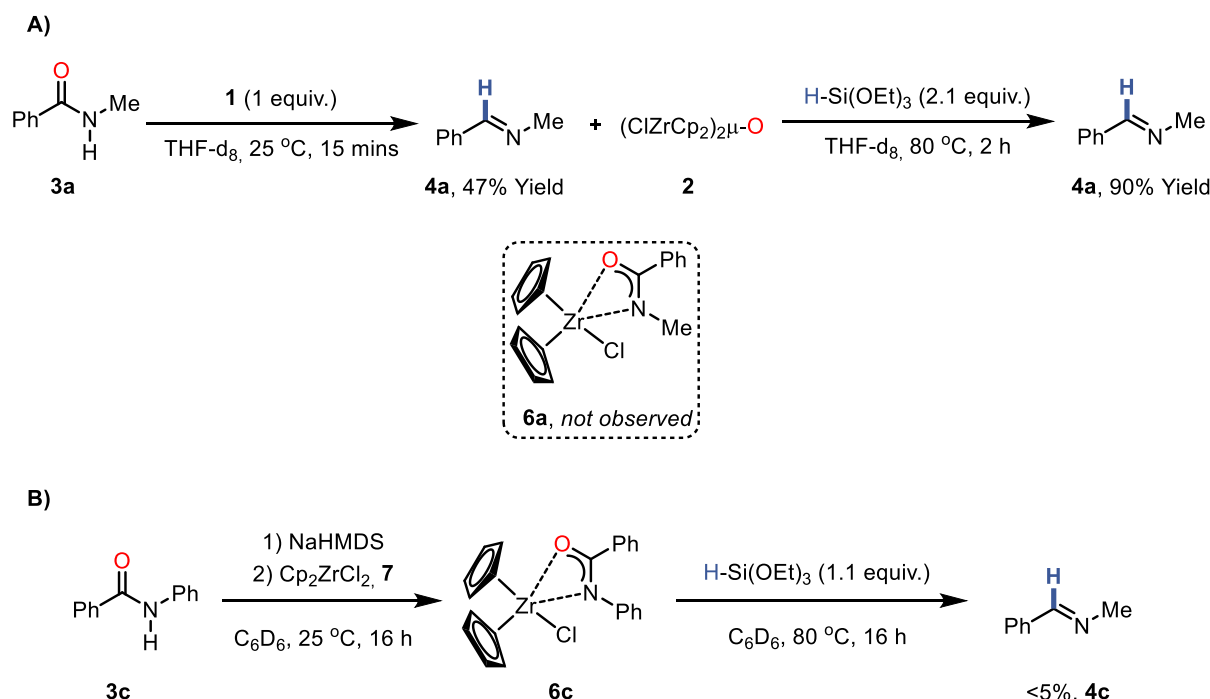
With these optimised conditions in hand, we explored the substrate scope of this reaction focusing on substrates with secondary amide functionalities. By first varying the amine portion of the substrate, a variety of alkyl and aryl benzamides **3a** – **3e** were tolerated under these conditions. The reaction does not appear to be sensitive to steric bulk on the amine portion, evidenced by the high yield for the conversion of *N*-cyclohexylbenzamide **3e** to the corresponding imine **4e**. Ether and furanyl functional groups were tolerated (**3f** and **3g**) and, interestingly, in the case of *N*-allylbenzamide **3h** the terminal alkene was not reduced, leading to clean formation of the desired imine product **4h**. Variation of the carbonyl portion of the substrates did not show a strong dependence on the electronics of *p*-substituted benzamides **3i** – **3k** and the nitro group of **3k** is not reduced under these conditions. The excellent yield for the *N*-benzylisobutyramide **3l** to the corresponding imine **4l** shows that the reaction is not influenced by steric bulk on the carbonyl portion and the product does not tautomerise to the enamide under these conditions. 6-Chloro-2-oxindole **3m** could also be deoxygenated with this system to form the aromatised indole product **4m**. Primary amine and terminal alkyne functional groups were not tolerated (**3n** and **3o**) due to catalyst deactivation and observed competitive hydrosilylation to give a complex mixture of alkenyl products,<sup>22</sup> respectively.



Scheme 2. Substrate scope for the Zr-catalysed reduction of amides to imines. Yield measured by  $^1\text{H}$  NMR against mesitylene as an internal standard, isolated yields in brackets.

During this study, we wished to gain further insight into the reaction mechanism through a series of stoichiometric reactions. We have already shown that the amide **3a** does not react directly with  $(\text{EtO})_3\text{SiH}$  (Table 1, Entry 8), which suggests that **1** is the reactive hydride species. The reaction of **3a** with **1** produced the corresponding imine **4a** in 47% yield with unreacted amide **3a** present after 15 mins at 25 °C with elimination of  $\text{H}_2$  (Signal at 4.55 ppm in the  $^1\text{H}$  NMR spectrum) (Scheme 3A). In contrast to the analogous reaction with tertiary amides, the expected amidatozirconocene product **6a**

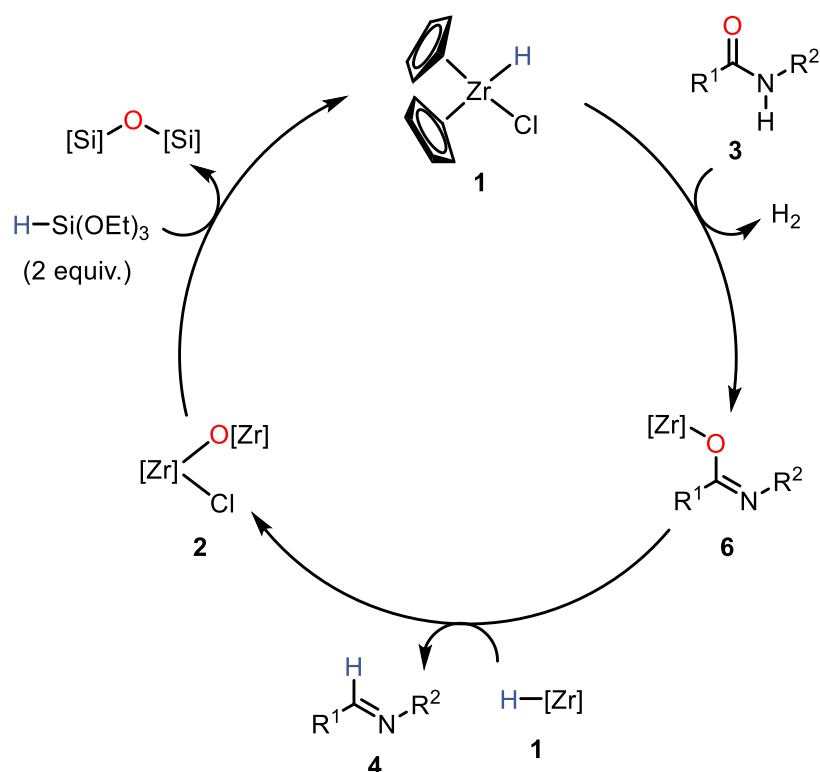
formed upon reaction of the amide with one equivalent of **1** was not observed. These results are consistent with the findings of Ganem and suggest initial deprotonation of the N–H bond by one equivalent of **1**,<sup>15</sup> followed by the rapid reaction of this intermediate with a second equivalent of **1** with concomitant formation of byproduct **2**. Addition of (EtO)<sub>3</sub>SiH (2 equiv.) did not result in any further conversion of the amide **3a** or further reduction of the imine at 25 °C. However, heating to 80 °C for 2 h resulted in full conversion of the amide **3a** and 90% yield of the imine **4a** with no observed formation of the corresponding amine product **5a**.



Scheme 3. Investigations of reaction mechanism through stoichiometric control experiments.

A model amidatozirconocene complex **6c** was synthesised from Cp<sub>2</sub>ZrCl<sub>2</sub> **7** and the sodium salt of **3c** following the procedure of Rosenthal and Schafer (Scheme 3B).<sup>23</sup> When the *in situ* formed complex **6c** was heated in the presence of one equivalent of (EtO)<sub>3</sub>SiH, there was no reaction and the formation of the corresponding imine product **4c** was not observed. Similarly, using complex **7** as the catalyst under standard catalytic conditions does not convert **3a** to **4a**. These results would suggest that complex **1** is the only hydride species that reacts directly with the amide and amide derivatives. Therefore, we propose that the only role of (EtO)<sub>3</sub>SiH is in the regeneration of **1** from **2** through  $\sigma$ -bond metathesis of Si–H and Zr–OR. Because the silane does not react directly with the amide derivatives the excellent chemoselectivity of catalyst **1** is preserved from its reported stoichiometric reactivity.<sup>18</sup> During the course of our investigations, Bayeh-Romero and co-workers described the *in situ* preparation of **1** from dichloride complex **7** and dimethoxy-(methyl)silane (DMMS) in the presence of Et<sub>2</sub>NH.<sup>24</sup> They then applied this method to the catalytic hydrosilylation of aldehydes

and ketones. Their mechanistic investigations support the intermediacy of complex **2** and its conversion to **1** in the presence of silane.



Scheme 4. Proposed catalytic cycle for the Zr-catalysed reduction of secondary amides to imines.

Therefore, we propose that this reaction proceeds *via* initial dehydrogenative deprotonation of the amide substrate **3** to form an amidatozirconocene intermediate **6** (Scheme 4). This intermediate undergoes exchange with a second hydride equivalent of **1** to form the desired imine product **4** and an oxo-bridged zirconocene byproduct **2**. This species can then react with an equivalent of silane to regenerate the active zirconocene hydride catalyst **1** through  $\sigma$ -bond metathesis with **2**.

## Conclusion

While the synthesis of valuable imine products by the catalytic reduction of secondary amides is a very appealing transformation, this had previously only been achieved using Ir(I) catalysts. We have shown that the classical organometallic reagent **1** can be used as a earth-abundant metal catalyst, in combination with a hydrosilane, to selectively form imines from secondary amides and avoid overreduction to amines. This catalytic system retains the excellent chemoselectivity and broad functional group tolerance that was observed for the original stoichiometric protocol. We expect that there are many more applications of this chemistry for the selective catalytic reduction of a wide variety of functionalities.



## Experimental

### Imine Synthesis

#### General Procedure A:

In a glovebox under a purified argon atmosphere, (EtO)<sub>3</sub>SiH (195 µL, 1.05 mmol) was added to a mixture of amide **3** (0.5 mmol) and Cp<sub>2</sub>Zr(H)Cl (13 mg, 0.050 mmol) in THF (2 mL) in a sealed round-bottom flask. The reaction was removed from the glovebox and heated at 80 °C with stirring for 16 h. The solvent was removed under vacuum and the crude reaction mixture was purified by filtration through a short alumina plug (activated, basic, Brockmann I) eluting with hexane (1% Et<sub>3</sub>N) or a gradient of hexane (1% Et<sub>3</sub>N) to hexane/EtOAc 9:1 (1% Et<sub>3</sub>N) to yield the pure imine product **4**.

#### General Procedure B:

In a glovebox under a purified argon atmosphere, (EtO)<sub>3</sub>SiH (117 µL, 0.63 mmol) was added to a mixture of amide **3** (0.3 mmol) and Cp<sub>2</sub>Zr(H)Cl (7.8 mg, 0.030 mmol) in THF-d<sub>8</sub> (0.5 mL) in a J. Young NMR tube with mesitylene (20.9 µL, 0.15 mmol) as internal standard. The reaction was removed from the glovebox and heated at 80 °C for 16 h. The reaction mixture was analyzed by <sup>1</sup>H NMR spectroscopy and the yield of imine product **4** was determined by integration against the mesitylene signals. The identity of the product was verified by <sup>1</sup>H, <sup>13</sup>C and (<sup>1</sup>H,<sup>13</sup>C)-HSQC NMR spectroscopic analysis and compared to NMR spectra previously reported in the literature.

## Acknowledgements

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