Controlled reduction of carboxamides to alcohols or amines by zinc hydrides

Ong, Derek Yiren; Yen, Zhihao; Yoshii, Asami; Imbernon, Julia Revillo; Takita, Ryo; Chiba, Shunsuke

2019

Ong, D. Y., Yen, Z., Yoshii, A., Imbernon, J. R., Takita, R., & Chiba, S. (2019). Controlled Reduction of Carboxamides to Alcohols or Amines by Zinc Hydrides. *Angewandte Chemie International Edition*, 58(15), 4992–4997. doi:10.1002/anie.201900233

<https://hdl.handle.net/10356/144604>

<https://doi.org/10.1002/anie.201900233>

This is the accepted version of the following article: Ong, D. Y., Yen, Z., Yoshii, A., Imbernon, J. R., Takita, R., & Chiba, S. (2019). Controlled Reduction of Carboxamides to Alcohols or Amines by Zinc Hydrides. *Angewandte Chemie International Edition*, 58(15), 4992–4997., which has been published in final form at doi:10.1002/anie.201900233. This article may be used for non-commercial purposes in accordance with the Wiley Self-Archiving Policy [<https://authorservices.wiley.com/authorresources/Journal-Authors/licensing/self-archiving.html>].

Controlled Reduction of Carboxamides to Alcohols or Amines by Zinc Hydrides

Derek Yiren Ong,^a Zhihao Yen,^a Asami Yoshii,^a Julia Revillo Imbernon,^a Ryo Takita^{*b} and Shunsuke Chiba^{*a}

Abstract: New protocols for controlled reduction of carboxamides to alcohols or amines were established using combination of sodium hydride (NaH) and zinc halides (ZnX₂). Use of the different halide on ZnX₂ dictates the selectivity, where the NaH-ZnI₂ system delivers alcohols and that with ZnCl₂ gives amines. Extensive mechanistic studies by experimental and theoretical approaches imply that polymeric zinc hydride (ZnH₂)_∞ is responsible for alcohol formation, whereas dimeric zinc chloride hydride (H-Zn-Cl)₂ is the key species for production of amines.

Carboxamides have enriched chemical reactivity, and thus have been utilized as adaptive materials in a series of synthetic transformations for production of fine chemicals in various fields.^[1] Among them, reduction of carboxamides, commonly mediated by metal hydrides, is one of the most frequently used processes, that potentially delivers three possible products; aldehydes, alcohols, and amines (Scheme 1A).^[2,3] Aldehydes are synthesized when tetrahedral anionic carbinol amine intermediates **I**, formed via the first hydride transfer, are kept intact prior to the aqueous quench. On the other hand, alcohols or amines could be formed when the tetrahedral intermediates **I** fragment through C-N or C-O bond scission, respectively, and the resulting aldehydes or imine/iminium intermediates are reduced by the second hydride. At present, the state-of-the-art approaches for reduction of amides to alcohols are catalytic hydrogenation by well-defined pincer complexes based on Ru, Fe, and Mn under a highly pressurized H₂ atmosphere,^[4] whereas those for production of amines are facilitated by hydrosilylation^[5] with various metals^[6] or organoboranes^[7] as catalysts or through electrophilic activation of amides with triflic anhydride.^[8,9] Methodologies leveraging means of single-electron-reduction have recently been emerged, enabling controlled reduction of amides.^[10] Nonetheless, implementation of the amide reduction with precise and predictable control of the C-N/C-O cleavage for the formation of alcohol/amine still remains a challenge, that requires the sophisticated design of the reaction settings. Herein, we report concise protocols for controlled reduction of carboxamides to alcohols or amines by

the NaH-ZnX₂ system (Scheme 1B). The halide ions on the ZnX₂ play a critical role on the selectivity: use of ZnI₂ offers selective synthesis of alcohols, whereas ZnCl₂ allows for the formation of amines. The discovery, optimization, scope and limitation as well as the detailed mechanistic investigation are described.

A. Reduction of carboxamides

B. Controlled reduction of amides to alcohols or amines (this work)

Scheme 1. Reduction of carboxamides

We have recently uncovered a concise protocol to activate NaH in the presence of dissolving iodides such as NaI/LiI in THF and the composite performs unprecedented reductive transformations such as hydrodeacylation of α -quaternary benzyl cyanides,^[11] hydrodehalogenation of haloarenes,^[12,13] and controlled reduction of *N,N*-dimethylcarboxamides to aldehydes.^[11,14] In these reactions, it is assumed that activated NaH could be generated through counter ion metathesis between polymeric inactive NaH with dissolving NaI/LiI.^[15] Stimulated by these findings, our attention is directed to use of NaH for generation of new metal hydrides of interest through the counter ion metathesis with the corresponding metal halides and exploration of their reactivity.

There have been reported a number of examples on synthesis and characterization of molecular zinc hydrides in either dimeric bridged hydride form or monomeric mono-hydride form with proper chelating ligands, while their reactivity has been examined only for reduction of simple and reactive carbonyl compounds.^[16-18] Ashby previously reported formation of polymeric (ZnH₂)_∞ by mixing NaH and ZnI₂ in THF for 24 h,^[19] whereas its detailed reactivity for the hydride reduction has thus

[a] D. Y. Ong, Z. Yen, A. Yoshii, J. Revillo Imbernon, Prof. S. Chiba
Division of Chemistry and Biological Chemistry
School of Physical and Mathematical Sciences
Nanyang Technological University, Singapore 637371 (Singapore)
E-mail: shunsuke@ntu.edu.sg

[b] Prof. R. Takita
Graduate School of Pharmaceutical Sciences, The University of
Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
E-mail: takita@mol.f.u-tokyo.ac.jp

Supporting information for this article is given via a link at the end of the document.

far not been examined. Considering that the counter ion metathesis between NaH and ZnX_2 ($\text{X} = \text{I}, \text{Br}, \text{Cl}$) includes a double hydride-halide exchange, we assume that their reaction kinetics will become different depending on the halide ion, thus resulting in formation of different zinc hydride complexes having unique chemical reactivity. Based on these backgrounds, we first examined the reaction of amide **1a** with NaH (3 equiv) and ZnI_2 (1.5 equiv) in THF (Table 1, entry 1). We found that the reaction at 40 °C afforded alcohol **2a** in 76% yield as the major product with 22% yield of amine **3a**. Interestingly, decreasing of the amount of ZnI_2 to 1 equiv could accelerate the process and improved the yield of alcohol **2a** to 88% (entry 2). Moreover, addition of 1 equiv of NaI could suppress the formation of amine completely to form alcohol **2a** as a sole product in 95% yield (entry 3). In the sharp contrast, it was found that the reaction with ZnBr_2 or ZnCl_2 (1.5 equiv) in the presence of NaH (3 equiv) delivered amine **3a** as the major product (entries 4 and 5). Furthermore, increase of the amounts of NaH and ZnCl_2 to 5 equiv and 2.5 equiv, respectively, renders the process more selective and efficient (entry 6). The reaction at 60 °C completed the process within 30 min, giving amine **3a** in 90% yield (entry 7). It should be noted that both protocols could be implemented in 40 mmol scale, emphasizing the scalable nature of the present protocols (Table 1, entries 3 and 7).

With the optimized reaction conditions (Table 1, entry 3 for formation of alcohols **2**; entry 7 for formation of amines **3**), we next investigated the scope and limitations of this controlled reduction of carboxamides **1** (Scheme 2). For reduction of aromatic amides (**1b-1t**), the process was not influenced by the presence of a sterically demanding aromatic ring (for **1c-1e**) and tolerated substitution of different electronic nature such as electro-donating groups (for **1f-1n**) and electron-withdrawing groups including halogen atoms that are often susceptible to the common hydride reduction conditions (for **1o-1t**) (Scheme 2A). Amides based on electron-rich 5-membered heteroaromatic rings such as indole **1u**, pyrrole **1v**, benzofuran **1w**, benzothiophene **1x** and thiophene **1y** as well as electron-deficient 6-membered ring ones including quinoline **1z** and pyridine **1aa** were also compatible (Scheme 2B). We found that the current protocols are amenable to reduce a series of aliphatic amides (Scheme 2C). Sterically congested α -quaternary amides **1ab-1af** could be reduced smoothly and selectively to the corresponding alcohols **2** or amines **3**. We

also observed that the reduction of amides **1ag-1al** having enolizable α -protons proceeds well in general to afford the corresponding alcohols or amines in good yields except for conversion of cyclopropanecarboxamide **1ak** and α -secondary amide **1al** into the corresponding alcohols **2ak** and **2al**, respectively, that is concomitant with formation of a significant amount of the corresponding amines **3**.

Table 1: Optimization of reaction conditions.^[a]

Run	NaH (equiv)	ZnX_2 (equiv)	additive (equiv)	Temp [°C]	t [h]	yield [%] ^[b]	
						2a	3a
1	3	ZnI_2 (1.5)	–	40	1.5	76	22
2	3	ZnI_2 (1)	–	40	3	88	11
3	3	ZnI_2 (1)	NaI (1)	40	7	95 (97) ^[c]	0
4	3	ZnBr_2 (1.5)	–	40	7	18	53
5	3	ZnCl_2 (1.5)	–	40	6	8	62
6	5	ZnCl_2 (2.5)	–	40	2.5	6	88
7	5	ZnCl_2 (2.5)	–	60	0.5	4	90 (89) ^[c]

[a] The reactions were conducted using 0.5 mmol of **1a** in THF (2.5 mL). [b] ¹H NMR yields. [c] Isolated yields in the reactions of 40 mmol scale.

Scheme 2. Substrate scope. [a] The reactions were conducted using 0.5 mmol of amides **1**. Isolated yields of alcohols **2** and amines **3** are given. [b] The reaction was conducted using 5 equiv of NaH, 2 equiv of ZnI₂ and 2 equiv of NaI. [c] The reaction was conducted using 7 equiv of NaH and 3.5 equiv of ZnCl₂. [d] **1aj** >98% ee; **2aj** >97% ee; **3aj** >98% ee measured by the Mosher method (see the SI). [e] Amine **3ak** was formed in 35% yield. [f] Amine **3al** was formed in 31% yield.

Scheme 3. Reduction of enantioenriched amides.

It is noteworthy that the reactions of α -enantioenriched amides **1am** and **1am'** derived from the Myers chiral auxiliary^[20] under the NaH-ZnI₂ system delivered alcohols (S)- and (R)-**2am** with complete retention of the α -chirality (Scheme 3).

To identify the active zinc hydride species, we designed several experiments as shown in Scheme 4. By following the Ashby's protocol,^[19] zinc hydride polymer (ZnH₂)_∞ **4** was prepared and its IR spectroscopy analysis showed one strong absorption band at 1443 cm⁻¹ (Scheme 4A). Amide **1a** was then added to the mixture of the resulting (ZnH₂)_∞ **4**, that provided alcohol **2a** in 92% yield. Interestingly, when a 3:1:1 mixture of NaH, ZnI₂, and NaI was stirred at 24 °C for 3 h, formation of (ZnH₂)_∞ **4** could be observed by the IR spectroscopy, while no other zinc hydride species was found from the mixture (Scheme 4B).^[21] Lower frequency shift of the band was observed when

NaD^[22] was used as a deuteride source. These experimental observation suggested that $(\text{ZnH}_2)_\infty$ **4** is responsible for the alcohol formation. On the other hand, treatment of a 2:1 mixture of NaH and ZnCl_2 within 10 min in THF afforded a distinct zinc hydride species having an absorption at 1648 cm^{-1} in the IR spectrum and a broad peak at δ 3.71 in the ^1H NMR spectrum (Scheme 4C). We detected mass of zinc hydride chloride dimer with two THF molecules by the cold-spray TOF mass. Based on the reported data^[23] as well as the theoretical prediction, we characterized this zinc hydride chloride dimer as chloride bridged terminal hydride **5**,^[24] which should be the reactive species for the formation of amines. We found that the second hydride-chloride exchange from **5** to $(\text{ZnH}_2)_\infty$ **4** would be much slower. This could be ascertained by the incubation study of the NaH- ZnCl_2 system for the reduction of **1a** (Scheme 4D). While the direct treatment of **1a** with NaH and ZnCl_2 gave alcohol **2a** in less than 4% yield with 90% yield of amine **3a** (Table 1, entry 7), treatment of **1a** after incubation of the mixture of NaH and ZnCl_2 for 5 h significantly increased the amount of alcohol **2a** to 54% yield with 44% yield of amine **3a**. Incubation for 12 h completely switched the selectivity toward formation of alcohol **2a**.

A. Preparation of $(\text{ZnH}_2)_\infty$ by Ashby's protocol

B. Formation of $(\text{ZnH}_2)_\infty$ from the NaH- ZnI_2 -NaI system

C. Formation of $(\text{H-Zn-Cl})_2$ from the NaH- ZnCl_2 system

D. Incubation of the NaH- ZnCl_2 system

Scheme 4. Characterization of the active zinc hydride species.

To gain the insights into the detailed reaction pathway and selectivity, DFT calculations for model reactions of benzamide with ZnH_2 dimer as the model of $(\text{ZnH}_2)_\infty$ **4**^[25] or zinc hydride

chloride dimer **5** were thus carried out at the ω B97XD/SDD&6-31+G* (scrf = smd, THF) level of theory. In the cases of both complexes, by taking advantage of the flexible conformation change in dimeric structures, the efficient amide reduction lead to the formation of stable tetrahedral intermediates (i.e. **INT1'** complexes). Thus, the selectivity for benzyl alcohol or amine formation should be determined kinetically by the energy barriers of the subsequent C–O/C–N bond scission processes. With the ZnH_2 dimer (Scheme 5A), both oxygen and nitrogen atoms can coordinate to two zinc centers in **INT1'** _{$\text{ZnH}_2/\text{C-N}$} and the C–N bond scission efficiently proceeds with the activation barrier of +16.0 kcal/mol. In contrast, the C–O scission process begins from the stable **INT1'** _{$\text{ZnH}_2/\text{C-O}$} in which two zinc centers of dimeric species activates the oxygen atom. The C–O bond is cleaved, concomitant with the degradation of dimeric structure and formation of Zn–O–Zn species in **INT2** _{$\text{ZnH}_2/\text{C-O}$} , which requires a rather high energy ($\Delta G^\ddagger$ +35.5 kcal/mol). The further reductions into benzyl alcohol/amine were found to proceed readily with the generated zinc hydride in **INT2** complexes (see the SI), while other hydride species may also be possibly involved. Scheme 5B depicts the reaction pathways promoted by the zinc hydride chloride dimer. With the aid of Lewis acidic monomeric $\text{ZnCl}_2(\text{thf})$ generated in the formation of tetrahedral intermediate, the C–O bond cleavage is kinetically feasible via **TS2** _{$\text{ZnHCl}/\text{C-O}$} ($\Delta G^\ddagger$ +21.3 kcal/mol) to afford the iminium intermediate **INT2** _{$\text{ZnHCl}/\text{C-O}$} . On the other hand, the C–N bond scission starts from the stable complex **INT1'** _{$\text{ZnHCl}/\text{C-N}$} having the O,N-chelation to one zinc center, and requires a higher activation energy ($\Delta G^\ddagger$ +26.3 kcal/mol). Thus, these calculated results clearly explain that the amide reduction by both NaH- ZnI_2 and NaH- ZnCl_2 system proceeds smoothly and selectively. In particular, given that 1) the flexible conformation change is profitable for the first amide reduction, 2) the dimeric ZnH_2 species efficiently activates the tetrahedral intermediate for the C–N scission process, and 3) the formation of Lewis acidic ZnCl_2 facilitates the dissociation of Zn–O–Zn species, the structural and electronical requirements on each active species are responsible for the controlled reduction process.

The present protocols offer concise and cost-economical alternatives for controlled reduction of bench-stable carboxamides into alcohols and amines. Further studies on the chemical reactivity of these zinc hydrides are under investigation.

Acknowledgements

This work was supported by funding from Nanyang Technological University (NTU) (for S.C.), the Singapore Ministry of Education (Academic Research Fund Tier 1: RG10/17 for S.C.), and Takeda Science Foundation (for R.T.). Computations were performed using Research Center for Computational Science at Okazaki, Japan. We thank Prof. Subodh G. Mhaisalkar (School of Materials Science and Engineering, NTU) and Prof. Han Sen Soo (School of Physical and Mathematical Sciences, NTU) for the assistance in powder XRD experiments.

A. Reaction pathways of benzamide reduction promoted by ZnH_2 dimeric species B. Reaction pathways of benzamide reduction promoted by ZnHCl dimeric species

Scheme 5. DFT calculations for model reactions of benzamide with $(\text{ZnH}_2)_2$ or $(\text{ZnHCl})_2$ species. Energy changes and bond lengths at the $\omega\text{B97XD/SDD} \& 6\text{-}31+\text{G}^*$ (scrf = smd, THF) level of theory are shown in kcal/mol and Å, respectively.

Keywords: amides • alcohols • amines • reduction • zinc hydrides

- [1] For recent reviews, see: a) D. Kaiser, A. Bauer, M. Lemmerer, N. Maulide, *Chem. Soc. Rev.* **2018**, *47*, 7899; b) D. Kaiser, N. Maulide, *J. Org. Chem.* **2016**, *81*, 4421.
- [2] *Reductions by the Aluminio and Borohydride in Organic Synthesis*, 2nd ed. (Ed.: J. Seyden-Penne), Wiley, New York, 1997.
- [3] For recent reviews, see: a) A. Volkov, F. Tinnis, T. Slagbrand, P. Trillo, H. Adolfsson, *Chem. Soc. Rev.* **2016**, *45*, 6685; b) A. M. Smith, R. Whyman, *Chem. Rev.* **2014**, *114*, 5477; c) J. Magano, J. R. Dunetz, *Org. Process Res. Dev.* **2012**, *16*, 1156; d) P. A. Dub, T. Ikariya, *ACS Catal.* **2012**, *2*, 1718; e) D. Addis, S. Das, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 6004; *Angew. Chem.* **2011**, *123*, 6128.
- [4] With Ru: a) L. Rasu, J. M. John, E. Stephenson, R. Endean, S. Kalapugama, R. Clement, S. H. Bergens, *J. Am. Chem. Soc.* **2017**, *139*, 3065; b) L. Shi, X. Tan, J. Long, X. Xiong, S. Yang, P. Xue, H. Lv, X. Zhang, *Chem. Eur. J.* **2017**, *23*, 546; c) J. R. Cabrero-Antonino, E. Alberico, H.-J. Drexler, W. Baumann, K. Junge, H. Junge, M. Beller, *ACS Catal.* **2016**, *6*, 47. With Fe: d) N. M. Rezayee, D. C. Samblanet, M. S. Sanford, *ACS Catal.* **2016**, *6*, 6377. With Mn: e) V. Papa, J. R. Cabrero-Antonino, E. Alberico, A. Spanneberg, K. Junge, H. Junge, M. Beller, *Chem. Sci.* **2017**, *8*, 3676.
- [5] J. Pesti, G. L. Larson, *Org. Process Res. Dev.* **2016**, *20*, 1164.
- [6] With Mo: a) F. Tinnis, A. Volkov, T. Slagbrand, H. Adolfsson, *Angew. Chem. Int. Ed.* **2016**, *55*, 4562; *Angew. Chem.* **2016**, *128*, 4638. With Rh: b) S. Das, Y. Li, C. Bornschein, S. Pisiewicz, K. Kiersch, D. Michalik, F. Gallou, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2015**, *54*, 12389; *Angew. Chem. Int. Ed.* **2009**, *48*, 9511; *Angew. Chem.* **2009**, *121*, 9675; h) S. Zhou, K. Junge, D. Addis, S. Das, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 9507; *Angew. Chem.* **2009**, *121*, 9671. With Ni: i) B. J. Simmons, M. Hoffmann, J. Hwang, M. K. Jackl, N. K.

- Garg, *Org. Lett.* **2017**, *19*, 1910. With Cu: j) S. Das, B. Join, K. Junge, M. Beller, *Chem. Commun.* **2012**, *48*, 2683. With Zn: k) O. O. Kovalenko, A. Volkov, H. Adolfsson, *Org. Lett.* **2015**, *17*, 446; l) A. Volkov, F. Tinnis, T. Slagbrand, I. Pershagen, H. Adolfsson, *Chem. Commun.* **2014**, *50*, 14508; m) S. Das, D. Addis, S. Zhou, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 1770.
- [7] a) A. Chardon, T. Mohy El Dine, R. Legay, M. De Paolis, J. Rouden, J. Blanchet, *Chem. Eur. J.* **2017**, *23*, 2005; b) D. Mukherjee, S. Shirase, K. Mashima, J. Okuda, *Angew. Chem. Int. Ed.* **2016**, *55*, 13326; *Angew. Chem.* **2016**, *128*, 13520; c) E. Blondiaux, T. Cantat, *Chem. Commun.* **2014**, *50*, 9349; d) R. C. Chadwick, V. Kardelis, P. Lim, A. Adronov, *J. Org. Chem.* **2014**, *79*, 7728; e) Y. Li, J. A. Molina de La Torre, K. Grabow, U. Bentrup, K. Junge, S. Zhou, A. Brückner, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 11577; *Angew. Chem.* **2013**, *125*, 11791.
- [8] a) P. Q. Huang, Q.-W. Lang, Y.-R. Wang, *J. Org. Chem.* **2016**, *81*, 4235; b) G. Pelletier, W. S. Bechara, A. B. Charette, *J. Am. Chem. Soc.* **2010**, *132*, 12817. With Hantzsch's ester: c) G. Barbe, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 18.
- [9] For hydrogenation catalyzed by frustrated Lewis pair, see: N. A. Sitte, M. Bursch, Stefan Grimme, J. Paradies, *J. Am. Chem. Soc.* **2019**, *141*, 159.
- [10] a) B. Zhang, H. Li, Y. Ding, Y. Yan, J. An, *J. Org. Chem.* **2018**, *83*, 6006; b) S. R. Huq, S. Shi, R. Diao, M. Szostak, *J. Org. Chem.* **2017**, *82*, 6528; c) M. Szostak, M. Spain, A. J. Eberhart, D. J. Procter, *J. Am. Chem. Soc.* **2014**, *136*, 2268.
- [11] a) P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.* **2016**, *55*, 3719; *Angew. Chem.* **2016**, *128*, 3783; b) G. H. Chan, D. Y. Ong, S. Chiba, *Org. Synth.* **2018**, *95*, 240.
- [12] D. Y. Ong, C. Tejo, K. Xu, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.* **2017**, *56*, 1840; *Angew. Chem.* **2017**, *129*, 1866.
- [13] With KH, see: J. P. Barham, S. E. Dalton, M. Allison, G. Nocera, A. Young, M. P. John, T. McGuire, S. Campos, T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc.* **2018**, *140*, 11510.
- [14] G. H. Chan, D. Y. Ong, Z. Yen, S. Chiba, *Helv. Chim. Acta* **2018**, *101*, e1800049.
- [15] Z. Hong, D. Y. Ong, S. K. Muduli, P. C. Too, G. H. Chan, Y. L. Tnay, S. Chiba, Y. Nishiyama, H. Hirao, H. S. Soo, *Chem. Eur. J.* **2016**, *22*, 7108.
- [16] A.-K. Wiegand, A. Rit, J. Okuda, *Coord. Chem. Rev.* **2016**, *314*, 71.
- [17] T. Ohkuma, S. Hashiguchi, R. Noyori, *J. Org. Chem.* **1994**, *59*, 217.
- [18] M. Uchiyama, S. Furumoto, M. Saito, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1997**, *119*, 11425.
- [19] J. J. Watkins, E. C. Ashby, *Inorg. Chem.* **1974**, *13*, 2350.
- [20] A. G. Myers, B. H. Yang, H. Chen, L. McKinsty, D. J. Kopecky, J. L. Gleason, *J. Am. Chem. Soc.* **1997**, *119*, 6496.
- [21] For materials characterization by powder XRD, elementary analysis, and ICP OES, see the SI.
- [22] H. Jenkner, US Patent US3116112A, **1953**.
- [23] a) A. Rit, A.-K. Wiegand, D. Mukherjee, T. P. Spaniol, J. Okuda, *Eur. J. Inorg. Chem.* **2018**, 1114; b) P. A. Lummis, M. R. Momeni, M. W. Lui, R. McDonald, M. J. Ferguson, M. Miskolzie, A. Brown, E. Rivard, *Angew. Chem. Int. Ed.* **2014**, *53*, 9347; *Angew. Chem.* **2014**, *126*, 9501; c) E. C. Ashby, A. B. Goel, *Inorg. Chem.* **1981**, *20*, 1096.
- [24] The DFT calculation at the M06-2X/cc-pVTZ (scrf = smd, THF) level of theory indicated that the bridging hydride species is less stable than the terminal hydride **5**. In addition, the amide reduction with this species was found to proceed slower; see the SI.
- [25] The calculations for the reduction with the monomeric ZnH_2 or ZnHCl species resulted in higher activation barrier: see the SI.

COMMUNICATION

Derek Yiren Ong,^a Zhihao Yen,^a Asami Yoshii,^a Julia Revillo Imbernon,^a Ryo Takita^{*b} and Shunsuke Chiba^{*a}

Page No. – Page No.

Controlled Reduction of Carboxamides to Alcohols or Amines by Zinc Hydrides

New protocols for controlled reduction of carboxamides to alcohols or amines were established using combination of sodium hydride (NaH) and zinc halides (ZnX_2). Use of the different halide on ZnX_2 dictates the selectivity, where the $NaH-ZnI_2$ system delivers alcohols and that with $ZnCl_2$ gives amines. Extensive mechanistic studies by experimental and theoretical approaches imply that polymeric zinc hydride $(ZnH_2)_\infty$ is responsible for alcohol formation, whereas dimeric zinc chloride hydride $(H-Zn-Cl)_2$ is the key species for production of amines.