



Cite this: *Chem. Commun.*, 2025, 61, 9460

Received 21st January 2025,  
Accepted 15th May 2025

DOI: 10.1039/d5cc00399g

rsc.li/chemcomm

# Boron appended Ru-NHC catalyzed selective deoxygenative hydrogenation of tertiary amides and desulfurization of thioamides†

Raju Sharma,<sup>a</sup> Gowtham Kenguva,<sup>b</sup> Rambabu Dandela<sup>b</sup> and Prosenjit Daw<sup>ID</sup>\*<sup>a</sup>

Herein, we disclosed a selective hydrogenation of tertiary amides and desulfurization of thioamides to amines with phenylsilane as a reductant, using a bifunctional Ru-NHC complex **1** appended with a Lewis acid in the secondary coordination sphere. The catalytic process was further utilized to synthesize biologically relevant amine drug molecules in good yields.

Amine functionality is prevalent as a key motif in many biologically active natural products and has important applications in pharmaceuticals and agrochemicals.<sup>1,2</sup> Amides are naturally abundant or are easily synthesized from their carboxylic acid derivatives.<sup>3</sup> In this regard, the selective deoxygenative hydrogenation of amides offers an attractive route for amine synthesis.<sup>4,5</sup> However, with higher chemical inertness and competitive C–O/C–N cleavage of the amide bond, selective hydrogenative (C–O) cleavage is highly challenging. Thus, to activate and selectively deoxygenative hydrogenation of amides, Lewis acid additives are usually required along with the reducing agents. Several transition and main group metals, viz. Ru,<sup>6</sup> Ir,<sup>7,8</sup> Mn,<sup>4</sup> and Mg,<sup>9</sup> have been explored for the selective hydrogenation of secondary and tertiary amides using external Lewis acid additives in the presence of H<sub>2</sub> or silanes as a reductant. Furthermore, without the aid of an external Lewis acid, a few transition metal complexes were also found to catalyze the deoxygenative hydrogenation of various tertiary amides to amines using silanes as reductants.<sup>10–12</sup> In addition to that, some metal-free approaches have been reported for deoxygenative hydrogenation of various tertiary amides that rely on the use of a Lewis acidic boron catalyst and stoichiometric amounts of silane reagents or ammonia borane as the hydride source<sup>13–17</sup> (Scheme 1). Although the reported homogeneous catalysts or metal-free approaches were

found to be effective towards amide deoxygenative hydrogenation, a higher pressure of H<sub>2</sub> gas or higher silane concentration along with Lewis acid additives are required. Thus, the development of an active molecular catalyst appended with Lewis acidic functionality using a mild reductant is highly desirable for the selective amide deoxygenative hydrogenation to amines under additive-free conditions.

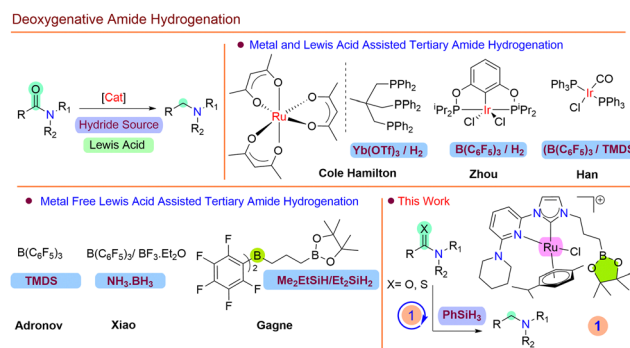
The design of homogeneous systems appended with Lewis acidic boranes in the secondary coordination sphere (SCS) has gained significant attention due to their unique ability to capture and activate various incoming substrate molecules during catalysis.<sup>18</sup> Several transition metal complexes with appended Lewis acidic arms in SCS (9-BBN, -Bpin, -BCy<sub>2</sub>) have been reported and utilized in various catalytic transformations like hydrazine activation,<sup>19,20</sup> CO<sub>2</sub> reduction,<sup>21</sup> alkyne hydrogenation,<sup>22</sup> nitrile activation,<sup>23</sup> etc.

In this work, we report the synthesis of a Ru-NHC complex **1** appended with pinacolboron as a Lewis acidic arm in the SCS, which was used as a catalyst for the selective hydrogenation of various tertiary amides and thioamides to amines in high yields using phenylsilane as a reductant. To the best of our knowledge, a well-characterized molecular catalyst with an appended Lewis acidic boron arm in SCS has not yet been

<sup>a</sup> Department of Chemical Sciences, Indian Institute of Science Education and Research Berhampur, Transit Campus, (Govt. ITI Building), Engg. School Junction, Berhampur 760010, Odisha, India. E-mail: pdaw@iiserbpr.ac.in

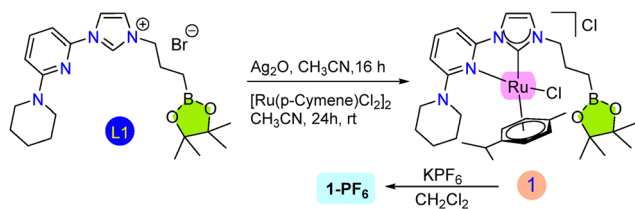
<sup>b</sup> Department of Industrial and Engineering Chemistry, Institute of Chemical Technology, Bhubaneswar 751013 Odisha, India

† Electronic supplementary information (ESI) available. CCDC 2346559 and 2349798. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d5cc00399g>



Scheme 1 Lewis acid-assisted amide hydrogenation.





Scheme 2 Synthesis of metal complexes.

utilized for the selective deoxygenative hydrogenation of tertiary amides and thioamides to amines.

Ligand **L1** was synthesized using piperidine-substituted pyridine imidazole with  $\text{Br}(\text{CH}_2)_3\text{Bpin}$  in dry acetonitrile (Scheme 2 and Fig. S27–S31, ESI<sup>†</sup>).<sup>24</sup> The molecular structure of **L1** is depicted in Fig. 1. The treatment of **L1** with  $\text{Ag}_2\text{O}$  followed by the addition of  $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$  in dry acetonitrile yielded complex **1** as a light yellow solid in 90% yield (Scheme 2). The formation of **1** was confirmed using  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{11}\text{B}$  and ESI-HRMS spectroscopic techniques (Fig. S44–S49, ESI<sup>†</sup>). Furthermore, treatment of complex **1** with 1.5 equiv. of  $\text{KPF}_6$  in dry  $\text{CH}_2\text{Cl}_2$  readily afforded the complex **1-PF<sub>6</sub>** as a light brown solid (Fig. S52–S59, ESI<sup>†</sup>). The single crystal data of **1-PF<sub>6</sub>** features a piano stool geometry around the cationic Ru-center where the appended boron arm remains as a pendant (Fig. 1). **1-BF<sub>4</sub>** was synthesized by the treatment of **1** with  $\text{AgBF}_4$  in acetonitrile (Fig. S75–S80, ESI<sup>†</sup>).

The catalytic reactivity of complex **1** was examined towards selective hydrogenation (C–O cleavage) of *N,N*-dimethylbenzamide (**4a**) to the corresponding amine (**5a**) (Table 1). The product **5a** was observed in 97% NMR yield using **1** (1 mol %),  $\text{PhSiH}_3$  (1.1 equiv. w.r.t. **4a**), and toluene (1 mL) at 80 °C for 36 h (entry 1, Table 1). The selectivity of the reaction was monitored by NMR and GC-MS analysis, where no C–N bond cleavage products (dimethylamine or benzyl alcohol) of **4a** were observed (Fig. S81, ESI<sup>†</sup>). A decreased yield of **5a** was observed by lowering the phenylsilane concentration, temperature and reaction time (entries 2–5). Varying other silanes and solvents resulted in a lower yield of **5a** (entries 6–8, Table 1 and details in Table S1, ESI<sup>†</sup>). No **5a** formation was observed in the absence of a catalyst (entry 9), while using **1-PF<sub>6</sub>** and **1-BF<sub>4</sub>**, 94% and 96% NMR yield of **5a** were detected (entries 10 and 11, Fig. S82 and S91, ESI<sup>†</sup>).

With the optimized conditions (Table 1, entry 1), the reduction of various tertiary amides was tested (Table 2).

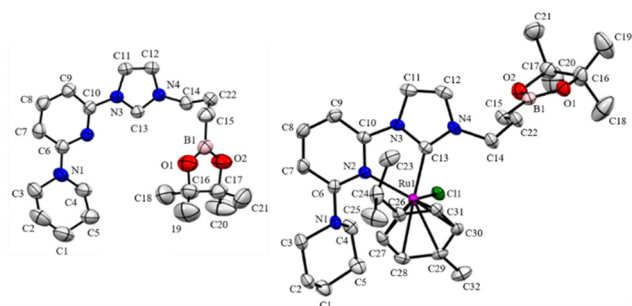


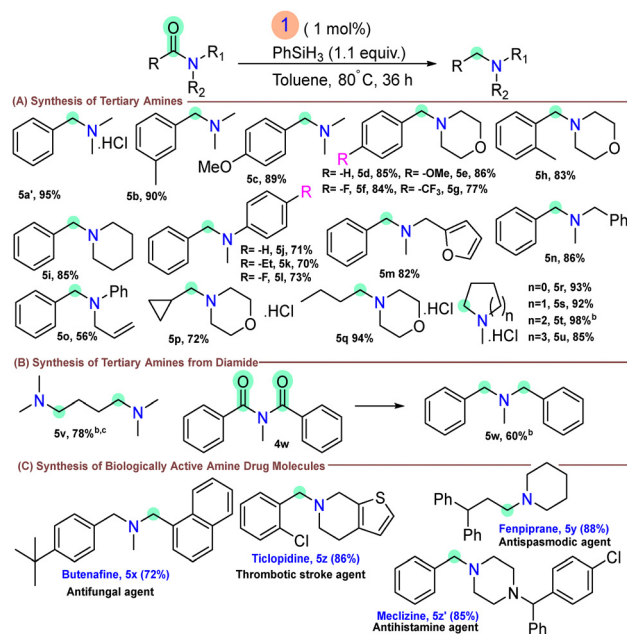
Fig. 1 Crystal structure of **L1** and **1-PF<sub>6</sub>**. Hydrogen atoms and counter anion are omitted for clarity.

Table 1 Optimization of deoxygenative hydrogenation of tertiary amides<sup>a</sup>

Entry	Catalyst (1 mol%)	Silanes (equiv.)	Yield <sup>b</sup> (%)
1	<b>1</b>	$\text{PhSiH}_3$ (1.1)	97
2	<b>1</b>	$\text{PhSiH}_3$ (1)	85
3	<b>1</b>	$\text{PhSiH}_3$ (0.8)	70
4 <sup>c</sup>	<b>1</b>	$\text{PhSiH}_3$ (1.1)	75
5 <sup>d</sup>	<b>1</b>	$\text{PhSiH}_3$ (1.1)	88
6	<b>1</b>	$\text{Ph}_2\text{SiH}_2$ (1.1)	55
7	<b>1</b>	$\text{Et}_3\text{SiH}$ (1.1)	NR
8 <sup>e</sup>	<b>1</b>	$\text{PhSiH}_3$ (1.1)	61
9	—	$\text{PhSiH}_3$ (1.1)	NR
10	<b>1-PF<sub>6</sub></b>	$\text{PhSiH}_3$ (1.1)	94
11	<b>1-BF<sub>4</sub></b>	$\text{PhSiH}_3$ (1.1)	96

<sup>a</sup> Reaction conditions: **4a** (0.503 mmol, 1 equiv.), catalyst (1 mol%), silane (*x* equiv. w.r.t. **4a**), solvent (1 mL), 80 °C, 36 h. <sup>b</sup> Product **5a** was detected by GC-MS and its yields were calculated by  $^1\text{H}$  NMR spectroscopy using mesitylene as the IS. <sup>c</sup> Reaction was performed at 60 °C. <sup>d</sup> Reaction was performed for 24 h. <sup>e</sup> THF as solvent. NR = no reaction.

Benzamide derivatives with electron-donating groups (–Me, –OMe) afforded good isolated yields (**5b–5c**). *N*-Benzoyl morpholine or piperidine substrates with electron-donating and -withdrawing substituents (–OMe, –Me, –F, –CF<sub>3</sub>) yielded the desired amines in 77–86% isolated yield (**5d–5i**). *N*-Methyl-*N*-phenylbenzamide (**4j**) with both electron-donating and -withdrawing groups (–Et, –F) yielded **5j–5l** in a moderate yield.

Table 2 Substrates scope for the hydrogenation of various tertiary amides to amines<sup>a</sup>

<sup>a</sup> Reaction conditions: amide (0.503 mmol, 1 equiv.), **1** (1 mol %),  $\text{PhSiH}_3$  (1.1 equiv. w.r.t. amide), toluene (1 mL), 36 h. Isolated yields. <sup>b</sup> Using 2.2 equiv. of  $\text{PhSiH}_3$ , 120 °C, 36 h. <sup>c</sup> NMR yield, mesitylene as the IS.

Further, amides bearing a benzylic phenyl, heterocyclic ring, alkene, strained 3-membered cyclopropane ring, aliphatic amide and cyclic lactam 5–8 membered rings were found to be compatible and the desired amines were isolated in good yields (**5m–5u**).

Interestingly, **5v–5w** was isolated in good to moderate yield *via* selective cleavage of both aliphatic and aromatic diamides **4v** and **4w** (Table 2b). The deoxygenative hydrogenation of secondary amide was also examined using complex **1**, where the NMR yield of 58% was achieved using *N*-phenylbenzamide as the substrate (Fig. S171–S173, ESI†). Furthermore, to demonstrate the practical applicability of the developed reaction protocol, a few biologically active tertiary amine drug molecules such as antimycotic agent, butenafine (**5x**); fempiprane (**5y**) having antiallergic and antispasmodic activity; thrombotic stroke agent, ticlopidine (**5z**); and antihistamine agent, meclizine (**5z'**) were prepared with good isolated yields under the optimized reaction conditions using catalyst **1** (Table 2c). A scale-up reaction of **4a** (3 mmol) was performed under the optimized reaction conditions, where 98% NMR yield of **5a** formation was achieved (Fig. S210, ESI†).

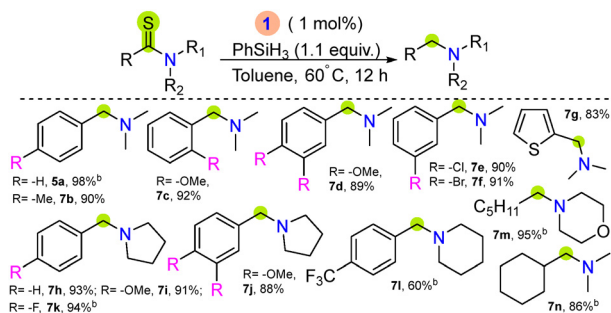
Furthermore, the catalytic efficiency of complex **1** was examined towards desulfurizative hydrogenation of tertiary thioamides. Thioamides are isosteres of amides found in many natural products and are versatile precursors for the synthesis of organic amines.<sup>25,26</sup> The reductive desulfurization of thioamides using transition metals with silanes or H<sub>2</sub> gas also offers an attractive pathway for amine generation, and a few reports have been disclosed.<sup>27–29</sup> The major challenges for such catalytic conversion include competitive C–S/C–N cleavage and catalyst poisoning in the presence of sulfur-containing molecules.<sup>27</sup> The optimal reaction conditions were achieved using 1 mol% of complex **1**, *N,N*-dimethylbenzothioamide, **6a** (0.503 mmol), 1.1 equiv. PhSiH<sub>3</sub> in dry toluene at 60 °C for 12 hours (Table S2, entry 5, and Fig. S92, ESI†) afforded 98% NMR yield of **5a**. Subsequently, the substrate scope for various tertiary thioamides was studied, where electron-donating and -withdrawing, heterocyclic, and aliphatic functionalized substrates afforded the corresponding amines in high yield under the optimized reaction conditions (Table 3). The hydrogenation

of primary thioamide was also examined using **1**, where dehydrosulfurizative product nitrile was observed, and no selective amine product was detected (Table S3 and Fig. S3B, ESI†).

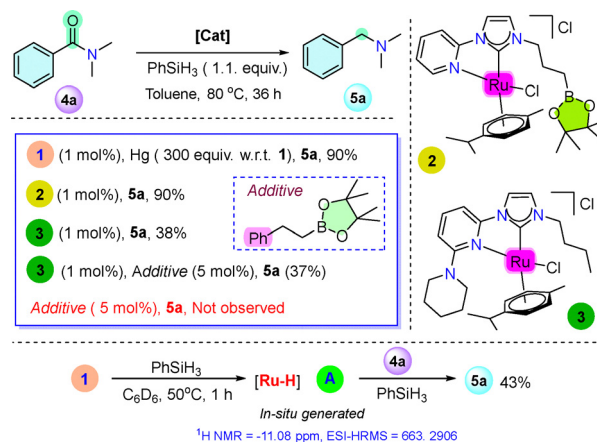
In order to get insight into the reaction mechanism, a series of control experiments were performed. To check the homogeneity of the catalytic process, a mercury drop experiment was performed (300 equiv. of Hg w.r.t. **1**), where a 90% NMR yield of amine **5a** was observed (Scheme 3 and Fig. S9, ESI†). Furthermore, to understand the role of the appended Lewis acidic pinacoloboron and Lewis basic piperidine arm in the SCS, two new ruthenium complexes **2** and **3** were synthesized (Scheme 3 and Fig. S61–S66, S68–S72, ESI†) and utilized for the deoxygenative hydrogenation of **4a** under the optimized reaction conditions, which afforded 90% and 38% of **5a**, respectively (Scheme 3 and Fig. S4, S5, ESI†). Furthermore, a catalytic reaction was performed using catalyst **3** and external alkyl-Bpin additives, Ph(CH<sub>2</sub>)<sub>2</sub>Bpin (5 mol%) under the optimized reaction conditions, where only 37% of **5a** was observed (Scheme 3 and Fig. S6, ESI†) whereas only Ph(CH<sub>2</sub>)<sub>2</sub>Bpin (5 mol%), **4a** and PhSiH<sub>3</sub> (1.1 equiv.) (without any metal complex) showed no amine **5a** formation (Scheme 3 and Fig. S7, ESI†).

Furthermore, treatment of catalyst **1** and PhSiH<sub>3</sub> (1:1) at 50 °C for 1 hour depicted a singlet peak at –11.08 ppm in C<sub>6</sub>D<sub>6</sub> and –12.25 ppm in CDCl<sub>3</sub> in <sup>1</sup>H NMR corresponding to the Ru–H intermediate (**A**), additionally a peak at *m/z* = 633.2906 was also observed in ESI-HRMS analysis (Fig. S10–S12, ESI†). Furthermore, to examine the active role of Ru–H an NMR scale stoichiometric reaction was performed where an *in situ* generated intermediate (**A**) (**1** and PhSiH<sub>3</sub> (1:1) in C<sub>6</sub>D<sub>6</sub>) was treated with amide **4a** (1 equiv.), and heating for 1 hour at 80 °C, almost full formation of amine **5a** was observed in <sup>1</sup>H NMR (Fig. S13, ESI†). Additionally, intermediate (**A**) was generated using 1 mol% of **1** and PhSiH<sub>3</sub> in an NMR tube and was transferred into a reaction containing amide **4a** (1 mmol) and PhSiH<sub>3</sub> (0.5 mmol) in toluene and heated at 80 °C for 36 hours, affording a 43% NMR yield of amine **5a** (Fig. S14, ESI†). These results depicted that intermediate (**A**) might act as an active intermediate during the catalytic process. A variable temperature (from

**Table 3** Substrate scope for the hydrogenation of tertiary thioamides to amines<sup>ab</sup>



<sup>a</sup> Reaction conditions: tertiary thioamide (0.503 mmol, 1 equiv.), **1** (1 mol %), PhSiH<sub>3</sub> (1.1 equiv. w.r.t. thioamide), toluene (1 mL), 12 h. Isolated yields. <sup>b</sup> NMR yield using mesitylene as IS.



**Scheme 3** Control experiments.



25 °C to −40 °C) NMR experiment was performed with a 1 : 10 mixture of **1** and amide **4a** in acetone- $d_6$ ; however, no significant change was observed in  $^1\text{H}$  and  $^{11}\text{B}$  NMR. However, variable temperature NMR studies (25 °C to −20 °C) with a 1 : 20 mixture of **1** and aliphatic amide, *N,N*-dimethylacetamide (DMA), revealed a minor peak at 22.48 ppm in  $^{11}\text{B}$  NMR upon lowering the temperature to −20 °C (Fig. S217, ESI†). Furthermore, using **1** with an excess of DMA, a peak at 22.29 ppm was observed in  $^{11}\text{B}$  NMR at room temperature (Fig. S218, ESI†),<sup>30</sup> and under optimized reaction conditions, 87% NMR yield of *N,N*-dimethylethanamine was observed (Fig. S220, ESI†). Moreover, a strong interaction was observed using a mixture of **1** and dimethylaminopyridine (DMAP) (1 : 5), where a significant up-field shift in  $^1\text{H}$  NMR was observed for methylene (−CH<sub>2</sub>) protons (0.91 to 0.47 ppm) adjacent to the −Bpin arm upon decreasing the temperature, whereas  $^{11}\text{B}$  NMR showed an up-field shift from 32.30 to 12.80 ppm (Fig. S16 and S17, ESI†).<sup>31</sup> These results depicted that the appended Lewis acidic boron arm in SCS of complex **1** can act as a directing group for substrate binding and activation during catalysis. An ESI-HRMS control experiment was performed using a 1 : 1 : 1 mixture of **1**, PhSiH<sub>3</sub>, and **4a** in toluene at 60 °C, where the formation of amine **5a** was observed within 10 minutes, and the Ru-H intermediate (**A**) ( $m/z$  = 633.2906) was detected. Additionally, a peak at  $m/z$  = 802.3511 corresponding to amine **5a** bound Ru-complex [**1**-Cl<sup>−</sup> + **5a**]<sup>+</sup> was also observed (Fig. S18, ESI†). 1,3-Diphenyldisiloxane, (PhSiH<sub>2</sub>)<sub>2</sub>O, and polysiloxanes were identified in ESI-HRMS as by-products during the catalysis. The treatment of (PhSiH<sub>2</sub>)<sub>2</sub>O and **4a** in the presence of catalyst **1** afforded 35% of **5a** under the optimized catalytic conditions, depicting that (PhSiH<sub>2</sub>)<sub>2</sub>O also acts as an active hydride source (Fig. S19 and S216, ESI†).<sup>32,33</sup>

Based on control experiments and previous reports on Lewis acid-assisted amide deoxygenative hydrogenation,<sup>4,6,7,13,15–17</sup> a plausible mechanism was proposed (Fig. S221, ESI†). The [Ru-H] (**A**) might be the active species during the catalytic cycle and facilitate hydride insertion into the amide, which can be activated by the appended boron Lewis acid arm of the catalyst<sup>13,17</sup> along with the silane intermediate. The phenylsilane can regenerate the active [Ru-H] (**A**) via a  $\sigma$ -bond metathesis pathway<sup>33</sup> and affords disiloxane, which might further act as a hydride source with the formation of polysiloxanes during the catalytic cycle, and subsequent hydride transfer from (**A**) affords the desired amine product.

In summary, a bifunctional Ru-NHC complex **1** was synthesized and utilized as an efficient catalyst for the selective hydrogenation of various tertiary amides and thioamides to amines under ambient conditions. The catalytic protocol was also utilized to synthesize biologically relevant amine drug molecules in good yield. The presence of Lewis acid in the

SCS of complex **1** was found to enhance the catalytic activity via substrate activation.

P. D. thanks IISER Berhampur, Central Advance Instrument Facility (CAIF), and ANRF, SERB, DST India for the core research grant (CRG/2023/001880) for financial support. RS thanks IISER Berhampur for the fellowship. R. D. and G. K. assisted with SCXRD studies.

## Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for **L1** and **1-PF<sub>6</sub>** have been deposited in the CCDC, and the CCDC numbers are 2346559 and 2349798, respectively.†

## Conflicts of interest

There are no conflicts to declare.

## References

- 1 K. Eller, *et al.*, *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, 2015, pp. 1–55.
- 2 A. Ricci, *Modern Amination Methods*, Wiley-VCH, Weinheim, 2000.
- 3 R. M. Lanigan and T. D. Sheppard, *Eur. J. Org. Chem.*, 2013, 7453–7465.
- 4 Y. Q. Zou, *et al.*, *ACS Catal.*, 2018, **8**, 8014–8019.
- 5 A. M. Smith and R. Whyman, *Chem. Rev.*, 2014, **114**, 5477–5510.
- 6 J. Coetzee, *et al.*, *Chem. – Eur. J.*, 2013, **19**, 11039–11050.
- 7 M. L. Yuan, *et al.*, *ACS Catal.*, 2016, **6**, 3665–3669.
- 8 F. Han, *et al.*, *Sci. China: Chem.*, 2023, **66**, 1094–1100.
- 9 N. L. Lampland, *et al.*, *ACS Catal.*, 2015, **5**, 4219–4226.
- 10 S. Park and M. Brookhart, *J. Am. Chem. Soc.*, 2012, **134**, 640–653.
- 11 S. Pisiewicz, *et al.*, *Chem. – Eur. J.*, 2014, 2345–2349.
- 12 C. M. Macaulay, *et al.*, *Dalton Trans.*, 2019, **48**, 9581–9587.
- 13 D. Mukherjee, *et al.*, *Angew. Chem., Int. Ed.*, 2016, **55**, 13326–13329.
- 14 R. C. Chadwick, *et al.*, *J. Org. Chem.*, 2014, **79**, 7728–7733.
- 15 A. Chardon, *et al.*, *Chem. – Eur. J.*, 2017, **23**, 2005–2009.
- 16 Y. Pan, *et al.*, *Adv. Synth. Catal.*, 2019, **361**, 2301–2308.
- 17 M. T. Peruzzi, *et al.*, *Chem. Commun.*, 2018, **54**, 5855–5858.
- 18 M. W. Drover, *Chem. Soc. Rev.*, 2022, **51**, 1861–1880.
- 19 J. J. Kiernicki, *et al.*, *Inorg. Chem.*, 2019, **58**, 1147–1154.
- 20 O. Tutusaus, *et al.*, *J. Am. Chem. Soc.*, 2013, **135**, 3403–3406.
- 21 E. E. Norwine, *et al.*, *J. Am. Chem. Soc.*, 2022, **144**, 15038–15046.
- 22 K. N. T. Tseng, *et al.*, *J. Am. Chem. Soc.*, 2016, **138**, 10378–10381.
- 23 M. L. Clapson, *et al.*, *Chem. – Eur. J.*, 2023, **29**, e202203763.
- 24 M. Toure, *et al.*, *Dalton Trans.*, 2015, **44**, 7139–7143.
- 25 R. N. Hurd and G. Delamater, *Chem. Rev.*, 1961, **61**, 45–86.
- 26 T. N. Hansen and C. A. Olsen, *Chem. – Eur. J.*, 2024, **30**, e202303770.
- 27 Z. Wang, *et al.*, *Angew. Chem., Int. Ed.*, 2023, **62**, e202215963.
- 28 J. Luo, *et al.*, *J. Am. Chem. Soc.*, 2020, **142**, 21628–21633.
- 29 K. Fukumoto, *et al.*, *Organometallics*, 2013, **32**, 2889–2892.
- 30 J. Li, *et al.*, *J. Am. Chem. Soc.*, 2020, **142**, 13011–13020.
- 31 F. Lima, *et al.*, *Angew. Chem., Int. Ed.*, 2016, **55**, 14085–14089.
- 32 J. A. Buonomo, *et al.*, *Synthesis*, 2018, **50**, 278–281.
- 33 P. Pandey and J. K. Bera, *Chem. Commun.*, 2021, **57**, 9204–9207.

