Ir-Catalyzed Reversible Acceptorless Dehydrogenation/Hydrogenation of *N*-Substituted and Unsubstituted Heterocycles Enabled by a Polymer-Cross-Linking Bisphosphine

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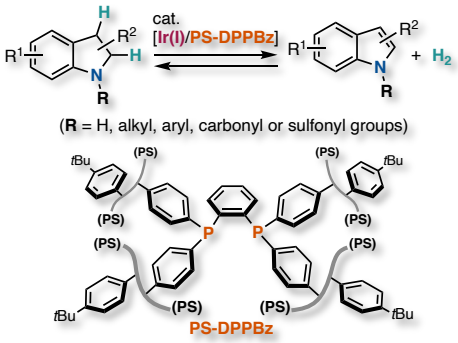
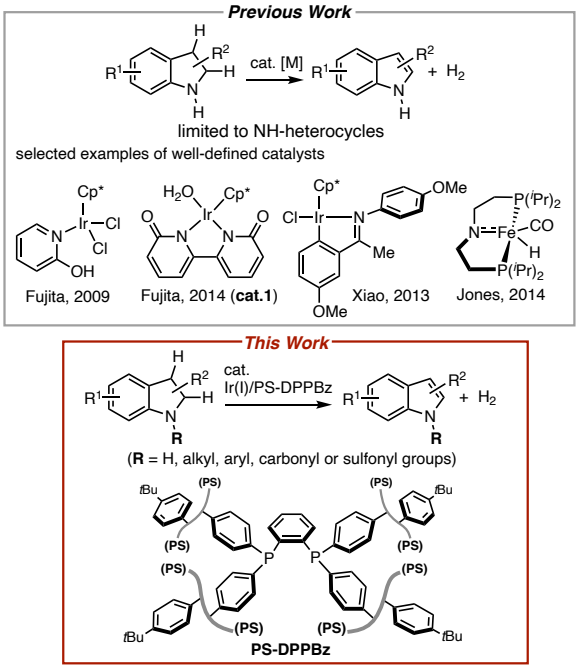


ABSTRACT: The polystyrene-cross-linking bisphosphine ligand PS-DPPBz was effective for the Ir-catalyzed reversible acceptorless dehydrogenation/hydrogenation of *N*-heterocycles. Notably, this protocol is applicable to the dehydrogenation of *N*-substituted indoline derivatives with various *N*-substituents with different electronic and steric natures. A reaction pathway involving oxidative addition of an *N*-adjacent C(sp^3)–H bond to a bisphosphine-coordinated Ir(I) center is proposed for the dehydrogenation of *N*-substituted substrates.

The dehydrogenation of *N*-heterocycles is a fundamentally important transformation for the construction of unsaturated heterocycles, such as indoles and quinolines, that are found in biological molecules.[1] Typically, these transformations can be achieved through the stoichiometric use of strong oxidants such as DDQ and $KMnO_4$ or through catalytic reactions employing olefinic hydrogen acceptors in stoichiometric amounts.[2] Compared to these reactions, catalytic acceptorless dehydrogenations can be cleaner and atom-economical processes, producing only molecular hydrogen as a side product.[3,4] In addition, catalytic acceptorless dehydrogenation has the potential to be a chemical hydrogen storage process.[5] The pioneering work by Fujita et al. shows promising efficiency of metal-ligand bifunctional Ir(III) catalysts with 2-hydroxypyridine-type ancillary ligands (Scheme 1, top).[3a,d,h] Importantly, the same catalyst systems were able to promote hydrogenation as a backward reaction, demonstrating the reversibility of the process. Later, Jones and co-workers reported iron and cobalt catalyst systems for similar reversible processes,[3e,g] while Xiao and co-workers developed a cyclometalated imino-Ir(III) catalyst.[3c] Regardless of these advances, the catalytic acceptorless dehydrogenation/hydrogenation of *N*-heterocycles is largely limited to reactions involving heterocyclic compounds with one or more free N–H bonds. Although several novel protocols have emerged more recently for the dehydrogenation of *N*-substituted heterocycles using photoredox catalysts in combination with a cobalt or a palladium catalyst,[6] a frustrated Lewis pair catalyst,[7] or a quinone catalyst,[8] electron-withdrawing groups on the N atom such as acetyl or tosyl groups completely inhibited the reaction.

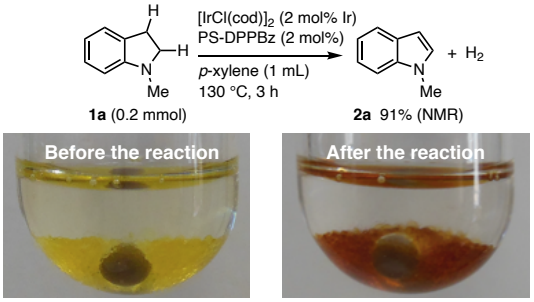
Here, we report the heterogeneous catalytic acceptorless dehydrogenation of *N*-heterocycles enabled by a combination of $[IrCl(cod)]_2$ and the polystyrene-cross-linking bisphosphine PS-DPPBz (Scheme 1, bottom).[9] Applicability toward indoline-type *N*-heterocycles with electron-donating or -withdrawing *N*-substituents is a notable feature of this catalysis. The same (PS-DPPBz)-Ir catalyst system also promoted backward hydrogenation of *N*-heteroarenes with molecular hydrogen.

Scheme 1. Acceptorless Dehydrogenation by Transition Metals



The acceptorless dehydrogenation of *N*-methylindoline (**1a**) in the presence of $[IrCl(cod)]_2$ (2 mol% Ir) and PS-DPPBz (2 mol%) proceeded in *p*-xylene at 130 °C over 3 h to give *N*-methylindole (**2a**) in 91% NMR yield (Scheme 2).[10] The commercially available Fujita's bipyridonate-Cp*Ir(III) catalyst (**cat.1**, structure shown in Scheme 1) also caused the dehydrogenation of **1a** under the same condition but in a substantially lower yield (47%) than that with the (PS-DPPBz)-Ir catalyst.

Scheme 2. Ir-Catalyzed Acceptorless Dehydrogenation of *N*-Methylindoline (1a)



During the reaction with (PS-DPPBz)-Ir catalyst, the polymer-bound catalyst changed its color from yellow to dark red, while the solution phase remained colorless (Scheme 2). This observation indicates that virtually all Ir species was retained in the polymer matrix. The recovered catalyst was reusable for the dehydrogenation albeit with significant reduction in the product yield (1st run, 87%; 2nd run, 52%; 3rd run, 46%). The decrease in the activity of the recovered catalysts should be due to partial structure change of the polymer-bound catalyst to an inactive form rather than to metal leaching as the solution remained colorless. The ^{31}P CP/MAS NMR signal of the recovered catalyst appeared with nearly the same chemical shift value to that of the (PS-DPPBz)-Ir catalyst precursor but with apparent broadening.[11]

The use of the polymer ligand PS-DPPBz is crucial for efficient dehydrogenation of **1a** (Figure 1). The soluble counterpart of PS-DPPBz, 1,2-bis(diphenylphosphino)benzene (DPPBz), induced only a little activity, indicating the critical importance of the polystyrene cross-linking. Introduction of sterically demanding substituents (*t*Bu) on the *P*-Ph groups (SciOPP) of the soluble ligand DPPBz increased its catalytic activity, but the yield was much lower than that with PS-DPPBz (16% vs 91%). DPPE, DEtPE and DCyPE with an ethylene linker between the two P atoms were also less effective. Larger bite-angle bisphosphines (Xantphos), monophosphines (PPh_3) and bipyridine-based ligands (dtbpy) exhibited no catalytic activity.[12]

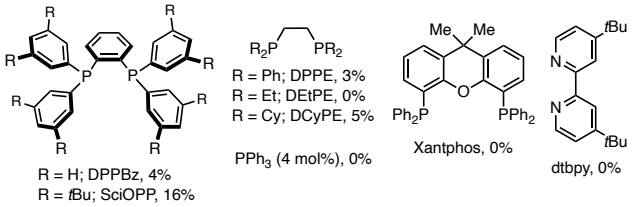


Figure 1. Effect of Homogeneous Ligands on the Yield of Dehydrogenation of **1a**. Conditions: **1a** (0.2 mmol), $[IrCl(cod)]_2$ (2 mol% Ir), ligand (2 mol%), *p*-xylene (1 mL), 130 °C, 3 h. Yield of **2a** was determined by ^1H NMR analysis of the crude product.

Next, we examined the scope of *N*-substituted indolines with the (PS-DPPBz)-Ir system (4 mol% Ir, *p*-xylene, 130–160 °C, 10–48 h, Scheme 3). Not only electron-neutral (**2b**) and donating (**2c**) substituents but also electron-withdrawing chloro and nitro (**2d** and **2e**) substituents were tolerated in the carbon framework of the *N*-methylindoline scaffold. *cis*-1,2,3-Trimethylindoline (*cis*-**1f**) underwent efficient dehydrogenation, while its *trans* isomer did not participate in the dehydrogenation at all, indicating that the *cis* arrangement of the two vicinal hydrogen atoms was crucial for the dehydrogenation.

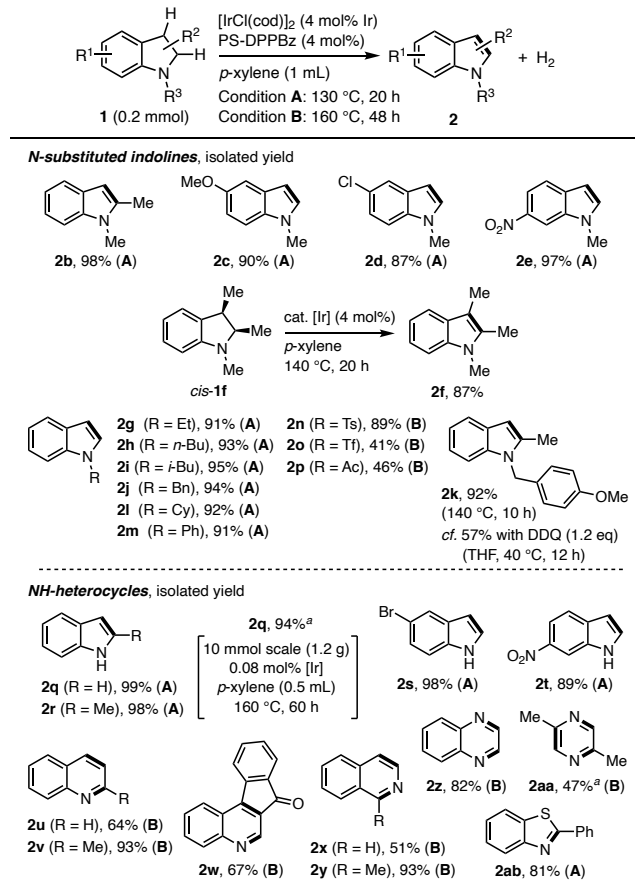
Importantly, various *N*-substituents were tolerated in the indoline scaffold (**2g-2p**). Even in the presence of β-hydrogen atoms in the *N*-alkyl substituent as in Et, *n*-Bu, *i*-Bu and Cy groups, the dehydrogenation occurred at the indoline ring with exclusive site-selectivity. It is also noteworthy that branching was tolerated at the positions α or β to the N atom. Thus, this protocol is useful for the synthesis of *N*-alkylindoles since the direct *N*-alkylation of indole derivatives under basic conditions often suffers from competitive elimination reactions of the alkylating reagents.[13] Moreover, the reaction of **1k** bearing a 4-methoxybenzyl group at the N atom, which should be sensitive to the oxidation conditions, occurred cleanly to give **2k** in high yield, while the oxidation with stoichiometric DDQ (in THF at 40 °C for 12 h) produced **2k** in only 57% yield along with unidentified

byproducts. A phenyl group on the N atom was also tolerated (**2m**).

The indoline (**1n**) with a strongly electron-withdrawing *N*-tosyl group underwent efficient dehydrogenation to give **2n** in 89% yield, whereas Fujita's catalyst **cat.1** did not promote the reaction. *N*-Trifluoromethylsulfonyl or *N*-acyl-substituted indolines were also suitable substrates (**1o** and **1p**) although the yields were moderate.

The (PS-DPPBz)-Ir catalyst system is also applicable to the acceptorless dehydrogenation of NH-heterocycles (**1q**-**1ab**). The reaction of **1q** was conducted on a gram-scale with a reduced catalyst loading of 0.08 mol% (10 mmol scale, 94% NMR yield, TON 1175) with reasonable hydrogen gas release (~210 mL, 94% based on H_2). Two- or three-fold dehydrogenation occurred from tetrahydroquinoline-, tetrahydroisoquinoline-, tetrahydroquinoxaline- and piperazine-type substrates to give the corresponding *N*-heteroarenes. 2-Phenyl-2,3-dihydrobenzothiazole (**1ab**) also participated in this reaction.

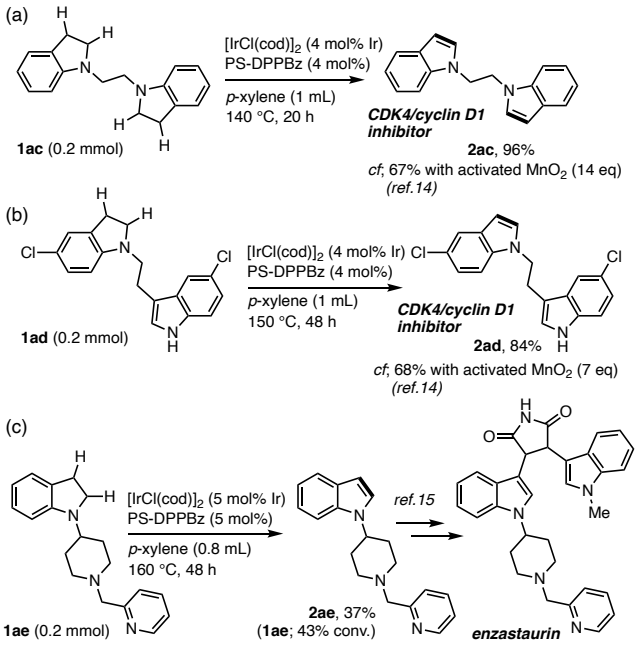
Scheme 3. Scope of *N*-Heterocycles for Acceptorless Dehydrogenation



Reaction conditions: **1** (0.2 mmol), $[IrCl(cod)]_2$ (4 mol% Ir), PS-DPPBz (4 mol%), *p*-xylene (1 mL), 130 °C, 20 h (condition **A**) or 160 °C, 48 h (condition **B**). Isolated yields are shown. [a]Yields are determined by ^{1}H NMR analysis of the crude product.

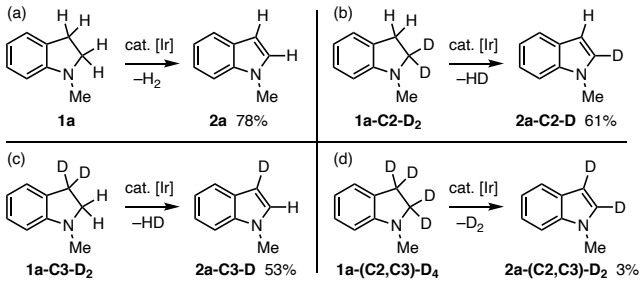
To demonstrate the utility of this catalytic acceptorless dehydrogenation, we applied the protocol to the synthesis of pharmacologically active molecules having *N*-substituted indoline scaffolds. The dehydrogenation of indolines **1ac** and **1ad** proceeded smoothly to provide CDK4/cyclin D1 inhibitors **2ac** and **2ad**, respectively, in high yields (Scheme 4a,b). When the corresponding dehydrogenative transformations were conducted using a large excess of activated MnO_2, the yields were only moderate.[14] Compound **1ae**, having piperidine and pyridine moieties, was transformed to the precursor of enzastaurin (**2ae**)[15] in 37% yield (5 mol% Ir, 43% conv. of **1ae**, Scheme 4c).

Scheme 4. Synthesis of Pharmacologically Active Molecules



To gain insights into the mechanism, the reactions of deuterated *N*-methylindolines were conducted. The dehydrogenation of 2,2- and 3,3-di-deuterated *N*-methylindolines [2 mol% (PS-DPPBz)-Ir, 130 °C, for 2 h] proceeded at only slightly reduced rates compared to that of nondeuterated *N*-methylindoline (61% and 53% ^{1}H NMR yields vs. 78%, Scheme 5a–c). A deuteration effect in the reaction of 2,2,3,3-tetradeuterated *N*-methylindoline (3%, Scheme 5d) was much more significant than expected from the combination of the effects of the deuteration at the C2 and C3 positions.

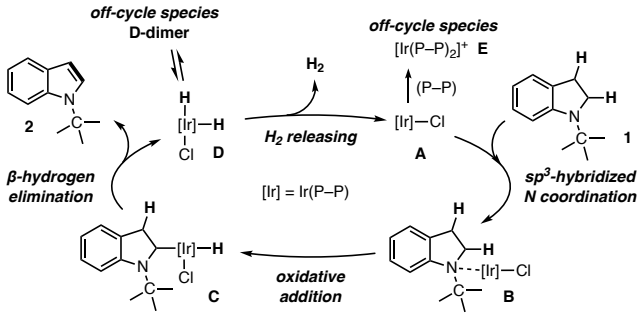
Scheme 5. Deuterium Isotope Experiments



Conditions: **1** (0.2 mmol), $[IrCl(cod)]_2$ (2 mol% Ir), PS-DPPBz (2 mol%), *p*-xylene (1 mL), 130 °C, 2 h. Yield was determined by ^{1}H NMR analysis of the crude product.

A possible reaction pathway for the (PS-DPPBz)-Ir-catalyzed acceptorless dehydrogenation of *N*-substituted indolines (**1**) is given in Scheme 6, which is distinct from the well-established pathway for the acceptorless dehydrogenation of NH-heterocycles, in which metal–ligand cooperation is essential for NH deprotonation and H_2 release from the catalyst as in Fujita's Cp*Ir(III) catalyst system.[16] The reaction starts from a coordination of the N atom of **1** to bisphosphine-Ir(I) complex **A**. Oxidative addition of an *N*-adjacent C(sp^3)–H bond to the indoline-bound Ir(I) center in **B** gives Ir(III) monohydride **C**.[17,18] Subsequent β-hydrogen elimination provides dehydrogenated product **2** and Ir(III) dihydride species **D**.[19] The stereochemical requirement of the *cis*-arrangement of the two hydrogen atoms at the C2 and C3 positions evidenced by the reaction of *cis*- and *trans*-**1f** (Scheme 3) is supportive of the involvement of this step. Finally, H_2 is released from **D** with the regeneration of **A**.

Scheme 6. Plausible Reaction Pathway

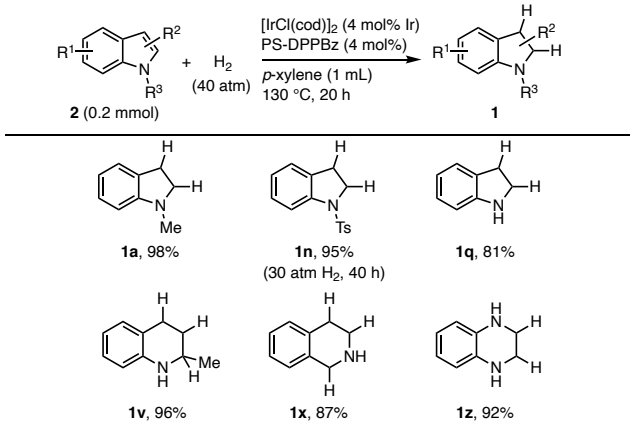


Based on the proposed reaction pathway and the KIE profiles obtained in the experiments with the C2- and/or C3- deuterated **1a** derivatives (Scheme 5), the oxidative addition (**B** to **C**) and the β-hydride elimination (**C** to **D**) steps should not be critical in determining the overall reaction rate. Thereby, the step of hydrogen release from the dihydridoiridium species (**D**), which involves dissociation of two Ir–D bonds, is likely the most influential.

As proven in our prior studies on the beneficial use of PS-DPPBz for the first-row transition metal catalysis,[9] the bisphosphine motif of PS-DPPBz should be spatially isolated in the polymer matrix swollen in the organic medium. We assume that this property would be preserved in the present iridium catalysis, rendering the (PS-DPPBz)-Ir catalytic center more resistant from the formation of inactive species such as bischelated (tetra-P-coordinated) iridium(I) complex (**E**)[20] and a dimer of chlorodihydridoiridium(III) complex (**D-dimer**)[21] than the homogeneous system.[22]

In view of the potential for organic hydride hydrogen storage, the development of efficient methods for reversible acceptorless dehydrogenation and hydrogenation with the same catalyst remains an important challenge.[5] Thus, the applicability of the (PS-DPPBz)-Ir system for hydrogenation of *N*-heteroarenes with molecular hydrogen, as the backward reaction of dehydrogenation, was examined. As illustrated in Scheme 7, a variety of *N*-substituted and unsubstituted indoles (**2a**, **2n** and **2q**) and six-membered heteroarenes (**2v**, **2x** and **2z**) were hydrogenated in high yields at 30 or 40 atm H_2 pressure.

Scheme 7. Hydrogenation of *N*-Heteroarenes



Conditions: **2** (0.2 mmol), $[IrCl(cod)]_2$ (4 mol% Ir), PS-DPPBz (4 mol%), H_2 (40 atm), *p*-xylene (1 mL), 130 °C, 40 h. Isolated yields are shown.

In summary, a polystyrene-cross-linking bisphosphine-Ir complex (PS-DPPBz)-Ir showed high activities for the acceptorless dehydrogenation of *N*-heterocycles. The protocol is applicable to the dehydrogenation of *N*-substituted indoline-type substrates, applicability to which has not been well explored with the reported catalytic systems. A catalytic reaction pathway involving oxidative addition of the *N*-adjacent C(sp^3)–H bond to the bisphosphine-Ir(I) species is proposed. The same Ir catalyst was applicable to backward hydrogenation of *N*-heteroarenes with molecular hydrogen. Further applications of this protocol for organic synthesis and hydrogen storage are in progress.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: ################.

Experimental procedures and the characterization of all new compound (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant Number JP17H04877 in Young Scientists (A), JP20H04793 in Hybrid Catalysis and the Iwatani Naoji Foundation to T.I., and by JSPS KAKENHI Grant Number JP15H05801 in Precisely Designed Catalysts with Customized Scaffolding and JP18H03906 in Grant-in-Aid for Scientific Research (A) to M.S. D.Z. thanks JSPS for a scholarship support. We thank Prof. Atsushi Kobayashi and Mr. Nobutaka Yoshimura (Hokkaido University) for the GC measurement.

REFERENCES

(1) (a) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. Biomedical Importance of Indoles. *Molecules* **2013**, *18*, 6620–6662. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274.

(2) (a) Dobereiner, G. E.; Crabtree, R. H. Dehydrogenation as a Substrate-Activating Strategy in Homogeneous Transition-Metal Catalysis. *Chem. Rev*. **2010**, *110*, 681–703. (b) Choi, J.; MacArthur, A. H. R.; Brookhart, M.; Goldman, A. S. Dehydrogenation and Related Reactions Catalyzed by Iridium Pincer Complexes. *Chem. Rev.* **2011**, *111*, 1761–1779.

(3) For the homogeneous catalysis, see: (a) Yamaguchi, R.; Ikeda, C.; Takahashi, Y.; Fujita, K. Homogeneous Catalytic System for Reversible Dehydrogenation-Hydrogenation Reactions of Nitrogen Heterocycles with Reversible Interconversion of Catalytic Species. *J. Am. Chem. Soc.* **2009**, *131*, 8410–8412. (b) Muthaiah, S.; Hong, S. H. Acceptorless and Base-Free Dehydrogenation of Alcohols and Amines using Ruthenium-Hydride Complexes. *Adv. Synth. Catal*. **2012**, *354*, 3045–3053. (c) Wu, J.; Talwar, D.; Johnston, S.; Yan, M.; Xiao, J. Acceptorless Dehydrogenation of Nitrogen Heterocycles with a Versatile Iridium Catalyst. *Angew. Chem., Int. Ed.* **2013**, *52*, 6983–6987. (d) Fujita, K.; Tanaka, Y.; Kobayashi, M.; Yamaguchi, R. Homogeneous Perdehydrogenation and Perhydrogenation of Fused Bicyclic N-Heterocycles Catalyzed by Iridium Complexes Bearing a Functional Bipyridonate Ligand. *J. Am. Chem. Soc.* **2014**, *136*, 4829–4832. (e) Chakraborty, S.; Brennessel, W. W.; Jones, W. D. A Molecular Iron Catalyst for the Acceptorless Dehydrogenation and Hydrogenation of *N*-Heterocycles. *J. Am. Chem. Soc.* **2014**, *136*, 8564–8567. (f) Manas, M. G.; Sharninghausen, L. S.; Lin, E.; Crabtree, R. H. Iridium Catalyzed Reversible Dehydrogenation–Hydrogenation of Quinoline Derivatives under Mild Conditions. *J. Organomet. Chem*. **2015**, *792*, 184–189. (g) Xu, R.; Chakraborty, S.; Yuan, H.; Jones, W. D. Acceptorless, Reversible Dehydrogenation and Hydrogenation of *N*-Heterocycles with a Cobalt Pincer Catalyst. *ACS Catal.* **2015**, *5*, 6350–6354. (h) Fujita, K.; Wada, T.; Shiraishi, T. Reversible Interconversion between 2,5-Dimethylpyrazine and 2,5-Dimethylpiperazine by Iridium-Catalyzed Hydrogenation/Dehydrogenation for Efficient Hydrogen Storage. *Angew. Chem., Int. Ed.* **2017**, *56*, 10886–10889. (i) Vivancos, Á.; Beller, M.; Albrecht, M. NHC-Based Iridium Catalysts for Hydrogenation and Dehydrogenation of *N*-Heteroarenes in Water under Mild Conditions. *ACS Catal.* **2018**, *8*, 17–21.

(4) For the selected heterogeneous catalysis, see: (a) Mikami, Y.; Ebata, K.; Mitsudome, T.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. Reversible Dehydrogenation-Hydrogenation of Tetrahydroquinoline-Quinoline Using a Supported Copper Nanoparticle Catalyst. *Heterocycles* **2011**, *2*, 1371–1377. (b) Moromi, S. K.; Siddiki, S. M. A. H.; Kon, K.; Toyao, T.; Shimizu, K. Acceptorless Dehydrogenation of *N*-Heterocycles by Supported Pt Catalysts. *Catal. Today*. **2017**, *281*, 507–511. (c) Deraedt, C.; Ye, R.; Ralston, W. T.; Toste, F. D.; Somorjai, G. A. Dendrimer-Stabilized Metal Nanoparticles as Efficient Catalysts for Reversible Dehydrogenation/Hydrogenation of *N*-Heterocycles. *J. Am. Chem. Soc.* **2017**, *139*, 18084–18092. (d) Jaiswal, G.; Landge, V. G.; Jagadeesan, D.; Balaraman, E. Iron-Based Nanocatalyst for the Acceptorless Dehydrogenation Reactions. *Nat. Commun.* **2017**, *8*, 2147.

(5) (a) Sartbaeva, A.; Kuznersov, V. L.; Wells, S. A.; Edward, P. P. Hydrogen Nexus in a Sustainable Energy Future. *Energy Environ. Sci*. **2008**, *1*, 79–85. (b) Eberle, U.; Felderhoff, M.; Schüth, F. Chemical and Physical Solution for Hydrogen Storage. *Angew. Chem., Int. Ed.* **2009**, *48*, 6608–6630. (c) Armaroli, N.; Balzani, V. The Hydrogen Issue. *ChemSusChem*, **2011**, *4*, 21–36. (d) Preuster, P.; Papp, C.; Wasserscheid, P. Liquid Organic Hydrogen Carriers (LOHCs): Toward a Hydrogen-free Hydrogen Economy. *Acc. Chem. Res.* **2017**, *50*, 74–85.

(6) (a) Kato, S.; Saga, Y.; Kojima, M.; Fuse, H.; Matsunaga, S.; Fukatsu, A.; Kondo, M.; Masaoka, S.; Kanai, M. Hybrid Catalysis Enabling Room-Temperature Hydrogen Gas Release from *N*-Heterocycles and Tetrahydronaphthalenes. *J. Am. Chem. Soc.* **2017**, *139*, 2204–2207. (b) He, K.-H.; Tan, F.-F.; Zhou, C.-Z.; Zhou, G.-J.; Yang, X.-L.; Li, Y. Acceptorless Dehydrogenation of *N*-Heterocycles by Merging Visible Light Photoredox Catalysis and Cobalt Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 3080–3084. For a highlight review, see: (c) Yin, Q.; Oestreich, M. Photocatalysis Enabling Acceptorless Dehydrogenation of Benzofused Saturated Rings at Room Temperature. *Angew. Chem., Int. Ed.* **2017**, *56*, 7716–7718.

(7) Maier, A. F. G.; Tussing, S.; Schneider, T.; Flörke, U.; Qu, Z.-W.; Grimme, S.; Paradies, J. Frustrated Lewis Pair Catalyzed Dehydrogenative Oxidation of Indolines and Other Heterocycles. *Angew. Chem., Int. Ed.* **2016**, *55*, 12219–12223.

(8) (a) Wendlandt, A. E.; Stahl, S. S. Bioinspired Aerobic Oxidation of Secondary Amines and Nitrogen Heterocycles with a Bifunctinal Quinone Catalyst. *J. Am. Chem. Soc.* **2014**, *136*, 506–512. (b) Wendlandt, A. E.; Stahl, S. S. Modular *o*-Quinone Catalyst System for Dehydrogenation of Tetrahydroquinolines under Ambient Conditions. *J. Am. Chem. Soc.* **2014**, *136*, 11910−11913. (c) Wendlandt, A. E.; Stahl, S. S. Quinone-Catalyzed Selective Oxidation of Organic Molecules. *Angew. Chem., Int. Ed.* **2015**, *54*, 14638−14658. (d) Li, B.; Wendlandt, A. E.; Stahl, S. S. Replacement of Stoichiometric DDQ with a Low Potential *o*-Quinone Catalyst Enabling Aerobic Dehydrogenation of Tertiary Indolines in Pharmaceutical Intermediates. *Org. Lett.* **2019**, *21*, 1176–1181.

(9) (a) Iwai, T.; Harada, T.; Shimada, H.; Asano, K.; Sawamura, M. A Polystyrene-Cross-Linking Bisphosphine: Controlled Metal Monochelation and Ligand-Enabled First-Row Transition Metal Catalysis. *ACS Catal*. **2017**, *7*, 1681–1692. (b) Yamazaki, Y.; Arima, N.; Iwai, T.; Sawamura, M. Heterogeneous Nickel-Catalyzed Cross-Coupling between Aryl Chlorides and Alkyllithiums Using a Polystyrene-Cross-Linking Bisphosphine Ligand. *Adv. Synth. Catal.* **2019**, *361*, 2250–2254. (c) Nishizawa, A.; Takahira, T.; Yasui, K.; Fujimoto, H.; Iwai, T.; Sawamura, M.; Chatani, N.; Tobisu, M. Nickel-Catalyzed Decarboxylation of Aryl Carbamates for Converting Phenols into Aromatic Amines. *J. Am. Chem. Soc.* **2019**, *141*, 7261–7265.

(10) Toluene was also a useful solvent (88%). See the Supporting Information for details of solvent effects.

(11) See the Supporting Information for the ^{31}P CP/MAS NMR spectra of the polymer-supported Ir catalysts.

(12) See the Supporting Information for details of ligand effects.

(13) (a) Ling, L.; Cao, J.; Hu, J.; Zhang, H. Copper-Catalyzed *N*-Alkylation of Indoles by *N*-Tosylhydrazones. *RSC Adv.* **2017**, *7*, 27974–27980. (b) Merschaert, A.; Boquel, P.; Van Hoeck, J.-P.; Gorissen, H.; Borghese, A.; Bonnier, B.; Mockel, A.; Napora, F. Novel Approaches towards the LTD_4/E_4 Antagonist, LY290154. *Org. Process Res. Dev.* **2006**, *10*, 776–783. (c) Singh, P.; Verma, P.; Yadav, B.; Komath, S. S. Synthesis and Evaluation of Indole-Based New Scaffolds for Antimicrobial Activities-Identification of Promising Candidates. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 3367–3372.

(14) Aubry, C.; Wilson, A. J.; Emmerson, D.; Murphy, E.; Chan, Y. Y.; Dickens, M. P.; García, M. D.; Jenkins, P. R.; Mahale, S.; Chaudhuri, B. Fascaplysin-Inspired Diindolyls as Selective Inhibitors of CDK4/Cyclin D1. *Bioorg. Med. Chem.* **2009**, *17*, 6073–6084.

(15) Wang, M.; Xu, L.; Gao, M.; Miller, K. D.; Sledge, G. W.; Zheng, Q.-H. [^{11}C]Enzastaurin, The First Design and Radiosynthesis of a New Potential PET Agent for Imaging of Protein Kinase C. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 1649–1653.

(16) (a) Li, H.; Jiang, J.; Lu, G.; Huang, F.; Wang, Z.-X. On the "Reverse Gear" Mechanism of the Reversible Dehydrogenation/Hydrogeantion of a Nitrogen Heterocycle Catalyzed by a Cp*Ir Complex: A Computational Study. *Organometallics* **2011**, *30*, 3131–3141. (b) Fujita, K. Development and Application of New Iridium Catalysts for Efficient Dehydrogenation Reactions of Organic Molecules. *Bull. Chem. Soc. Jpn.* **2019**, *92*, 344–351.

(17) Selected examples of direct transformations of *N*-adjacent C(sp^3)–H bonds. For Rh or Ir catalysis, see: (a) Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. Carbonylation at sp^3 C—H Bonds Adjacent to a Nitrogen Atom in Alkylamines Catalyzed by Rhodium Complexes. *J. Am. Chem. Soc.* **2000**, *122*, 12882–12883. (b) Sakaguchi, S.; Kubo, T.; Ishii, Y. A Three-Component Coupling Reaction of Aldehydes, Amines, and Alkynes. *Angew. Chem., Int. Ed.* **2001**, *40*, 2534–2536. (c) DeBoef, B.; Pastine, S. J.; Sames, D. Cross-Coupling of sp^3 C—H Bonds and Alkenes: Catalytic Cyclization of Alkene—Amide Substrates. *J. Am. Chem. Soc.* **2004**, *126*, 6556–6557. (d) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. Cationic Ir(I)-Catalyzed sp^3 C–H Bond Alkenylation of Amides with Alkynes. *Org. Lett.* **2009**, *11*, 1821–1823. (e) Pan, S.; Endo, K.; Shibata, T. Ir(I)-Catalyzed Enantioselective Secondary sp^3 C–H Bond Activation of 2-(Alkylamino)pyridines with Alkenes. *Org. Lett.* **2011**, *13*, 4692–4695. (f) Kawamorita, S.; Miyazaki, T.; Iwai, T; Sawamura, M. Rh-Catalyzed Borylation of *N*-Adjacent C(sp^3)–H Bonds with a Silica-Supported Triarylphosphine Ligand. *J. Am. Chem. Soc.* **2012**, *134*, 12924–12927. (g) Lahm, G.; Opatz, T. Unique Regioselectivity in the C(sp^3)–H α-Alkylation of Amines: The Benzoxazole Moiety as a Removable Directing Group. *Org. Lett.* **2014**, *16*, 4201–4203. (h) Tahara, Y.; Michino, M.; Ito, M.; Kanyiva, K. S.; Shibata, T. Enantioselective sp^3 C–H Alkylation of γ-Butyrolactam by a Chiral Ir(I) Catalyst for the Synthesis of 4-Substituted γ-Amino Acids. *Chem. Commun.* **2015**, *51*, 16660–16663. (i) Tran, A. T.; Yu, J.-Q. Practical Alkoxythiocarbonyl Auxiliaries for Iridium(I)-Catalyzed C–H Alkylation of Azacycles. *Angew. Chem., Int. Ed.* **2017**, *56*, 10530–10534. (j) Torigoe, T.; Ohmura, T.; Suginome, M. Asymmetric Cycloisomerization of *o*-Alkenyl-*N*-Methylanilines to Indolines by Iridium-Catalyzed C(sp^3)–H Addition to Carbon–Carbon Double Bonds. *Angew. Chem., Int. Ed.* **2017**, *56*, 14272–14276. (k) Reyes, R. L.; Sato, M.; Iwai, T.; Sawamura, M. Asymmetric Synthesis of α-Aminoboronates via Rhodium-Catalyzed Enantioselective C(sp^3)–H Borylation. *J. Am. Chem. Soc.* **2020**, *142*, 589–597. For Ru catalysis, see: (l) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. $Ru_3(CO)_{12}$-Catalyzed Coupling Reaction of sp^3 C–H Bonds Adjacent to a Nitrogen Atom in Alkylamines with Alkenes. *J. Am. Chem. Soc.* **2001**, *123*, 10935–10941. (m) Schinkel, M.; Wang, L.; Bielefeld, K.; Ackermann, L. Ruthenium(II)-Catalyzed C(sp^3)–H α-Alkylation of Pyrrolidines. *Org. Lett.* **2014**, *16*, 1876–1879. For Pd catalysis, see: (n) Jain, P.; Verma, P.; Xia, G.; Yu, J.-Q. Enantioselective Amine α-Functionalization via Palladium-catalysed C–H Arylation of Thioamides. *Nat. Chem.* **2017**, *9*, 140–144 and references cited therein.

(18) For a related review on the direct transformation of *N*-adjacent C(sp^3)–H bonds in heterocycles, see: Campos, K. R. Direct sp^3 C–H bond Activation Adjacent to Nitrogen in Heterocycles. *Chem. Soc. Rev.* **2007**, *36*, 1069–1084.

(19) For a related paper from our group on bisphosphine-iridium(III) dihydride species, which was utilized in transfer hydrogenation of alkenes with 1,4-dioxane as hydrogen donor: see: Zhang, D.; Iwai, T.; Sawamura, M. Iridium-Catalyzed Alkene-Selective Transfer Hydrogenation with 1,4-Dioxane as Hydrogen Donor. *Org. Lett.* **2019**, *21*, 5867–5872.

(20) For the DPPE-bischelation to an Ir(I) complex, see: Geier, M. J.; Vogels, C. M.; Decken, A.; Westcott, S. A. Acetylacetonato(phosphane)iridium Complexes: Synthesis and Catalytic Activity in the Cyclization of Alkynoic Acids. *Eur. J. Inorg. Chem.* **2010**, *2010*, 4602–4610.

(21) For the dimerization of a chlorodihydridoiridium(III)-bisphosphine complex, see: Tani, K.; Iseki, A.; Yamagata, T. Efficient Transfer Hydrogenation of Alkynes and Alkenes with Methanol Catalysed by Hydrido(methoxo)iridium(III) Complexes. *Chem. Commun.* **1999**, 1821–1882.

(22) NMR studies on coordination of DPPBz to Ir complexes were conducted. The details are shown in Supporting Information.