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

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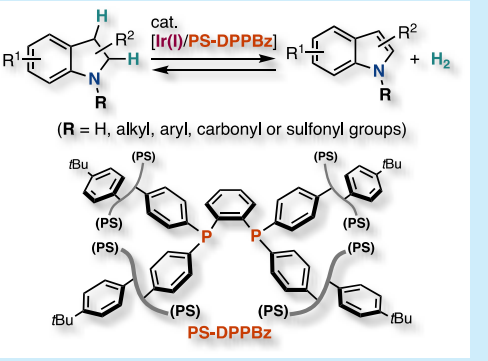
ABSTRACT: The polystyrene-cross-linking bisphosphine ligand PS-DPPBz was effective for the Ir-catalyzed reversible acceptorless dehydrogenation/hydrogenation of *N*-heterocycles. Notably, this protocol is applicable to the dehydrogenation of N-substituted indoline derivatives with various N-substituents 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 and co-workers 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.

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.

During the reaction with (PS-DPPBz)-Ir catalyst, the polymer-bound catalyst changed its color from yellow to

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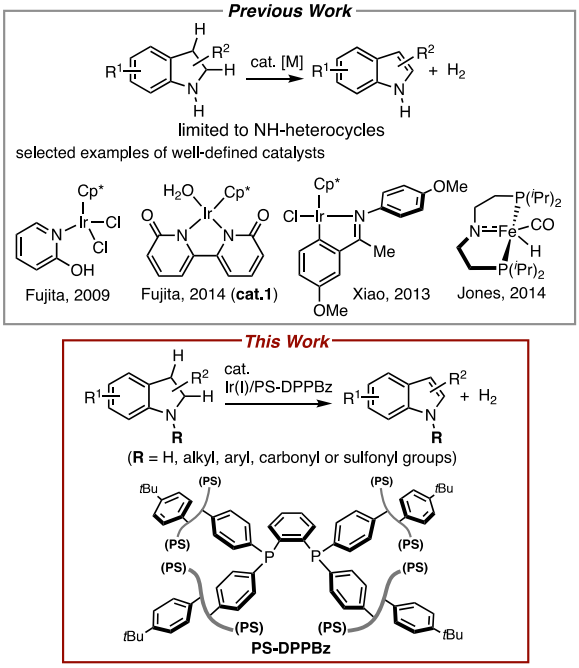
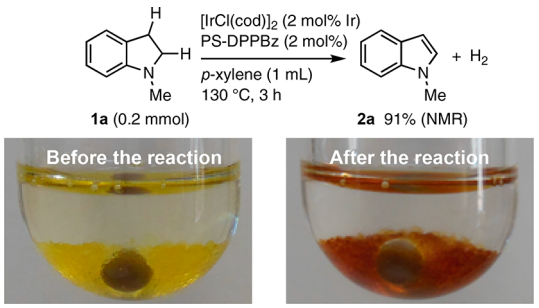
Scheme 1. Acceptorless Dehydrogenation by Transition Metals



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



dark red while the solution phase remained colorless (Scheme 2). This observation indicates that virtually all Ir species were retained in the polymer matrix. The recovered catalyst was reusable for the dehydrogenation albeit with significant reduction in the product yield (first run, 87%; second run, 52%; third 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

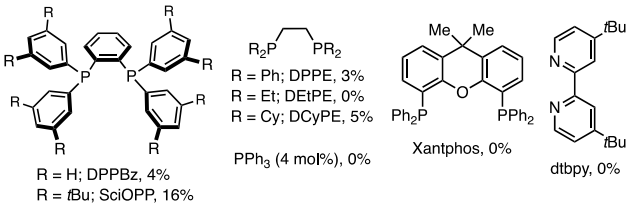
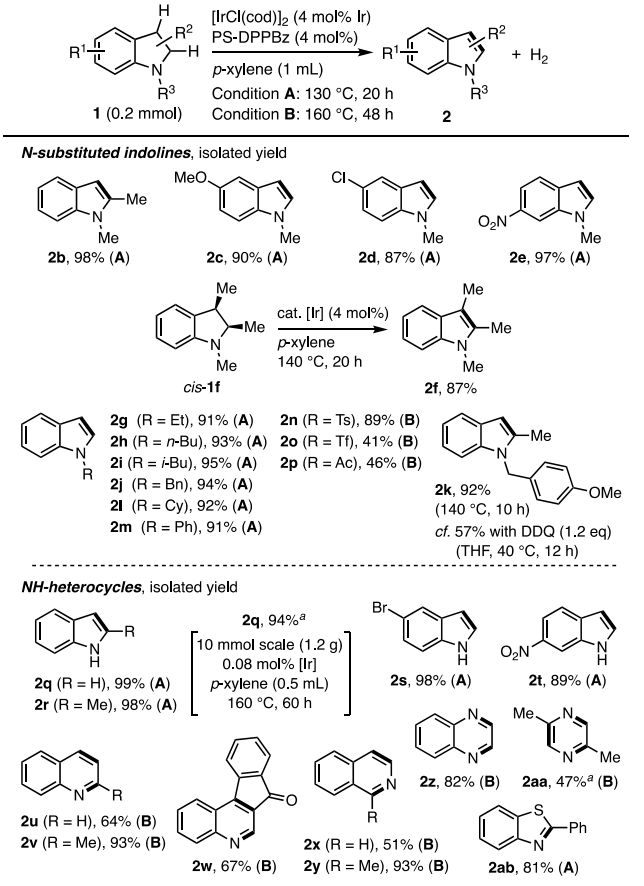


Figure 1. Effect of homogeneous ligands on the yield of dehydrogenation of **1a**. Conditions: **1a** (0.2 mmol), $[IrCl(cod)]_2$ (2 mol % Ir), ligand (2 mol %), *p*-xylene (1 mL), 130 °C, 3 h. Yield of **2a** was determined by ^{1}H NMR analysis of the crude product.

effective. Larger bite-angle bisphosphines (Xantphos), monophosphines (PPh_3), and bipyridine-based ligands (dtbpy) exhibited no catalytic activity.[12]

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

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



[a]Yields are determined by ^{1}H NMR analysis of the crude product. [b]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.

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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.

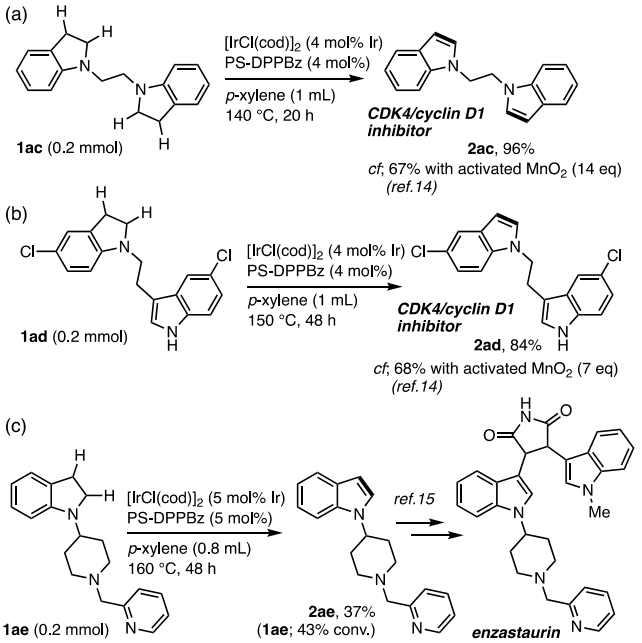
The (PS-DPPBz)-Ir catalyst system is also applicable to the acceptorless dehydrogenation of NH-heterocycles (**1q**−**1ab**). The reaction of **1q** was conducted on the gram scale with a reduced catalyst loading of 0.08 mol % (10 mmol scale, 94% NMR yield, TON 1175) with reasonable hydrogen gas release (~210 mL, 94% based on H_2). Two- or 3-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.

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).

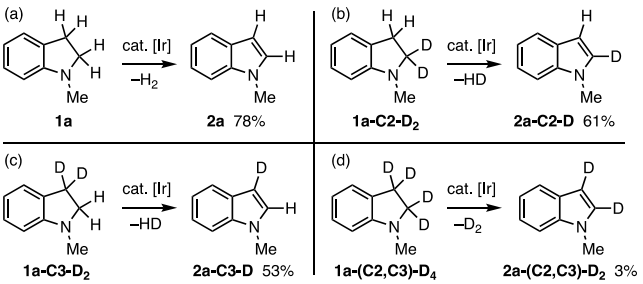
To gain insights into the mechanism, the reactions of deuterated *N*-methylindolines were conducted. The dehydrogenation of 2,2- and 3,3-dideuterated *N*-methylindolines [2 mol % (PS-DPPBz)-Ir, 130 °C, for 2 h] proceeded at only slightly reduced rates compared to that of nondeuterated *N*-methylindoline (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.

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

Scheme 4. Synthesis of Pharmacologically Active Molecules

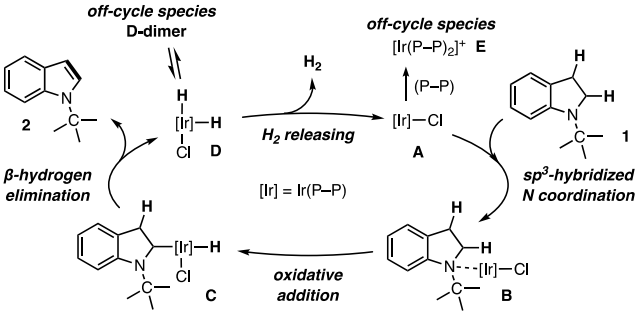


Scheme 5. Deuterium Isotope Experiments[a]



[a]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.

Scheme 6. Plausible Reaction Pathway



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**.

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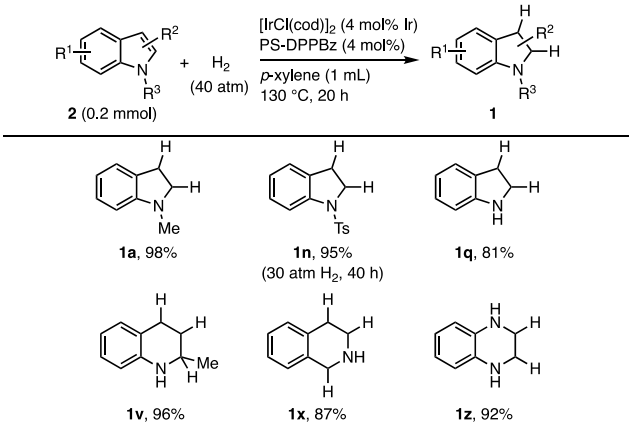
Based on the proposed reaction pathway and the kinetic isotope effect profiles obtained in the experiments with the C2- and/or C3- deuterated **1a** derivatives (Scheme 5), the oxidative addition (**B** to **C**) and the β-hydride elimination (**C** to **D**) steps should not be critical in determining 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

Scheme 7. Hydrogenation of *N*-Heteroarenes[a]



[a]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, 20 h. Isolated yields are shown.

(**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.

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 at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01905.

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

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Notes

The authors declare no competing financial interest.

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(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.

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