

Communication

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Hybrid Catalysis Enabling Room-Temperature Hydrogen Gas Release from *N*-Heterocycles and Tetrahydronaphthalenes

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Supporting Information Placeholder

ABSTRACT: Hybrid catalyst systems to achieve acceptorless dehydrogenation of *N*-heterocycles and tetrahydronaphthalenes—model substrates for liquid organic hydrogen carriers were developed. A binary hybrid catalysis comprising an acridinium photo-redox catalyst and a palladium metal catalyst was effective for the dehydrogenation of *N*-heterocycles, whereas a ternary hybrid catalysis comprising an acridinium photo-redox catalyst, a palladium metal catalyst, and a thiophosphoric imide organocatalyst achieved dehydrogenation of tetrahydronaphthalenes. These hybrid catalyst systems allowed for two-molar equivalent hydrogen gas release from six-membered *N*-heterocycles and tetrahydronaphthalenes under mild conditions, i.e., visible light irradiation at room temperature. The combined use of two or three different catalyst types was essential for the catalytic activity.

Catalytic acceptorless dehydrogenation (CAD) from saturated organic compounds, such as *N*-heterocycles and hydrocarbons, to produce unsaturated molecules and hydrogen gas is a fundamentally important chemical process with numerous applications in organic synthesis¹ as well as for a potential future “hydrogen society”.² This process is generally very difficult, however, because desaturation of organic compounds is generally unfavorable in terms of the enthalpy factor. Iridium complexes are prevalent catalysts for dehydrogenation of *N*-heterocycles.³ Crabtree and Jones independently reported base metal (nickel,^{4a} iron,^{4b} and cobalt^{4c})-catalyzed dehydrogenation of *N*-heterocycles.⁴ Further, Grimme and Paradies^{5a} and our group^{5b} recently achieved organocatalyzed dehydrogenation of *N*-heterocycles by a Lewis acidic borane.⁵ Despite the significant progress, forcing conditions with a reaction temperature higher than 100 °C are often required, except for Crabtree’s electrocatalytic example.^{4a} For CAD from hydrocarbons, iridium–pincer complexes provide a privileged catalyst platform.⁶ Beller recently reported that Vaska-type rhodium complexes [Rh(PR₃)₂(CO)Cl] exhibit improved reactivity.⁷ Nevertheless, CAD from hydrocarbons generally requires even harsher conditions than *N*-heterocycles, such as high tem-

perature (up to 200 °C) or UV light irradiation. This is partly due to the great energy barrier for initiating the catalytic cycle, i.e., C(sp³)–H metalation through oxidative addition to iridium or rhodium complexes. Sorensen reported the first example of room-temperature CAD from alkanes by combining two sequential hydrogen atom-transfer steps mediated by tetrabutylammonium decatungstate and cobaloxime pyridine chloride catalysts, respectively, under near-UV irradiation conditions.⁸ This pioneering base metal CAD from hydrocarbons has room for improvement, however, especially with regard to its efficiency (up to 19% yield based on substrates). Here we developed binary and ternary hybrid catalyst systems, enabling CAD from *N*-heterocycles and tetrahydronaphthalenes, respectively, at room temperature under visible light irradiation conditions.

Our approach for realizing room-temperature CAD is based on facilitating the initiation step in the overall catalytic cycle, i.e., formation of metal amide or organometallic species from *N*-heterocycles or hydrocarbons. This is possible through one-electron oxidation of the substrates directly or indirectly mediated by a photo-redox catalyst,⁹ followed by capture of the resulting radical with a metal catalyst.^{10,11} Based on this idea, we first studied CAD from *N*-heterocycles using 1-phenyltetrahydroisoquinoline (**1a**) as a model substrate.

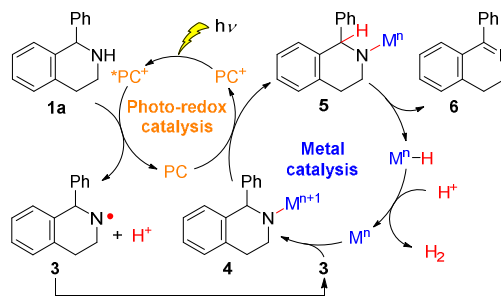
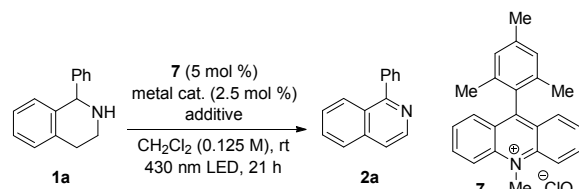


Figure 1. Working hypothesis for CAD of 1-phenyltetrahydroisoquinoline (**1a**) by binary hybrid catalysis.

Our working hypothesis to achieve CAD from **1a** is illustrated in Figure 1. First, single electron transfer (SET) from **1a** to an ex-

cited photo-redox catalyst (*PC⁺) would produce aminyl radical **3**. Then, **3** would be intercepted by a metal catalyst (Mⁿ) to generate oxidized metal amide **4** bearing a metal with an n+1 oxidation state (Mⁿ⁺¹), which in turn would be reduced by a photo-redox catalyst acting as a reductant (PC), affording metal amide **5**.^{12,13} β-Hydride elimination from **5** would produce unsaturated 1-phenylidihydroisoquinoline (**6**) and metal hydride species Mⁿ-H, which would evolve hydrogen gas through reacting with the proton¹⁴ generated in the photo-oxidation step of **1a**. Further dehydrogenation from **6** would produce **2a** with a net generation of two-molar equivalents of hydrogen gas from **1a**.

Table 1. Optimization for CAD from 1a



entry	metal cat.	additive (mol %)	2a (%) ^a	6 (%) ^a
1	FeCl ₂	-	<1	6
2	NiCl ₂	-	6	20
3 ^b	NiCl ₂	-	<1	4
4 ^b	CuCl	-	<1	4
5	Pd(OAc) ₂	-	18	20
6	PdCl ₂ ·2MeCN	-	19	19
7	Pd(BF ₄) ₂ ·4MeCN	-	37	7
8	Pd(BF ₄) ₂ ·4MeCN	KSbF ₆ (5)	60	<1
9	Pd(BF ₄) ₂ ·4MeCN	KSbF ₆ (25)	96 (96) ^c	<1
10	-	KSbF ₆ (25)	11	<1
11 ^d	Pd(BF ₄) ₂ ·4MeCN	KSbF ₆ (25)	<1	9
12 ^e	Pd(BF ₄) ₂ ·4MeCN	KSbF ₆ (25)	5	<1

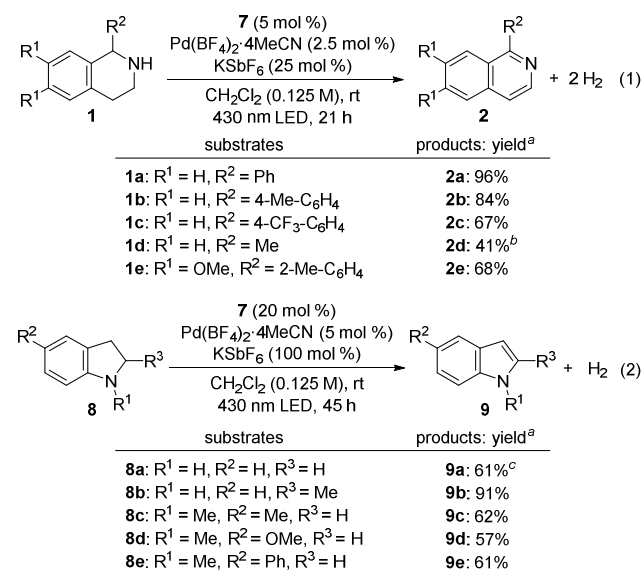
^aNMR yield using 1,1,2,2-tetrachloroethane as an internal standard. ^bIn the presence of 1,10-phenanthroline as a ligand for the metal catalyst. ^cIsolated yield in the parenthesis. ^dThe reaction was run without **7**. ^eThe reaction was run without photoirradiation.

Based on this scenario, we optimized CAD from **1a** using combinations of photo-redox catalysts (5 mol %) and metal catalysts (2.5 mol %) under 430 nm visible light irradiation at room temperature (Table 1).¹³ Although first-row transition metal catalysts were ineffective (entries 1–4), palladium catalysts afforded promising results (entries 5–7); specifically, combining acridinium photo-redox catalyst **7**¹⁵ and Pd(BF₄)₂·4MeCN catalyst produced moderate yield of isoquinoline **2a** (37%; entry 7). A survey of several photo-redox catalysts revealed that **7** produced the highest yield.¹³ To further improve the reactivity, we studied the effects of additives.¹³ The addition of 5 mol % KSbF₆ significantly accelerated the reaction, affording **2a** in 60% yield (entry 8). Finally, in the presence of 5 mol % **7**, 2.5 mol % Pd(BF₄)₂·4MeCN, and 25 mol % KSbF₆, **2a** was obtained in 96% yield (entry 9).¹⁶ The binary hybrid catalyst system was essential for the CAD process (entries 10–12). The yield of **2a** decreased dramatically when either of the two catalyst components was absent (11% without the palladium catalyst; entry 10, and <1% without the photo-redox catalyst; entry 11), or without photoirradiation (5%; entry 12).

We examined the substrate scope of the binary catalysis for CAD from *N*-heterocycles under the optimized conditions (Scheme 1). Various tetrahydroisoquinolines **1a–1e** containing an electron-donating or -withdrawing group were converted to the corresponding isoquinolines **2a–2e** in generally high yield (Scheme 1-(1)). 1-Methyltetrahydroisoquinoline (**1d**) bearing

higher hydrogen density was also a good substrate, giving **2d** in 41% yield. In addition, indolines **8**, either NH-free (**8a–8b**) or *N*-methylated (**8c–8e**), were competent substrates for the binary catalysis, affording indoles **9** in moderate to high yield (Scheme 1-(2)).

Scheme 1. Substrate Scope of CAD from *N*-Heterocycles Using Binary Hybrid Catalysis



^aIsolated yield. ^bThe reaction was run for 70 h. ^cThe reaction was run for 21 h.

We next examined CAD from a more difficult substrate, tetrahydronaphthalene (**10a**). It was previously reported that rhodium^{7c,7d} and iron^{4b} catalysts were applied to the dehydrogenation of **10a**, but only trace amounts of naphthalene (**11a**) were produced. We examined the binary hybrid catalysis conditions optimized for *N*-heterocycles with **10a**, but **11a** was not obtained at all.¹³ The lack of reactivity using the binary hybrid catalysis was likely due to the inability to generate a benzyl radical species (see **12** in Figure 2) from **10a**. Therefore, we attempted to further hybridize a third catalysis, an organocatalysis that would abstract a hydrogen atom from the benzylic C(sp³)-H bond (**10a** to **12**).¹⁷ For this purpose, we selected a sulfur-centered radical RS[•], which would be generated from a sulfur-containing organocatalyst (RSH) by photo-redox catalyzed one-electron oxidation. RSH bears a bond dissociation energy high enough to cleave the benzylic C(sp³)-H bond of **10a**.¹⁸

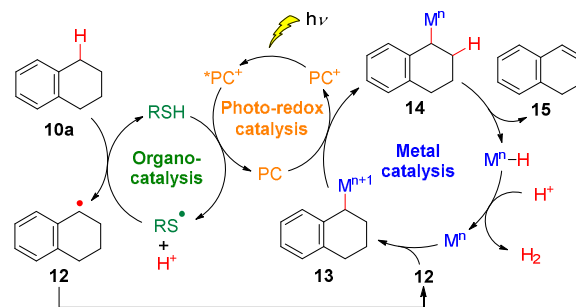


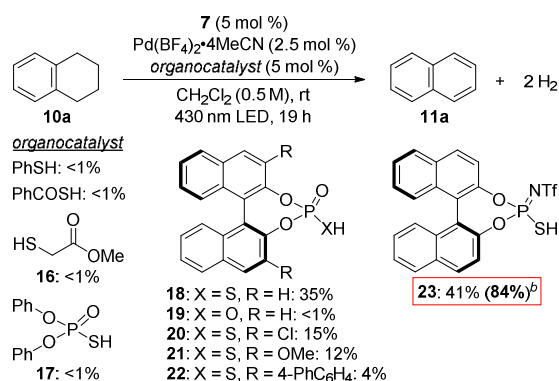
Figure 2. Working hypothesis for CAD of tetrahydronaphthalene (10a**) by ternary hybrid catalysis.**

Our hypothesis for CAD from a hydrocarbon substrate **10a** is illustrated in Figure 2. The sulfur-centered radical RS[•], generated

by SET from RSH to an oxidizing excited photo-redox catalyst ($^*PC^+$), would abstract the benzylic hydrogen atom of **10a**, producing benzyl radical **12**. Radical **12** would combine with a metal catalyst (M^n) to generate organometallic species **13** bearing a metal with an $n+1$ oxidation state (M^{n+1}), which in turn would be reduced by photo-redox catalyst acting as a reductant (PC), affording organometallic species **14**.¹⁰ β -Hydride elimination from **14** would produce unsaturated dihydronaphthalene (**15**) and metal hydride species M^n-H , which would evolve hydrogen gas through a reaction with the proton¹⁴ generated in the photo-oxidation step of the organocatalyst RSH. Repeating this cycle from **15** would produce **11a** with a net generation of two-molar equivalents of hydrogen gas from **10a**.

Based on this hypothesis, we surveyed organocatalysts (5 mol %) in the presence of **7** (5 mol %) and $Pd(BF_4)_2 \cdot 4MeCN$ (2.5 mol %) upon 430 nm LED irradiation at room temperature (Scheme 2).^{13,19} The CAD reaction from **10a** did not proceed using benzenethiol, thiobenzoic acid, or methyl 2-mercaptoacetate (**16**), whose thiyl radical generated *via* SET oxidation under photo-redox conditions was previously reported to generate a benzyl radical from benzyl ether substrates through $C(sp^3)-H$ abstraction.^{18a} On the contrary, thiophosphoric acid organocatalyst **18** exhibited moderate reactivity (35% yield). The observed reactivity of **18** was likely due to the high hydrogen atom abstraction ability of the electron-deficient sulfur-centered radical generated from **18**.²⁰ The binaphthyl backbone and SH functionality proved to be critical elements for the catalytic activity of **18**; almost no reaction proceeded using thiophosphoric acid **17** or phosphoric acid **19**. We studied the effects of substituents at the 2-positions of the binaphthyl backbone of **18**; reactivity was significantly decreased by introducing an electron-withdrawing group (**20**: 15%), an electron-donating group (**21**: 12%), or a sterically-demanding group (**22**: 4%). Finally, we found that thiophosphoric imide **23** was a better organocatalyst than **18**, producing **11a** in 41% yield. After optimizing the catalyst loadings, reaction temperature, time, and concentration, **11a** was obtained in 84% yield.¹⁶

Scheme 2. Effects of Organocatalyst in CAD of 10a^a



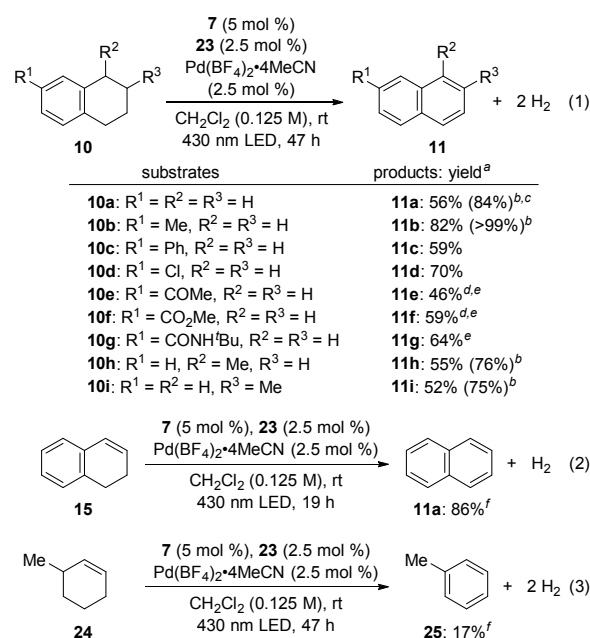
^aYield was determined by GC analysis because the product is volatile. ^bThe yield in parenthesis is for the reaction performed using 5 mol % **7**, 2.5 mol % **23**, and 2.5 mol % $Pd(BF_4)_2 \cdot 4MeCN$ for 60 h under temperature control (ca. 27–29 °C) with a 0.125 M concentration of **10a**.

To confirm that the ternary hybrid catalysis manifold is essential for the CAD process, we also conducted several control experiments.¹³ Almost no reactions occurred when any one of the three catalyst components was absent: the photo-redox catalyst, the metal catalyst, or the organocatalyst. Furthermore, exciting

the photo-redox catalyst **7** with visible light was also indispensable: no reaction proceeded under thermal conditions without light irradiation. These results indicate that the three different types of catalysis cooperatively played critical roles. Moreover, in contrast to the Beller's result using a rhodium catalyst,^{7c} intermediate dihydronaphthalene (**15**) was not detected at any point during the reaction course, indicating that the initial dehydrogenation from **10a** to **15** is more difficult than the second dehydrogenation from **15** to **11a**.

Under the optimized conditions, we investigated the substrate scope of this ternary hybrid catalysis (Scheme 3).²¹ Various substituents on the phenyl ring of tetrahydronaphthalenes were tolerated, including a methyl group (**10b**), an aryl group (**10c**), a halogen atom (**10d**), a keto group (**10e**), an ester group (**10f**), and an amide group (**10g**). The reactions of tetrahydronaphthalenes **10h** and **10i** bearing a methyl group at a saturated carbon also proceeded in high yield. Dihydronaphthalene **15** was a suitable substrate, giving **11a** in 86% yield in a shorter reaction time (19 h) than starting from **10a**. The results support our hypothesis that the two-molar hydrogen evolution proceeds in a stepwise manner through an intermediary of **15** (Figure 2). Dehydrogenation of 3-methylcyclohexene (**24**), albeit in moderate yield (17%), is a current limitation of this method. The result is still noteworthy, however, and demonstrates the potential of this ternary hybrid catalyst system for application in room-temperature CAD from aliphatic liquid organic hydrogen carriers containing higher hydrogen-per-molecular weight ratios.

Scheme 3. Substrate Scope of CAD from Tetrahydronaphthalene Derivatives and 3-Methylcyclohexene Using Ternary Hybrid Catalysis



^aIsolated yield is shown unless otherwise noted. ^bGC yield in the parenthesis. ^cThe reaction was run for 60 h. ^d5 mol % **23** was used. ^eThe reaction was run for 72 h. ^fGC yield.

In summary, we developed a binary hybrid catalyst system comprising an acridinium photo-redox catalyst and a palladium metal catalyst for CAD from *N*-heterocycles. Moreover, we achieved CAD from tetrahydronaphthalenes, devising a ternary hybrid catalyst system by combined use of an acridinium photo-redox catalyst, a palladium metal catalyst, and a thiophosphoric

imide organocatalyst. These are the first molecular catalysts for acceptorless dehydrogenation of *N*-heterocycles and hydrocarbons at room temperature and under visible light irradiation conditions. The complete release of two-molar equivalents of hydrogen gas from tetrahydroisoquinolines and tetrahydronaphthalenes is also unique in these processes. This study demonstrates that proper hybridization of different catalyst types enables CAD from *N*-heterocycles and hydrocarbons under mild conditions. Detailed studies to elucidate the reaction mechanism are ongoing in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interests.

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- (13) See Supporting Information (SI) for more details.

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- (16) Generation of two-molar equivalents of hydrogen gas was confirmed by a two-pot transfer hydrogenation experiment, connecting the reaction atmosphere of the dehydrogenation reaction to a rhodium-catalyzed hydrogenation reaction of cyclododecene performed in another vessel. For detailed experiments, see SI.

- (17) During preparation of this manuscript, MacMillan and coworkers reported a cross-coupling reaction between aliphatic substrates and aryl bromides by developing a triple catalysis involving an iridium photo-redox catalyst, a quinuclidine hydrogen atom transfer organocatalyst, and a nickel catalyst. See, Shaw, M. H.; Shurtleff, V. W.; Tarrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1304.

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- (19) A combination of **7** and Pd(BF₄)₂•4MeCN was also optimum in the case of CAD from **10a**. See SI.

- (20) Electrochemical and photochemical studies indicated that sulfur-centered radical species RS[•] would be generated from thiophosphate **18** via a single electron oxidation of **18** by the excited state of photo-redox catalyst **7**. SET from **18** to photo-excited **7** is also thermodynamically feasible, based on their oxidation potential values. See SI for details.

- (21) The ternary hybrid catalyst system produced less satisfactory results than the binary system in CAD from *N*-heterocycles (see Scheme 1): CAD from **1a** using **7** (5 mol %), **18** (2.5 mol %), and Pd(BF₄)₂•4MeCN (2.5 mol %) for 20 h afforded products **2a** and **6** in 15% and 12% yields, respectively.

