

# **Catalytic Acceptorless Dehydrogenation of Aliphatic Alcohols**

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# Catalytic Acceptorless Dehydrogenation of Aliphatic Alcohols

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**ABSTRACT:** We developed the first acceptorless dehydrogenation of aliphatic secondary alcohols to ketones under visible light irradiation at room temperature by devising a ternary hybrid catalyst system comprising a photoredox catalyst, a thiophosphate organocatalyst, and a nickel catalyst. The reaction proceeded through three main steps: hydrogen atom transfer from the  $\alpha$ -C-H bond of an alcohol substrate to the thiyl radical of the photo-oxidized organocatalyst, interception of the generated carbon-centered radical with a nickel catalyst, and  $\beta$ -hydride elimination. The reaction proceeded in high yield under mild conditions without producing side products (except H<sub>2</sub> gas) from various alcohols, including sterically hindered alcohols, a steroid, and a pharmaceutical derivative. This catalyst system also promoted acceptorless cross-dehydrogenative esterification from aldehydes and alcohols through hemiacetal intermediates.

#### Introduction

Oxidation of alcohols to carbonyl compounds is a crucial process in organic chemistry, and generally requires stoichiometric oxidants, such as metal oxo reagents, peroxides and perchlorates, hypervalent iodines, and molecular oxygen. Catalytic acceptorless dehydrogenation (CAD) is therefore a more favorable oxidation method, releasing molecular hydrogen as the sole side product.<sup>1</sup> Furthermore, CAD of alcohols is a fundamental chemical reaction for the potential future hydrogen economy using alcohols as an energy carrier.<sup>1</sup> Transition metal complexes are common catalysts for CAD of alcohols.<sup>2,3</sup> Most of the reaction conditions reported to date, however, are harsh (high temperature, typically at >100 °C<sup>2</sup> or UV irradiation<sup>3</sup>) because CAD of alcohols is thermodynamically unfavorable. Nevertheless, recent studies realized CAD of alcohols under visible light irradiation at room temperature through the binary combination of a homogeneous or heterogeneous photoredox catalyst and a transition metal catalyst (Figure 1a).<sup>4</sup> Although the overall process is thermodynamically uphill at room temperature, photoirradiation can overcome the kinetic barriers. Despite such progress, the substrate scope of CAD is predominantly limited to benzylic alcohols, with aliphatic alcohols generally exhibiting only low reactivity. Here we report a ternary hybrid catalyst system that allows for efficient CAD of both aromatic and aliphatic alcohols under visible light irradiation at room temperature (Figure 1b).

CAD of aliphatic alcohols has two main difficulties: 1) activation of aliphatic alcohols via hydrogen atom transfer (HAT) or an electron transfer process,<sup>5</sup> and 2) excessive reactivity of the  $\alpha$ -oxy carbon-centered radical species, which is prone to side reactions (e.g., pinacol coupling), following HAT. We hypothesized that a ternary hybrid catalyst system, which was previously developed for CAD of tetrahydronaphthalenes and 3-methyl cyclohexene,<sup>6</sup> could contribute to overcome those difficulties.<sup>7,8,9</sup> Our reaction design for CAD of aliphatic alcohols is shown in Figure 1b. A

thiyl radical (RS<sup>•</sup>) acting as a HAT catalyst is generated through single-electron oxidation of a thiophosphoric acid (TPA) organocatalyst by a photo-excited acridinium photoredox catalyst (\*Mes-Acr+).10 This HAT catalyst abstracts a hydrogen atom from an  $\alpha$ -C–H bond of the alcohol substrate, generating  $\alpha$ -oxy carbon-centered radical **3**. Then, a nickel(II) catalyst oxidatively intercepts **3**, giving presumed organonickel(III) species 4. Single-electron reduction of Ni(III) by the reduced form of the photoredox catalyst (Mes-Acr), followed by  $\beta$ -hydride elimination affords enol 6, which tautomerizes to product ketone 2. Hydrogen gas evolves through protonolysis of the nickel(II) hydride species. This strategy would enable activation of the unreactive  $\alpha$ -oxy C–H bond of aliphatic alcohols and suppress undesired side reactions by carbon-centered radical 3.

(a) Previous works





**Figure 1.** Overview of acceptorless dehydrogenation of alcohols at room temperature. (a) Previous works: binary combination of photoredox catalyst and a transition metal catalyst. (b) Present work: Ternary hybrid catalysis comprising a photoredox catalyst, an organocatalyst, and a nickel catalyst, enabling CAD from aliphatic alcohols.

## **Results and Discussion**

Assessment of HAT Ability of the Binary Catalyst System. On the basis of this hypothesis, we first assessed the ability of the binary catalyst system (mesityl acridinium [Mes-Acr<sup>+</sup>] and TPA) for HAT from stable C–H bonds with varied bond dissociation energies (BDEs) in the radical conjugate addition to benzalmalononitrile<sup>5,12</sup> (Table 1). Benzaldehyde, toluene, tetrahydrofuran, and methanol afforded the corresponding products in high yield (entries 1–4), while cyclohexane bearing a greater BDE was not sufficiently reactive (entry 5). Therefore, the binary catalyst combination showed promise for the intended HAT process from aliphatic alcohol **1** to radical **3** (Figure 1b), which constitutes the entrance to the designed hybrid catalysis.

Table 1. Assessment of HAT Ability of the BinaryCatalyst System.

CN

BDE

(kcal/mol)

88.7

89.8

92.1

96.1

100.0

Me

Mes-Acr

Me ClO₄

ĊМ

C-H bond dono

(5 equiv)

entry

1

2

з

5

C-H bond

donor

Mes-Acr<sup>+</sup> (5 mol %)

TPA (5 mol %)

CH<sub>2</sub>Cl<sub>2</sub> (0.10 M), rt

blue LED, 20 h

Ph

product

ĊN

CN

CN

O.

0<sup>~</sup>' `<sub>SH</sub>

TPA

ĊΝ

vield (%)<sup>a</sup>

quant.

76

91

(dr = 1/1)

68 (92<sup>b</sup>)

**7**b



mixture using 1,1,2,2-tetrachloroethane as an internal standard.  ${}^{b}10$  equiv C–H bond donor was used.

Optimization of the Reaction Conditions. We then combined the binary HAT catalyst system with the third component, a transition metal catalyst, for CAD of 2dodecanol (1a) as a model substrate (Table 2). The ternary hybrid catalyst system comprising Ni(NTf2)2•xH2O promoted the reaction in excellent yield (entry 1). When NiCl<sub>2</sub> was used instead of the cationic nickel salt, however, the yield dramatically decreased (entry 2). Pd(BF<sub>4</sub>)<sub>2</sub>•4MeCN afforded the target molecules, but the reactivity was lower than in the optimized conditions using the nickel catalyst (entry 3 vs. entry 1). In addition, Ni(BF<sub>4</sub>)<sub>2</sub>•xH<sub>2</sub>O had superior reactivity to Pd(BF<sub>4</sub>)<sub>2</sub>•4MeCN (entry 3 vs. entries 4 and 5). These results clearly indicate that the nickel salts are more suitable for CAD of alcohols than the palladium salt. This tendency was contrasting to our previous observations in CAD of hydrocarbons, where both palladium and nickel salts had almost the same reactivity.6 Control experiments confirmed that the three catalyst components and visible light irradiation were all critical for the reaction (entries 6-9).

When a representative dual catalysis comprising Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub> and quinuclidine, which was previously reported for hydrogen atom abstraction from α-C-H bonds of aliphatic alcohols,<sup>10a,b,e</sup> was used instead of Mes-Acr<sup>+</sup> and TPA, product 2a was obtained in only 2% yield (entry 10). MacMillan's group reported that tetrabutylammonium phosphate facilitated HAT from the α-C–H bonds of alcohols.<sup>10b</sup> When the phosphate additive was present, however, the combination of  $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$  and quinuclidine afforded **2a** in only 9% yield (entry 11). In addition, the phosphate completely abolished the reactivity of our hybrid catalysis (entry 12). We speculate that the phosphate would coordinate to the nickel catalyst, thus diminishing its cationic character, which is important for the catalyst activity (Table 2, entry 1 vs. entry 2). Moreover, other HATactive thiols<sup>10a,11</sup> were not effective for this catalyst system (entry 13, 14). Therefore, the optimized ternary hybrid catalyst system in entry 1 was uniquely active for CAD of aliphatic alcohols. A radical trapping experiment was conducted (entry 15): in the presence of 1 equiv TEMPO, the reaction did not proceed and 1a was recovered in 95%. This result supports an intermediary of a carbon-centered radical **3** in the catalytic cycle. Hydrogen gas evolution was confirmed by a two-pot transfer hydrogenation reaction: rhodium-catalyzed hydrogenation of cyclododecene proceeded in 84% yield using the hydrogen gas generated through CAD from cyclododecanol (1g) in a connected vessel.13

## **Table 2. Optimization of the Reaction Conditions**

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OH Me ⊖ Me 1a	Mes-Acr <sup>+</sup> (5 mol %) TPA (5 mol %) metal complex cat. (2.5 mol %) CH <sub>2</sub> Cl <sub>2</sub> (0.050 M), rt blue LED, 20 h	O Me <sub>t</sub> → Me + H <sub>2</sub> 2a
entry	metal complex cat.	<b>2a</b> (%) <sup>a</sup>
1 2 3 4 5 <sup>c</sup> 6 <sup>d</sup> 7 <sup>e</sup> 8	Ni(NTf)2*XH2O NiCl2*6H2O Pd(BF4)2*4MeCN Ni(BF4)2*XH2O Ni(BF4)2*XH2O Ni(NTf)2*XH2O Ni(NTf)2*XH2O Ni(NTf)2*XH2O	96 (78) <sup>b</sup> 22 51 91 96 <1 <1
o 9 <sup>f</sup> 10 <sup>g</sup> 11 <sup>g,h</sup> 12 <sup>h</sup> 13 <sup>i</sup>	Mi(NTf) <sub>2</sub> *xH <sub>2</sub> O Ni(NTf) <sub>2</sub> *xH <sub>2</sub> O	ND 2 9 ND 3
14 <sup>/</sup> 15 <sup>k</sup>	Ni(NTf)₂•xH₂O Ni(NTf)₂•xH₂O	1 trace

<sup>a</sup>Yield was determined by <sup>1</sup>H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. <sup>b</sup>Isolated yield in parentheses. <sup>c</sup>MeCN (10 mol %) was added. dWithout Mes-Acr+. eWithout TPA. fWithout photoirradiation. <sup>g</sup>Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub> and quinuclidine were used instead of Mes-Acr<sup>+</sup> and TPA, respectively. *h*Tetrabutylammonium phosphate (25 mol %) was added. 'Methyl thioglycolate was used instead of TPA. <sup>j</sup>Triisopropylsilanethiol was used instead of TPA. <sup>k</sup>1 equiv TEMPO was added.

Substrate Scope of CAD of Alcohols. Under the optimized conditions, we investigated the substrate scope (Figure 2). Simple linear aliphatic secondary alcohols afforded the product ketones in high yield (2a and 2b). Cycloalkanols were generally more reactive than linear alcohols, and various ring-size substrates afforded the corresponding cyclic ketones in excellent yields (2c-2h). Specifically, CAD of 1g was performed in a practical scale (5 mmol) by reducing the amount of Ni(NTf<sub>2</sub>)<sub>2</sub>•xH<sub>2</sub>O to 0.5 mol % and increasing the substrate concentration to 0.2 M, and product 2g was obtained in 91% yield, identical to the vield of the standard scale reaction (0.2 mmol). A benzylic alcohol bearing a more labile  $\alpha$ -C–H bond than aliphatic alcohols was a competent substrate, giving product 2i in quantitative yield. Various functional groups were tolerated under the reaction conditions (2j-2s), including ether (2k), halogens (21 and 2m), and pinacol boronate (2n), which is especially sensitive to oxidative conditions. Alcohols containing heteroaromatics, such as furan and thiophene, proceeded in good yield (2q and 2r). Also, an alcohol containing a benzyl ester moiety gave the target compound without degradation (2s). Steric congestion of the substrates did not deteriorate the reactivity (2t and 2u). The reaction was applicable to a natural product (epiandrosterone) and a drug (oxaprozin) derivative, giving product ketones **2v** and **2w**, respectively, both in high yield. Oxazole rings are susceptible to oxidation,14 but we observed no significant oxidation of the oxazole ring in 1w. These results clearly demonstrate the broad substrate scope and synthetic utility of CAD of secondary alcohols.

Mes-Acr<sup>+</sup> (5 mol %) TPA (5 mol %) ОН Ni(NTf)2•xH2O (2.5 mol %)  $H_2$ CH<sub>2</sub>Cl<sub>2</sub> (0.050 M), rt 2 blue LED, 20 h 2c n=1.88%<sup>b</sup> 2d n=2, 70%<sup>b</sup> **2e** n=3, 98%<sup>b</sup> `Me hex 2f n=4, quant. **2a** 78% 2b 85% 2g n=8, 91%; 91%<sup>c</sup> 2j R=H, 89% 2k R=OMe quant 2I R=CF3, 78% 2m R=Br, 96% Me <sup>t</sup>Bu 2n R=Bpin, 49% 2i quant.<sup>d,e</sup> **2h** 70% (from β-OH) R 20 R=OBz, 84% 2q X=0, 81% 2p R=NPhth, 86% 2r X=S, 88% OBn



2t 91%<sup>t</sup>

2u 72%

ö

**2s** 53%

<sup>a</sup>Yield is isolated yield unless otherwise noted. <sup>b</sup>Yield was determined by GC analysis of the crude mixture using dodecane as an internal standard. <sup>c</sup>5 mmol scale using 0.5 mol % Ni(NTf<sub>2</sub>)<sub>2</sub>•xH<sub>2</sub>O at 0.2 M. <sup>d</sup>Yield was determined by <sup>1</sup>H NMR analysis of the crude mixture using 1,1,2,2tetrachloroethane as an internal standard. eCH2Cl2 (0.2 M) was used.

ACDC between Aldehydes and Alcohols. Despite the broad substrate scope of CAD of secondary alcohols, the corresponding reaction from primary alcohols did not produce high yields, likely due to the lability of the product aldehydes containing a formyl C-H bond under the reaction conditions, which is weaker than the  $\alpha$ -C–H bond of the starting alcohols (see Table 1). In crude reaction mixtures of CAD of primary alcohols, we identified esters presumably generated through dehydrogenation of hemiacetals derived from the starting alcohols and dehydrogenated aldehydes.<sup>2a,15</sup> This observation led us to apply the ternary hybrid catalysis to acceptorless cross-dehydrogenative coupling (ACDC)<sup>16</sup> between aldehydes and alcohols (Figure 3). ACDC between aldehydes and alcohols is a challenging reaction due to the presence of many potential competing side reaction pathways, such as reduction and

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decarbonylation of aldehydes.<sup>2a,15c</sup> Despite these difficulties, Xiao's group<sup>15c</sup> and Milstein's group<sup>15d</sup> achieved ACDC between aldehydes and primary alcohols or two different alcohols as starting materials. These seminal works, however, still required high temperature and/or a stoichiometric amount of base.

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59 60 Figure 3. Concept of ACDC between Aldehydes and Alcohols



We assumed that cleavage of the weak formyl C–H bond of aldehyde **7** by our HAT catalyst system (Mes-Acr<sup>+</sup>-TPA) was an undesired side reaction pathway in ACDC, and thus the rapid formation of hemiacetal intermediate **9** would be critical. Therefore, we studied the (hemi)acetal formation step between **7d** and **8d** under various conditions. Since hemiacetal **9** is unstable, we observed acetal **11d** as the actual product in those studies (Figure 4). Interestingly, although either Ni(NTf<sub>2</sub>)<sub>2</sub>•xH<sub>2</sub>O or TPA did not promote the acetal formation by itself (entries 1 and 2), the combination of Ni(NTf<sub>2</sub>)<sub>2</sub>•xH<sub>2</sub>O and TPA afforded acetal **11d** in 57% yield (entry 3).<sup>17</sup>

Figure 4. Acetal Formation Promoted by  $Ni(NTf_2)_2$  and  $TPA^a$ 

$hex \qquad H \qquad $	TPA (5 r Ni(NTf) <sub>2</sub> •xH <sub>2</sub> C CH <sub>2</sub> Cl <sub>2</sub> (0. in dark	nol %) 9 (2.5 mol %) 050 M), rt , 21 h	0 <sup>CF3</sup> hex <sup>D</sup> CF3 11d
entry	Ni(NTf) <sub>2</sub> •xH <sub>2</sub> O	TPA	<b>11d</b> (%) <sup>a</sup>
1	+	-	trace
2	-	+	trace
3	+	+	57

 $^a\rm Yield$  was determined by  $^1\rm H$  NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard.

After optimization, the ACDC reaction between nonanal (7a) and 2,2,2-trichloroethanol (8a) proceeded under conditions that were identical to those of CAD of secondary alcohols (Figure 5). Trichloroethyl ester **10a** was obtained in 72% yield. Sterically more congested aldehydes **7b** and **7c** also afforded corresponding esters **10b** and **10c**, respectively, in good yield. In addition, 2,2,2trifluoroethanol produced trifluoroethyl ester **10d** in 43% yield. The ACDC also showed a range of functional group tolerance (**10e-i**), including ester (**10e-h** and **10l**), halogen (**10f**, **10g**, and **10i**), ether (**10h**), phthaloyl-protected amine (**10j**), and ketone (**10k**) functional groups. Yield was moderate in some entries, because acetals were formed as a main byproduct: e.g. acetal **11d** was obtained in 33% yield in the case of the synthesis of **10d**. The acetals were not converted to the esters under the present conditions. The present conditions were not applicable to the synthesis of amides or imides using amines or amides as substrates, instead of alcohols (**10m** and **10n**). Nevertheless, our result is the first example of ACDC between aldehydes and alcohols that proceeds at room temperature without using stoichiometric amounts of external reagents.<sup>18</sup>





<sup>a</sup>Yield is isolated yield unless otherwise noted. <sup>b</sup>Yield in parenthesis was determined by <sup>1</sup>H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard.

**Mechanistic Studies.** Finally, we conducted mechanistic studies for the CAD of secondary alcohols, especially for the desaturation step (Figure 6). We assumed that the desaturation step proceeds through  $\beta$ -hydride elimination of organonickel **5**, followed by tautomerization (Figure 1b). This hypothesis is consistent with the following experimental results. First, benzhydrol, which does not contain a  $\beta$ -C–H bond, produced benzophenone in only poor yield (11%: Figure 6a). This result was in sharp contrast to the result of dicyclohexylmethanol (**1u**), which has a structure similar to that of benzhydrol but has  $\beta$ -C–H bonds and greater steric hindrance and afforded product ketone **2u** in 72% yield (Figure 2). Benzhydrols were a reactive class of substrates in previously-developed conditions by

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other groups.<sup>4</sup> The low reactivity of benzhydrol in our system suggests that the reaction mechanism of the present CAD by the hybrid catalysis is distinct from that of the previous reactions. Similarly, the yield of CAD of 2adamantanol was moderate (27%: Figure 6b), probably because β-hydride elimination to generate an enol intermediate is not favorable due to Bredt's rule. Moreover, 21%-H (corresponding to 84%-H vs. single D) was incorporated at the  $\alpha$ -position of the keto group in 2g, which was produced from  $\beta$ -D<sub>4</sub>-1g (Figure 6c). The observed higher reactivity of a cationic nickel catalyst (Ni(NTf<sub>2</sub>)<sub>2</sub>•xH<sub>2</sub>O) compared with a NiCl<sub>2</sub> catalyst may also be attributable to the accelerated  $\beta$ -hydride elimination by a cationic nickel complex.<sup>6b,19</sup> On the basis of our previous observation that a thiyl radical (RS<sup>•</sup>) is generated through photooxidation of TPA by Mes-Acr+6a and the present finding that a carbon-centered radical was generated from methanol using the binary catalyst combination (Table 1), the mechanism depicted in Figure 1b is plausible.

## Figure 6. Mechanistic Information



<sup>*a*</sup>Yield was determined by <sup>1</sup>H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard.

## Conclusion

In conclusion, we developed CAD of aliphatic and aromatic alcohols under visible light irradiation at room temperature, mediated by the ternary hybrid catalyst system. The sequence of HAT from aliphatic alcohols containing high BDEs, oxidative interception of the resulting carbon-centered radical to organonickel species, and  $\beta$ -hydride elimination organized by the ternary hybrid catalysis, was key to achieving this synthetically-useful transformation. Moreover, expansion of the substrate scope of the ternary hybrid catalyst system from hydrocarbons<sup>6b</sup> to secondary aliphatic alcohols allowed us to obtain mechanistic information of the  $\beta$ -hydride elimination step of the complex catalyst system. The fact that nickel salts were superior to palladium salts is unique to the CAD of alcohols. The catalyst system was also applicable to ACDC between aldehydes and alcohols, producing esters through CAD of hemiacetal intermediates. The potent reactivity of the Ni(NTf<sub>2</sub>)<sub>2</sub>•xH<sub>2</sub>O–TPA combination to promote the formation of the hemiacetal intermediate was critical for the ACDC, avoiding undesired C–H abstraction of aldehydes by the TPA–Mes-Acr<sup>+</sup> HAT catalyst combination. Extension of the ternary hybrid catalysis to other dehydrogenation reactions is ongoing in our laboratory.

# ASSOCIATED CONTENT

## **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data (PDF)

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## Notes

The authors declare no competing financial interests.

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