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Organoborane-Catalyzed Hydrogenation of Unactivated Aldehydes with a Hantzsch Ester as a Synthetic NAD(P)H Analogue

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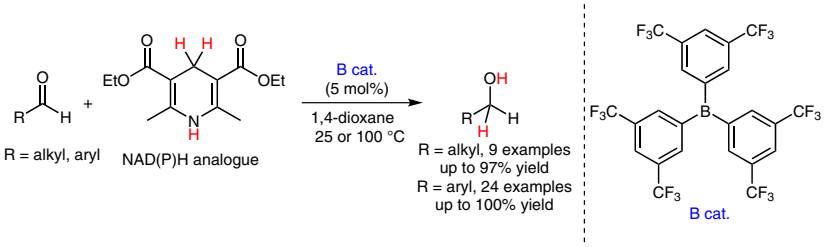

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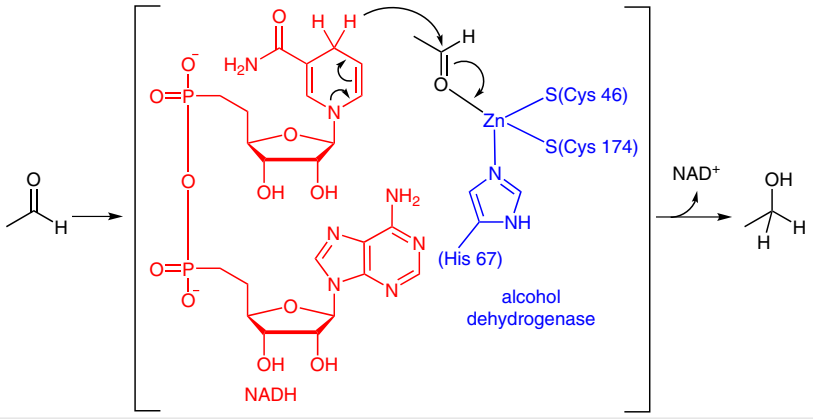
Abstract We have developed a method for the hydrogenation of unactivated aldehydes, using a Hantzsch ester as a NAD(P)H analogue in the presence of an electron-deficient triarylborane as a Lewis acid catalyst. Thus, tris[3,5-bis(trifluoromethyl)phenyl]borane efficiently catalyzes the hydrogenation of aliphatic aldehydes with a Hantzsch ester in 1,4-dioxane at 100 °C to give the corresponding aliphatic primary alcohols in up to 97% yield. Aromatic aldehydes also undergo the hydrogenation, even at 25 °C, to furnish the corresponding aromatic primary alcohols in up to 100% yield.

Key words alcohols, aldehydes, hydrogenation, NADH analogues, organoboranes

In nature, hydrogenation processes are typically mediated by a combination of enzymes and organic reduction cofactors such as NADH and NADPH.[1,2] For example, in the ethanol fermentation process, alcohol dehydrogenase promotes the hydrogenation of acetaldehyde with NADH under anaerobic conditions to give ethanol (Scheme 1).[1] In this enzymatic system, the hydrogenation of acetaldehyde occurs through the activation of the carbonyl group of acetaldehyde by the coordination of the carbonyl group to the zinc active center, which is followed by hydride transfer from NADH to acetaldehyde. Inspired by enzymatic reduction systems, various synthetic NAD(P)H analogues (Figure 1) have been developed and applied in organocatalyzed and metal-catalyzed hydrogenation reactions of unsaturated compounds, such as α,β-unsaturated carbonyls, imines, and α-keto esters.[3–7] Although several research groups have studied the hydrogenation of unactivated aldehydes with synthetic NAD(P)H analogues using Lewis[8] or Brønsted[9] acid catalysts, an efficient catalytic system has not yet been developed.

On the other hand, organoboron compounds have been used as Lewis acid catalysts for various organic transformations.[10] In particular, electron-deficient boron compounds,



Scheme 1 Active site of alcohol dehydrogenase for the reduction of acetaldehyde with NADH

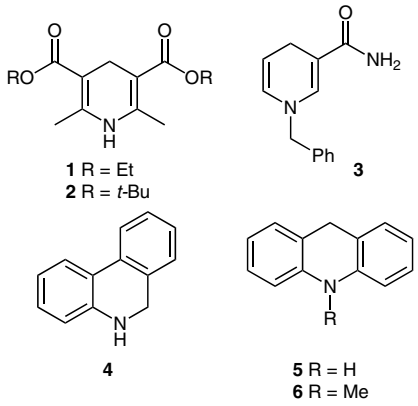
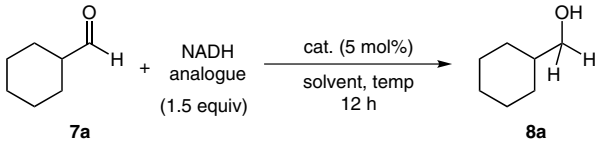


Figure 1 Typical synthetic NAD(P)H analogues

such as tris(pentafluorophenyl)borane, efficiently catalyze various organic transformations (e.g., the Mukaiyama aldol reaction and the Sakurai–Hosomi reaction) because of their high oxophilic Lewis acidities.[11] However, so far, the hydrogenation of unactivated aldehydes with synthetic NAD(P)H analogues using organoborane catalysts has been insufficiently investigated.[8h,12–14] Ohno and co-workers have reported that the reduction of benzaldehyde with a synthetic NADH analogue does not take place in the presence of even an excess amount of BF_3.[8h] Although Stephane, Crudden, and co-workers reported the formation of borohydrides by the stoichiometric reaction of tris(pentafluorophenyl)borane with Hantzsch esters, the reactivity of the resulting borohydrides for carbonyl reduction was not investigated.[15] If a suitable organoborane catalyst is used for the hydrogenation of unactivated aldehydes with a synthetic NAD(P)H analogue, the reaction should proceed efficiently to give alcohols. Therefore, we decided to use organoboranes as Lewis acid catalysts for the hydrogenation of unactivated aldehydes with a synthetic NADH analogue. Herein we report the hydrogenation of unactivated aliphatic and aromatic aldehydes with a Hantzsch ester as a synthetic NADH analogue in the presence of an electron-deficient triarylborane catalyst to give the corresponding primary alcohols in excellent yields.

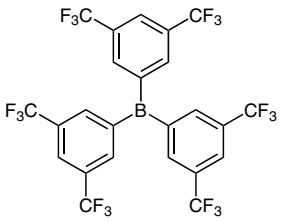
We initially examined the hydrogenation of cyclohexanecarbaldehyde (**7a**) with Hantzsch ester **1** as a synthetic NAD(P)H analogue, in the presence of $BF_3{\cdot}OEt_2$ as a Lewis acid catalyst, at 60 °C in toluene (Table 1, entry 1). The reaction gave cyclohexanemethanol (**8a**) in a yield of only 2%. When triethylborane and triphenylborane were used, the hydrogenation was sluggish (entries 2 and 3). We then used the electron-deficient triarylborane $B(C_6F_5)_3$ for this hydrogenation reaction. The hydrogenation took place to give **8a** in 28% yield (entry 4). We assumed that a triarylborane with a Lewis acidity higher than that of $B(C_6F_5)_3$ would show higher catalytic activity in the hydrogenation. In 2012, Ashley and co-workers reported the synthesis of tris[3,5-bis(trifluoromethyl)phenyl]borane (**9**) and the investigation of its Lewis acidity.[16] They demonstrated that the Lewis acidity of borane **9** is higher than that of $B(C_6F_5)_3$. We used borane **9** for the hydrogenation reaction; it provided the desired alcohol **8a** in 70% yield (entry 5). These results show that borane **9** is the optimal catalyst for this hydrogenation reaction. We also tested other synthetic NAD(P)H analogues (entries 6–10). The reaction was conducted using Hantzsch ester **2** to afford **8a** in 46% yield (entry 6). When *N*-benzyl-1,4-dihydronicotinamide (**3**), 5,6-dihydrophenanthridine (**4**), and dihydroacridines **5** and **6**

Table 1 Screening of Reaction Conditions for the Hydrogenation of Cyclohexanecarbaldehyde (**7a**)[a]



7a **8a**

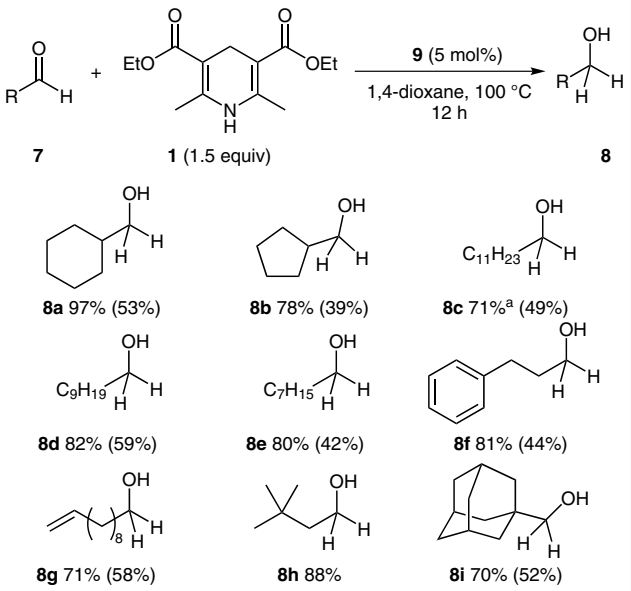
Entry	Catalyst	NADH analogue	Solvent	Temp (°C)	Yield (%)[b]
1	$BF_3{\cdot}OEt_2$	**1**	toluene	60	2
2	Et_3B	**1**	toluene	60	0
3	Ph_3B	**1**	toluene	60	0
4	$(C_6F_5)_3B$	**1**	toluene	60	28
5	**9**	**1**	toluene	60	70
6	**9**	**2**	toluene	60	46
7	**9**	**3**	toluene	60	0
8	**9**	**4**	toluene	60	13
9	**9**	**5**	toluene	60	13
10	**9**	**6**	toluene	60	6
11	**9**	**1**	DCE	60	72
12	**9**	**1**	THF	60	70
13	**9**	**1**	1,4-dioxane	60	78
14	**9**	**1**	MeCN	60	23
15	**9**	**1**	DMF	60	0
16	**9**	**1**	DMSO	60	0
17	**9**	**1**	*i*-PrOH	60	0
18	**9**	**1**	1,4-dioxane	100	97



[a] Reaction conditions: cyclohexanecarbaldehyde (**7a**, 0.25 mmol), NADH analogue (0.38 mmol, 1.5 equiv), catalyst (0.013 mmol, 5 mol%), solvent (1 mL).
[b] Determined by GC analysis with an internal standard (biphenyl).

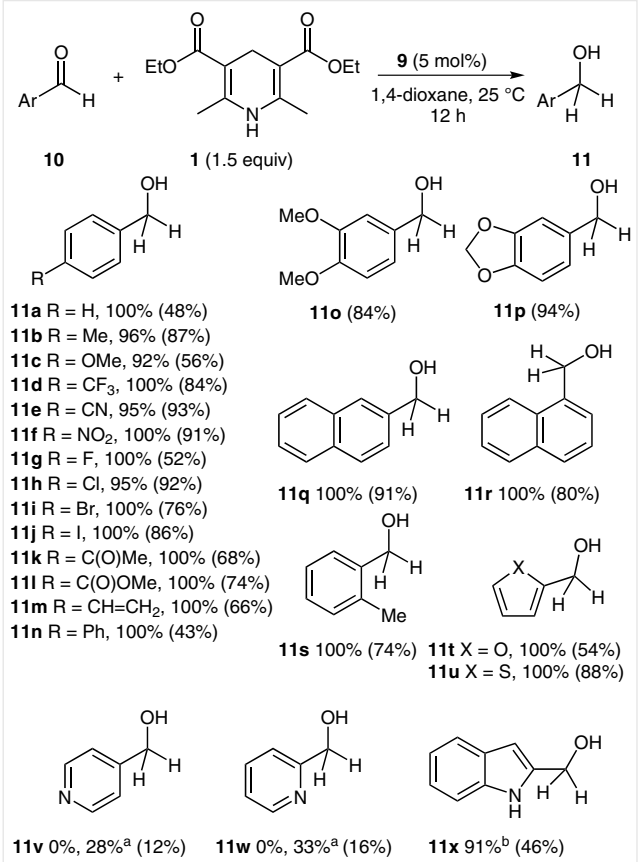
were used as synthetic NAD(P)H analogues, the hydrogenation reaction did not proceed efficiently (entries 7–10). These results indicate that Hantzsch ester **1** is the optimal hydrogen donor for this hydrogenation.[17] We then investigated the effect of the solvent on the reaction (entries 11–17). The reaction proceeded in 1,2-dichloroethane (DCE) and tetrahydrofuran (THF) to give **8a** in 72% and 70% yields, respectively (entries 11 and 12). When 1,4-dioxane was used as the solvent, the yield of **8a** increased to 78% (entry 13). On the other hand, the use of acetonitrile as the solvent led to a lower yield of **8a** (entry 14). No reaction occurred in *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), or isopropyl alcohol (entries 15–17). When the hydrogenation was carried out in 1,4-dioxane at 100 °C, the desired alcohol **8a** was obtained in 97% yield (entry 18).

With the optimized reaction conditions in hand, we next investigated the scope of aliphatic aldehydes that can be used in this hydrogenation protocol (Scheme 2). The hydrogenation of cyclopentanecarbaldehyde (**7b**) was performed at 100 °C in 1,4-dioxane to give cyclopentanemethanol (**8b**) in 78% yield. Linear aliphatic aldehydes **7c**–**f** underwent the reaction to afford the corresponding alcohols **8c**–**f** in 71–82% yields. The hydrogenation of 10-undecenal (**7g**) proceeded to give 10-undecen-1-ol (**8g**) in 71% yield. In this reaction, the terminal alkene group remained intact. The reactions of the sterically hindered substrates 3,3-dimethylbutylaldehyde (**7h**) and 1-adamantanecarbaldehyde (**7i**) gave 3,3-dimethyl-1-butanol (**8h**) and 1-adamantanemethanol (**8i**) in 88% and 70% yields, respectively.



Scheme 2 Scope of aliphatic aldehydes. *Reagents and conditions*: aliphatic aldehyde (**7**, 0.25 mmol), **1** (0.38 mmol, 1.5 equiv), **9** (0.013 mmol, 5 mol%), 1,4-dioxane (1 mL). The yields were determined by GC analysis using an internal standard (biphenyl or mesitylene). Isolated yields are described in parentheses. [a] Determined by ^{1}H NMR analysis using an internal standard ($Cl_2CHCHCl_2$).

Next, we studied the catalytic hydrogenation of aromatic aldehydes with Hantzsch ester **1** (Scheme 3). Borane **9** also effectively catalyzed the hydrogenation of aromatic aldehydes **10** with Hantzsch ester **1**, even at 25 °C, to give the corresponding benzyl alcohols **11** in excellent yields.[12] The hydrogenation of benzaldehyde (**10a**) gave benzyl alcohol (**11a**) in quantitative yield. Benzaldehyde derivatives bearing electron-donating (R = Me and OMe) and electron-withdrawing (R = CF_3, CN, and NO_2) groups in the *para* position (**10b**–**f**) underwent hydrogenation to afford the corresponding benzyl alcohols **11b**–**f** in 92–100% yields. The reaction of *para*-halogenated (R = F, Cl, Br, and I) benzaldehyde derivatives **10g**–**j** gave the corresponding benzyl alcohols **11g**–**j** in excellent yields. In the hydrogenation of 4-acetylbenzaldehyde (**10k**), the aldehyde group was selectively reduced; the ketone group remained intact. Ester and alkene groups also remained intact under the reaction conditions (**11l**,**m**). 3,4-Dimethoxybenzaldehyde (**10o**) and piperonal (**10p**)[18] underwent hydrogenation to afford alcohols **11o** and **11p** in 84% and 94% yields, respectively. The



Scheme 3 Scope of aromatic aldehydes. *Reagents and conditions*: aromatic aldehyde (**10**, 0.25 mmol), **1** (0.38 mmol, 1.5 equiv), **9** (0.013 mmol, 5 mol%), 1,4-dioxane (1 mL). The yields were determined by GC analysis using an internal standard (biphenyl or mesitylene). Isolated yields are described in parentheses. [a] The reaction performed at 100 °C. [b] Determined by ^{1}H NMR analysis using an internal standard ($Cl_2CHCHCl_2$).

reaction of 2-naphthylaldehyde (**10q**), 1-naphthylaldehyde (**10r**), and 2-methylbenzaldehyde (**10s**) took place to quantitatively afford alcohols **11q**, **11r**, and **11s**, respectively. We next tested the hydrogenation of heteroaromatic aldehydes. The hydrogenations of furan-2-carbaldehyde (**10t**) and thiophene-2-carbaldehyde (**10u**) were carried out at 25 °C to afford alcohols **11t** and **11u**, respectively, in quantitative yields. On the other hand, the reaction of pyridine derivatives **10v** and **10w** did not proceed at 25 °C. When the reaction temperature was elevated to 100 °C, the desired alcohols **11v** and **11w** were obtained in 28% and 33% yields, respectively. The strong coordination of the pyridine nitrogen to the boron center inhibited the reaction. On the other hand, indole-2-carboxaldehyde (**10x**) underwent the reaction at 25 °C to give **11x** in 91% yield.

In summary, we have developed the tris[3,5-bis(trifluoromethyl)phenyl]borane-catalyzed hydrogenation of unactivated aldehydes with a Hantzsch ester as a synthetic NADH analogue. The hydrogenation of a variety of aliphatic and aromatic aldehydes proceeded efficiently to give the corresponding primary alcohols in good to excellent yields. Mechanistic studies of this hydrogenation reaction are currently underway in our laboratory.[19]

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378846.

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(17) We also tested the other hydrogen donors, see the Supporting Information. The reaction with Hantzsch ester **2** provided the best result.

(18) **Typical Procedure for the Hydrogenation Reaction (10p, Scheme 3)**
In a glovebox, piperanal (**10p**, 38 mg, 0.25 mmol) and Hantzsch ester **1** (95 mg, 0.38 mmol) were added to a solution of tris[3,5-bis(trifluoromethyl)phenyl]borane (**9**, 8.1 mg, 0.013 mmol) in dry 1,4-dioxane (1 mL). After the reaction mixture was stirred at 25 °C for 12 h, the solvent was removed by evaporation under reduced pressure. The obtained crude material was purified by silica gel column chromatography (eluent: hexane–EtOAc, 9:1) to give piperonyl alcohol (**11p**, 36 mg, 94%) as a colorless solid. ^{1}H NMR (396 MHz, $CDCl_3$): δ = 2.02 (br s, 1 H, OH), 4.55 (s, 2 H, CH_2OH), 5.94 (s, 2 H, OCH_2O), 6.77 (d, *J* = 8.1 Hz, 2 H, ArH), 6.80 (d, *J* = 8.1 Hz, 2 H, ArH), 6.85 (s, 1 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.1, 101.0, 107.8, 108.1, 120.4, 134.8, 147.0, 147.7. MS (EI): *m/z* = 152 $[M]^+$.

(19) The reviewer pointed out the possible participation of borohydride species in the catalytic cycle (see ref. 15). However, the preliminary NMR experiment of borane **9** with Hantzsch ester **1** did not show the formation of borohydride species. Detailed mechanistic studies including DFT calculation are under investigation and will be reported in due course.