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Biomimetic hydrogenation: a reusable NADH co-enzyme model for hydrogenation of α,β-epoxy ketones and 1,2-diketones

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ABSTRACT

A biomimetic method has been developed to transform α,β-epoxy ketones or 1,2-diketones into corresponding β-hydroxy ketones or α-hydroxy ketones using a catalytic amount of BNAH or BNA^+Br^-. The regeneration of BNAH or BNA^+Br^- is achieved by a mixture of $HCOOH/Et_3N$. A radical mechanism is proposed to explain these observations.

$NAD(P)^+/NAD(P)H$ coenzyme couple plays an important role in the redox reaction of biological system (Scheme 1).[1] It is of great significance to simulate the function of the co-enzyme couple and apply them to synthetic organic chemistry. However, a great difficulty of this biocatalytic reduction is the use of a stoichiometric amount of the expensive NADH co-enzyme. In order to solve this problem, on one hand, great efforts have been made to turn NAD^+ into NADH,[2] generally mediated by enzyme or metallic complexes.[3,4] On the other hand, NAD(P)H models have become the focus of biomimetic chemistry over the past few decades. As the simplest NAD(P)H models,[5] Hantzsch ester and 1-benzyl-1,4-dihydronicotinamide (BNAH) are widely exploited. However, a stoichiometric amount of the NADH model compound needs to be used in most of these procedures.[6,7] It remains a challenge to achieve these reactions with a catalytic amount of NAD^+/NADH model (Scheme 2).[8,9]

Herein, we would report the hydrogenation of α,β-epoxy ketones and 1,2-diketones to form β-hydroxy ketones and α-hydroxy ketones in good to excellent yields mediated by a catalytic amount of BNA^+/BNAH. In 1977, Ohnishi and Tanimoto, reported that BNA^+ could be converted to BNAH by a mixture of $HCOOH/Et_3N$ in acetonitrile at room temperature,[10] but no corresponding following application was reported. It would be of great interest to accomplish the catalytic function of BNA^+, mediated by a mixture of $HCOOH/Et_3N$, especially in the absence of any metallic catalyst or enzyme.

The initial experiment was focused on whether the α,β-epoxy ketone (**1a**) could be converted to β-hydroxy ketone (**2a**) by formic acid and triethylamine in the presence of a NAD^+ model.[11] When we tested the effect of irradiation with a 450 W high-pressure mercury lamp ($\lambda > 300$ nm),[9,12] **2a** was obtained. Next, different solvents were employed as shown in Table 1. It was necessary for the reaction to proceed smoothly in a mixed organic/water solvent to compromise the solubility of both the substrate and the ionic catalyst. $AcOEt/H_2O$ (1:1) gave comparatively good isolated yields, while water or acetonitrile/water (1:1) gave moderate conversion and low yield (Table 1, entries 1 and 2). Thus $AcOEt/H_2O$ (1:1) was used in the following experiments.

Previous studies showed that $HCOOH/Et_3N$ plays an important role in the hydrogenation reaction.[13] We wondered whether or not the pH value has an influence on the reaction. Different proportions of formic acid and triethylamine were tested. It seems that a trace amount of product could be obtained in the acidic conditions while the conversion and the yield are greatly increased in the basic conditions (entry 4). When the amount of formic acid and triethylamine was approximately increased to 5 equiv and 6.3 equiv, a good yield was obtained within a short time (entry 5). However, use of more formic acid and triethylamine does not enhance the yield (entry 8). Use of more triethylamine appears to accelerate the conversion of the substrate (entries 5–7). In addition, some other amines can also work, such as diethylamine and *N,N*-diisopropylethylamine (entries 9 and 10).

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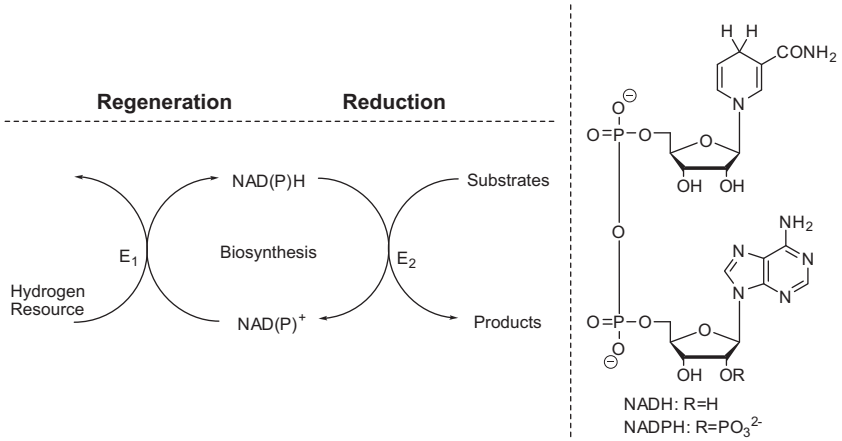
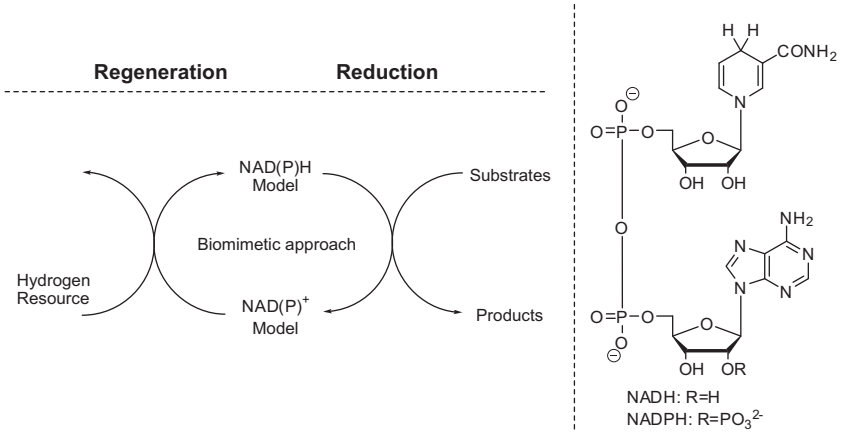
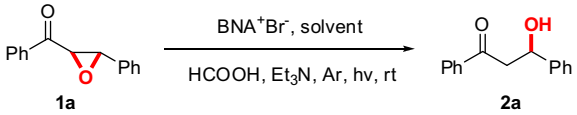


Scheme 1. NAD(P)H-mediated reduction reaction ($\mathbf{E_1}$: regeneration enzyme; $\mathbf{E_2}$: production enzyme).



Scheme 2. Biomimetic hydrogenation process.

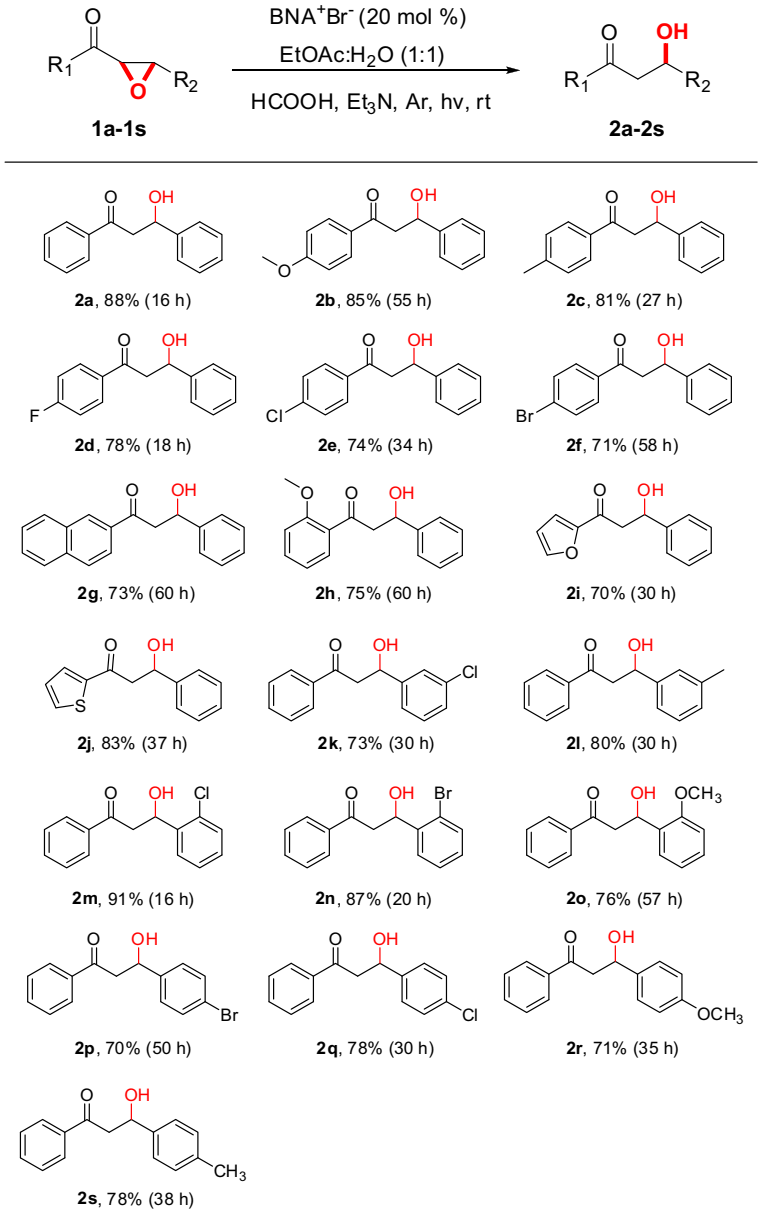
Table 1
Optimization of the conditions of hydrogenation of α,β-epoxy ketones to β-hydroxy ketones[a]



Entry	HCOOH (equiv)	Et_3N (equiv)	Solvent (v/v = mL:mL)	Catalyst (%)	Time (h)	Conversion (%)	Isolated yield (%)
1	5	6.3	H_2O	20	16	80	45
2	5	7.5	CH_3CN/H_2O = 2:2	10	30	76	33
3	5	6.3	Et_2O/H_2O = 2:2	10	16	98	68
4	4	5	EtOAc/H_2O = 2:2	10	30	97	47
5	5	6.3	EtOAc/H_2O = 2:2	10	16	95	78
6	5	5.5	EtOAc/H_2O = 2:2	10	16	85	73
7	5	10	EtOAc/H_2O = 2:2	10	14	95	51
8	10	11	EtOAc/H_2O = 2:2	10	16	98	69
9	5	6.3	EtOAc/H_2O = 2:2	10	28	90	70[b]
10	5	6.3	EtOAc/H_2O = 2:2	10	28	88	54[c]
11	5	6.3	EtOAc/H_2O = 2:2	10	16	<10	—[d]
12	5	6.3	EtOAc/H_2O = 2:2	10	24	<10	—[e]
13	5	6.3	EtOAc/H_2O = 2:2	—	20	24	7[f]
14	5	6.3	EtOAc/H_2O = 2:2	20	16	100	88
15	5	6.3	EtOAc/H_2O = 2:2	5	16	88	60

[a] Reactions under Ar and irradiation with a 450 W high-pressure mercury lamp (λ > 300 nm).
[b] Triethylamine is substituted by diethylamine.
[c] Triethylamine is substituted by *N*,*N*-diisopropylethylamine.
[d] At 70 °C without *hv*. '—'Means no product observed.
[e] At room temperature without *hv*. '—'Means no product observed.
[f] '––'Means no catalyst was added.

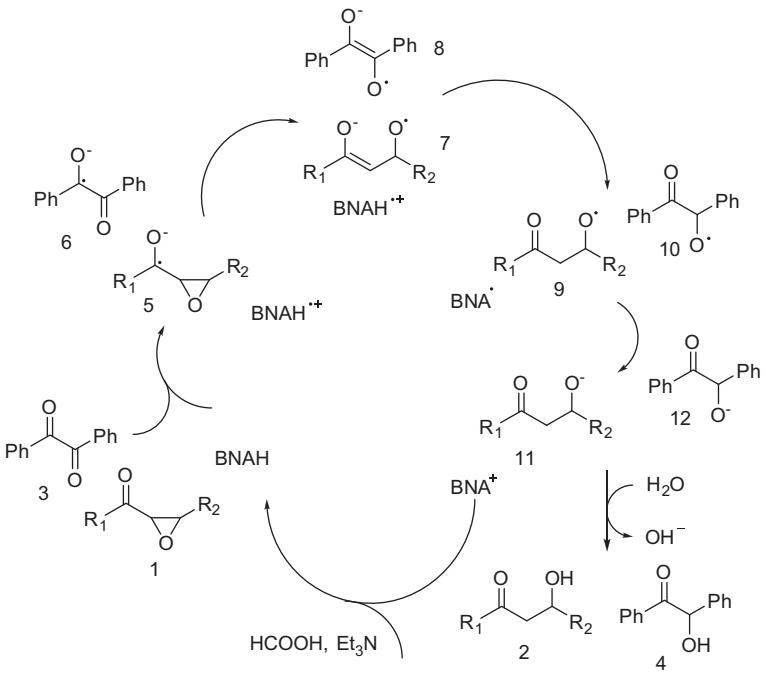
Table 2
Substrate scope of α,β-epoxy ketones[a,b]



[a] **1** (0.4 mmol), BNA^+ (0.08 mmol), HCOOH (5 equiv), Et_3N (6.3 equiv) were stirred in 4 mL EtOAc/H_2O (1:1) at room temperature under Ar and irradiation with a 450 W high-pressure mercury lamp (λ >300 nm).
[b] Isolated yields.

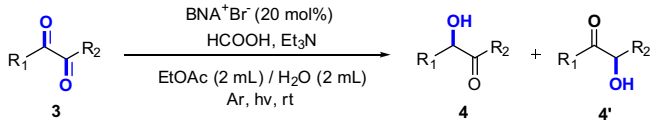
Other experimental conditions were also investigated. When the reaction was carried out at room temperature or heated at 70 °C without irradiation, no product was observed (entries 11 and 12). A high temperature led to the destruction of the catalyst in the presence of formic acid and triethylamine.[14] When the reaction was proceeded in the absence of BNA^+Br^-, both the conversion and the yield were poor (entry 13).[15] However, when the amount of BNA^+Br^- was decreased to 5 mol %, a moderate yield (60%) was obtained (entry 15). When the amount of BNA^+Br^- was increased to 20 mol %, a complete conversion and an excellent isolated yield (88%) were obtained (entry 14).

With the optimized conditions in hand, we explored the scope of this reaction. Various α,β-epoxy ketones were investigated with irradiation using 20 mol % of BNA^+Br^- as shown in Table 2. Good to excellent yields (70–91%) were obtained in the presence of electron-donating groups or electron-withdrawing groups. Substitution at the *ortho*, *para*, or *meta* positions can all be well tolerated (**2k**–**2s**). When the R_1 is substituted by the 2-furyl group or the 2-thienyl group, the reaction can also proceed smoothly (**2i** and **2j**). The reaction times varied with different substituents. When R_1 was substituted with electron-donating groups, the reaction times would be long (**2b**, **2h**). When R_1 was substituted with halogen-containing phenyl groups, the reaction times increased with weakening ability of electron-drawing (**2d–2f**). When R_2 is substituted with 2-halogen phenyl groups, the reaction can proceed well within a short time (**2m**, **2n**). In addition, when R_1 is substituted by



Scheme 3. A proposed mechanism for the reactions.

Table 3
Catalytic hydrogenation of 1,2-diketones mediated by BNA^+Br



Entry	R_1	R_2	Products	Yield[a] (%) (ratio[b] **4/4′**)
1	C_6H_5	C_6H_5 **3a**	**4a**	85
2	C_6H_5	4-FC_6H_4 **3b**	**4b/4b′**	62 (1.1:1)
3	C_6H_5	4-$MeOC_6H_4$ **3c**	**4c/4c′**	74 (6.3:1)

[a] Isolated yields.
[b] The ratio of **4/4′** was determined by ^1H NMR spectrum.

the *tert*-butyl or the methyl group, unfortunately, no detectable product was observed. This probably was due to that the aliphatic anionic radical **5** would be quite unstable if R_1 was substituted by aliphatic groups. So **1** can hardly be converted to **5** and the reaction can hardly proceed (see Scheme 3).

Further investigations were carried out on the feasibility of other type of substrates. To our surprise, benzil (**3a**) could be converted to benzoin (**4a**) with the above reaction condition, as shown in Table 3.[8d] However, it was difficult to convert benzil completely to benzoin. When the reaction time was extended to 66 h, a good yield (85%) was obtained using formic acid and triethylamine catalyzed by BNA^+Br^- (20 mol %) in the solvent of EtOAc/H_2O (1:1) (Table 3, entry 1). Next, we tested the selectivity of substituted benzil under this catalytic system. When we employed **3c** as the substrate, we found that the carbonyl groups next to the phenyl rings without electron-donating groups tended to be reduced easier (Table 3, entry 3). However, when one of the phenyl rings of benzil was substituted with the 4-fluoro phenyl group, the selectivity would be not obvious (Table 3, entry 2).

In order to study the possible mechanism of the reactions, more experiments were performed. When the reaction of reducing α,β-epoxy ketone (**1a**) was under the air instead of argon, both the conversion and the yield were poor, which was consistent with the phenomenon of the former work about the hydrogenation of α,β-epoxy ketones.[9,12b] In addition, a catalytic amount of BNAH could also reduce α,β-epoxy ketone as efficiently as BNA^+Br^-, indicating a turnover of the redox couple.[9]

Based on the above results and relevant literatures,[12b,16] a radical mechanism is proposed for this reaction, as shown in Scheme 3. First, BNA^+ is transformed into 1-benzyl-1,4-dihydronicotinamide (BNAH) in the presence of a mixture of HCOOH/Et_3N.[9,10,14,17] Second, an electron from BNAH is given to **1** (or **3**) to form an anionic radical **5** (or **6**) and $BNAH^{+\cdot}$. Third, a carbon–oxygen bond cleavage occurs to convert **5** (or **6**) into **7** (or **8**). Then, a proton is transferred from $BNAH^{+\cdot}$ to **7** (or **8**) followed by an enol/keto tautomerization to form **9** (or **10**) and BNA·. Next, **9** (or **10**) accepts an electron transferred from BNA· to turn into **11** (or **12**) while the BNA^+ is regenerated. At last, the reaction is completed with the protonation of **11** (or **12**) by water.

In conclusion, an efficient method has been developed to transform α,β-epoxy ketones or benzil into corresponding β-hydroxy ketones or benzoin using a BNAH (or BNA^+Br^-) as a catalyst. As far as we know, this is the first time to achieve the hydrogenation catalyzed by an NAD^+/NADH co-enzyme model employing the mixture of HCOOH/Et_3N in the absence of any metal complex or enzyme. More applications of this protocol are under exploration.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.047.

These data include MOL files and InChiKeys of the most important compounds described in this article.

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