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Biomimetic Asymmetric Hydrogenation: In Situ Regenerable Hantzsch Esters for Asymmetric Hydrogenation of Benzoxazinones

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Supporting Information

ABSTRACT: A catalytic amount of Hantzsch ester that could be regenerated in situ by Ru complexes under hydrogen gas has been employed in the biomimetic asymmetric hydrogenation of benzoxazinones with up to 99% ee in the presence of chiral phosphoric acid. The use of hydrogen gas as a reductant for the regeneration of Hantzsch esters makes this hydrogenation an ideal atom economic process.

Reduced nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) are recognized as a couple of the most important coenzymes found in living cells that play vital roles in reduction−oxidation (redox) metabolism (Figure 1A).[1] The reduced form of the coenzyme NAD(P)H acts as reductant for most of the reductases in the cell that need to reduce their substrates. Because coenzyme NAD(P)H is too expensive to be used in stoichiometric amounts, the oxidized form of the coenzyme has to be transformed into a reduced form for the next redox cycle in vivo through cellular respiration, such as glycolysis or the citric acid cycle (TCA cycle), which convert biochemical energy from nutrients into adenosine triphosphate (ATP).[2]

Owing to their importance in metabolism, NAD(P)H mimics have been a central point in biomimetic chemistry over the past few decades. As the simplest NAD(P)H model, Hantzsch esters (HEHs)[3] have been widely and successfully used as a hydrogen source in the biomimetic asymmetric transfer hydrogenation of C=C, C=N, and C=O bonds in the presence of organocatalysts[4,5] and metal catalysts.[6] Despite much progress having been achieved, most of the current research focuses on the hydride transfer ability and selectivity in redox reactions rather than the regeneration of Hantzsch ester.[7] Developing a biomimetic asymmetric hydrogenation system that simultaneously involves an asymmetric reduction process and the regeneration of Hantzsch ester is still a great challenge in the field of NAD(P)H mimics.

Hydrogen gas (H_2) is recognized as the most cost-effective reductant and yields no byproducts. Therefore, asymmetric hydrogenation processes that involve the use of transition metals in conjunction with hydrogen gas are ubiquitous methods to access various biologically active compounds.[8] Developing a biomimetic asymmetric hydrogenation reaction using H_2 as the reductant for the regeneration NAD(P)H models is of great interest in the field of NAD(P)H mimics (Figure 1B). Herein, we report an efficient method for in situ regeneration of Hantzsch ester from Hantzsch pyridine under hydrogen gas for chiral phosphoric acid catalyzed biomimetic asymmetric hydrogenation of benzoxazinones.[9−11]

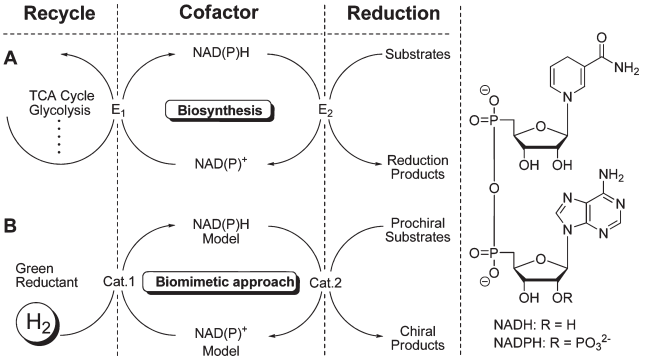
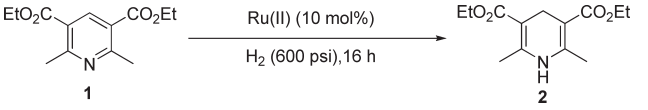


Figure 1. (A) NAD(P)H-mediated reduction reaction (E_1: regeneration enzyme; E_2: production enzyme). (B) Biomimetic hydrogenation process (Cat. 1: regeneration catalyst; Cat. 2: production catalyst).

Table 1. Generation of Hantzsch Ester 2 from Pyridine 1[a]



entry	cat.	solvent	T (°C)	conv. (%)[b]
1	$RuCl_2(PPh_3)_3$	toluene	25	---
2	Grubbs' cat. I	toluene	25	---
3	Grubbs' cat. II	toluene	25	---
4	$[Ru(p\text{-cymene})I_2]_2$	toluene	25	4
5	$[Ru(p\text{-cymene})I_2]_2$	toluene	50	10
6	$[Ru(p\text{-cymene})I_2]_2$	CH_2Cl_2	50	29
7	$[Ru(p\text{-cymene})I_2]_2$	THF	50	39
8[c]	$[Ru(p\text{-cymene})I_2]_2$	THF	50	62
9	$[Ru(p\text{-cymene})I_2]_2$	THF	70	64
10[d]	$[Ru(p\text{-cymene})I_2]_2$	THF	70	69

[a] **1** (0.02 mmol), Ru(II) (10 mol %), H_2 (600 psi), solvent (2 mL), 16 h. [b] Determined by ^1H NMR. [c] H_2 (1000 psi). [d] **2** (0.02 mmol) was added instead of **1**. After reaction, mixture **2**/**1** (69/31) was obtained.

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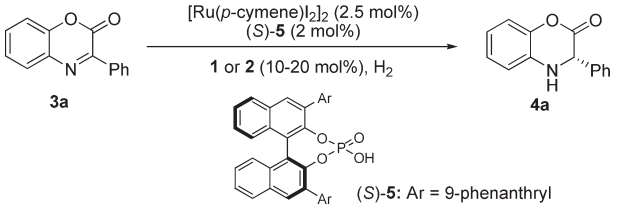
Table 2. In Situ Regeneration of Hantzsch Ester 2 for Biomimetic Asymmetric Hydrogenation of Benzoxazinone 3a[a]



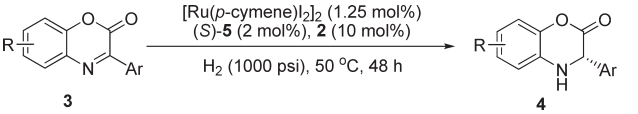
entry	solvent	H_2 (psi)	conv. (%)[b]	ee (%)[c]
1[d]	THF	600	<5	----
2[e]	THF	600	28	89
3	THF	600	23	95
4	CH_2Cl_2	600	18	97
5	THF/CH_2Cl_2 (3:1)	600	26	96
6	THF/CH_2Cl_2 (1:1)	600	40	97
7	THF/CH_2Cl_2 (1:3)	600	38	98
8	THF/CH_2Cl_2 (1:1)	800	47	96
9	THF/CH_2Cl_2 (1:3)	800	52	98
10	THF/CH_2Cl_2 (1:3)	1000	64	98
11[f]	THF/CH_2Cl_2 (1:3)	1000	>95	98
12[f,g]	THF/CH_2Cl_2 (1:3)	1000	>95	98
13[f,h]	THF/CH_2Cl_2 (1:3)	1000	>95	98
14[f,i]	THF/CH_2Cl_2 (1:3)	----	>95	98

[a] **3a** (0.10 mmol), **1** (20 mol %), [Ru(*p*-cymene)I_2]$_2$ (2.5 mol %), (*S*)-**5** (2 mol %), Solvent (2 mL), 16 h, 50 °C. [b] Determined by ^{1}H NMR. [c] Determined by HPLC. [d] No addition of **1**. [e] 70 °C. [f] 48 h. [g] **2** (20 mol %). [h] **3a** (0.20 mmol), **2** (10 mol %), [Ru(*p*-cymene)I_2]$_2$ (1.25 mol %), (*S*)-**5** (2 mol %). [i] **2** (120 mol %), with no addition of [Ru(*p*-cymene)I_2]$_2$.

The key point to realize in the above-mentioned idea is the high efficiency and selectivity for regenerating Hantzsch ester **2** from pyridine **1** which belongs to the partial hydrogenation of aromatic heterocycle. Based on our efforts in asymmetric hydrogenation and transfer hydrogenation of heteroaromatic compounds,[12,13] Ru(II) complexes were chosen as the catalysts for the reduction of pyridine **1** under hydrogen gas (Table 1). From the survey of some commercially available Ru(II) complexes, [Ru(*p*-cymene)I_2]$_2$ provided Hantzsch ester **2** with 4% conversion (entries 1−4). The primary screening of solvents showed that CH_2Cl_2 and THF were relatively good choices for the generation of Hantzsch ester **2** (entries 5−7). With increasing reaction temperature or pressure of hydrogen gas, an improvement in reaction conversion was observed (entries 8−9). Dehydroaromatization occurred in the controlled trial (entry 9 vs 10).

Further investigations were carried on the feasibility of in situ regeneration of Hantzsch ester **2** for biomimetic asymmetric hydrogenation in the presence of a Brønsted acid (Table 2). The inhibition of a background reaction of a substrate promoted by achiral Ru complexes is another challenge. Benzoxazinone **3a** emerged as a suitable model substrate owing to its inactivity under hydrogen gas without the addition of Hantzsch pyridine **1** (entry 1). Initially, a promising result (28% conversion, 89% ee) was obtained (entry 2).[11a] Examination of the solvent effects indicated that the solvent mixture DCM/THF was the best choice for the regeneration of Hantzsch ester **2** and transfer

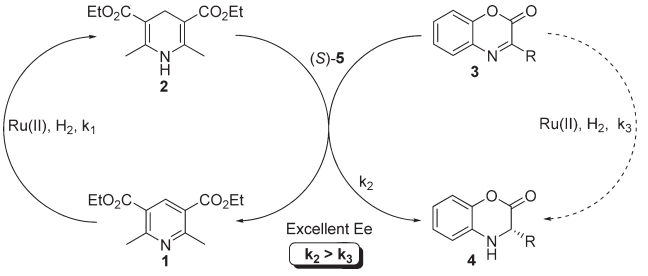
Table 3. Biomimetic Asymmetric Hydrogenation of Benzoxazinones 3 Using Catalytic Amount of Hantzsch Ester 2[a]



entry	R in **3**	Ar in **3**	yield (%)[b]	ee (%)[c]
1	H	Ph	93 (**4a**)	98 (*S*)
2	H	4-MeOC_6H_4	96 (**4b**)	98 (*S*)
3	H	4-MeC_6H_4	96 (**4c**)	99 (*S*)
4	H	3,4-$Me_2C_6H_3$	98 (**4d**)	98 (*S*)
5	H	4-ClC_6H_4	96 (**4e**)	99 (*S*)
6	H	4-BrC_6H_4	95 (**4f**)	99 (*S*)
7	H	4-FC_6H_4	94 (**4g**)	99 (*S*)
8	H	3-FC_6H_4	86 (**4h**)	98 (*S*)
9	H	2-Thienyl	59 (**4i**)	92 (*R*)
10	6-Cl	Ph	81 (**4j**)	98 (*S*)
11	6-Me	Ph	83 (**4k**)	96 (*S*)
12	7-Me	Ph	90 (**4l**)	94 (*S*)
13	6-^{t}Bu	Ph	68 (**4m**)	98 (*S*)

[a] **3** (0.20 mmol), **2** (10 mol %), [Ru(*p*-cymene)I_2]$_2$ (1.25 mol %), (*S*)-**5** (2 mol %), H_2 (1000 psi), THF/CH_2Cl_2 1/3 (2 mL), 48 h, 50 °C. [b] Isolated yields. [c] Determined by HPLC.

Scheme 1. Proposed Mechanism for Biomimetic Asymmetric Hydrogenation of Benzoxazinones 3 Using Catalytic Amount of Hantzsch Ester 2



hydrogenation of benzoxazinone **3a** (entries 3−7). A moderate conversion (67%) was obtained when the hydrogen pressure was increased to 1000 psi (entries 8−10). Prolonging the reaction time was good for achieving complete conversion (entry 11). The adoption of Hantzsch ester **2** instead of Hantzsch pyridine **1** gave the same result with respect to conversion and enantioselectivity (entry 12 vs 11). To our delight, reducing the amount of Hantzsch ester **2** to 10 mol % leads to no deterioration with regard to conversion and enantioselectivity (entry 13). Notably, this catalytic efficiency is identical to that of a pure organocatalytic process which consumed a stoichiometric amount of Hantzsch ester **2** (entry 13 vs 14).[11a]

Having established the optimized conditions, the scope of enantioselective synthesis of dihydrobenzoxazinones **4** using a catalytic amount of Hantzsch ester **2** was explored (Table 3). In general, good yields (86−98%) and excellent enantioselectivities (98−99% ee) were obtained in this biomimetic asymmetric hydrogenation regardless of the electronic properties of the phenyl ring of benzoxazinones **3** (entries 1−8). For heteroaromatic

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benzoxazinone **3i**, a moderate yield (59%) but high enantioselectivity (92% ee) was observed (entry 9). The reduction of 6- or 7-position substituted 2-phenyl benzoxazinones **3** gave dihydrobenzoxazinones **4** with excellent enantioselectivities (94−98% ee) and moderate to good yields (68−90%, entries 10−13).

A proposed mechanism is depicted in Scheme 1 to account for the biomimetic asymmetric hydrogenation of benzoxazinones **3** promoted by a metal/Brønsted acid relay catalyst[14,15] with a catalytic amount of Hantzsch ester **2**. It is assumed that chiral phosphoric acid (*S*)-**5** catalyzes the asymmetric transfer hydrogenation of benzoxazinones **3** with Hantzsch ester **2** first affording optically active products **4** and Hantzsch pyridine **1**. Subsequently, the undesirable product pyridine **1** undergoes hydrogenation to regenerate Hantzsch ester **2** for the next catalytic cycle in the presence of Ru complexes under hydrogen gas. The excellent enantioselectivities achieved in this enantioselective transfer hydrogenation is attributed to the fact that the reaction rate of this principal reaction, k_2, is faster than that of the undesired side reaction, k_3, which generates dihydrobenzoxazinones **4** in racemic form (Scheme 1).[16]

In summary, we have successfully developed an efficient method for the regeneration of Hantzsch ester from Hantzsch pyridine with Ru complexes as the catalyst under hydrogen gas. A catalytic amount of Hantzsch ester regenerated in situ has been employed in the chiral phosphoric acid promoted biomimetic asymmetric hydrogenation of benzoxazinones with up to 99% ee. The use of hydrogen gas as the reductant for the regeneration of Hantzsch ester makes this biomimetic asymmetric hydrogenation an ideal atom economic process. Further investigations on the application of the developed strategy and detailed mechanistic studies of the catalytic cycle are currently ongoing in our lab.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures and characterization data for the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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