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Autocatalytic Asymmetric Reduction of 2,6-Diacetylpyridine

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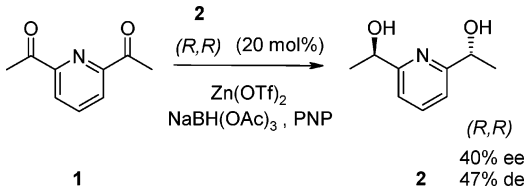
ABSTRACT



We report here that the C_2-symmetric diol 2,6-bis(1-hydroxyethyl)pyridine (2) can effect chiral-catalyzed reduction of 2,6-diacetylpyridine (1) and produce more of the diol (2) with the same configuration in an enantiomerically enriched form. The two carbonyl functionalities of (1) are reduced in 90% conversion to produce the enantio-enriched C_2-symmetric diol (40% ee, 47% de) using zinc trifluoromethanesulfonate and a catalytic amount of the chiral C_2-symmetric diol (2).

The first asymmetric example of an autocatalytic reaction was reported by Soai and co-workers, whereby dialkylzinc reagents were added to 3-pyridinecarboxyaldeyde to produce the enantio-enriched pyridyl alkanol.[1] This pioneering work was further developed over the years to produce an exceptionally efficient autocatalytic system in the form of diisopropylzinc addition to 5-pyrimidinecarboxyaldehydes.[2] Autocatalytic asymmetric reactions continue to generate considerable interest,[3] and autocatalytic self-replication can provide some valuable insight into replication reactions in nature.[4]

In our efforts to effect catalytic asymmetric reduction of 2,6-diacetylpyridine (**1**) using a chiral Zn(II) complex as a Lewis acid, we have discovered that the product of the reaction itself (**2**) can catalyze stereoselective reduction of **1** and produce more of the diol **2** with the same configuration (Table 1). To the best of our knowledge, this is the first reported example of an autocatalytic asymmetric reduction.

The C_2-symmetric diol (**2**) can be readily obtained, in high enantiomeric purity, through reduction of 2,6-diacetylpyridine (**1**) using stoichiometric amounts of chiral DIP-Cl.[5] Alternatively, the diol **2** can be produced by catalytic asymmetric hydrogenation of 2,6-diacetylpyridine 1.[6] The diol (**2**) has been shown to be a useful intermediate in the synthesis of other chiral ligands.[7] It has also been examined as a chiral ligand for the enantioselective addition of diethylzinc to aldehydes.[8]

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(4) (a) Siegel, J. S. *Nature* **2002**, *419*, 346. (b) Saghatelian, A.; Yokobayashi, Y.; Soltani, K.; Ghadiri, M. R. *Nature* **2001**, *409*, 797. (c) Bada, J. L. *Nature* **1995**, *374*, 594.

(5) (a) Ramachandran, P. V.; Chen, G. M.; Lu, Z. H.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 3795. (b) Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 2379. (c) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. In our hands, the reduction of 2,6-diacetylpyridine **1** with (+)-DIP-Cl afforded the (*R*,*R*)-diol **2** in 82% yield with 95% ee and 78% de.

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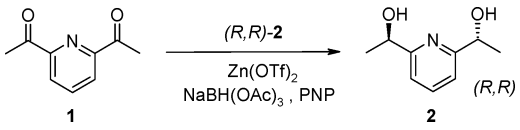
Table 1. Effect of Catalyst Loading on Autocatalytic Reduction of 2,6-Diacetylpyridine **1**



1 **2**

entry[a]	**2**[a] (mol %)	$Zn(OTf)_2$ (mol %)	ee[b] (%)	de[b] (%)
1	0	10	0	35
2	0	20	0	45
3	10	5	28	25
4	20	10	38	41
5	20	120	40	47

[a] Conversions were determined by ^{1}H NMR and were >80% after 24 h. [b] Ee and de were determined by chiral HPLC on a Chiralcel OD-H column and corrected for the added diol **2**.

In a typical reduction experiment, 2,6-diacetylpyridine (**1**) (10 mM) was treated with sodium triacetoxyborohydride (20 mM), *p*-nitrophenol (PNP) (60 mM), (*R*,*R*)-**2** (20 mol %), and zinc trifluoromethanesulfonate and stirred for 24 h at room temperature. The double reduction proceeded to 90% conversion in dichloromethane, and the diol (**2**) obtained after basic workup was determined by chiral HPLC to be enantiomerically enriched in the (*R*,*R*) form (40% ee and 47% de, Table 1, entry 5). The % conversion, ee, and de were corrected for the added diol **2**.

Interestingly, diastereoselectivity was observed even without addition of the chiral diol. When **1** was reduced in the presence of catalytic amounts of zinc trifluoromethanesulfonate, diol **2** was produced in a diastereomerically enriched form, where the homochiral form ((*R*,*R*)- and (*S*,*S*)-) of the diol predominates, but no enantiomeric excess was observed (Table 1, entries 1 and 2). The amount of zinc in the system can be reduced to catalytic amounts without significant change in selectivity (Table 1, entry 4), perhaps due to the poor solubility of the free zinc in dichloromethane.

The reducing system used in this reaction is generated in situ by a novel combination of sodium triacetoxyborohydride and *p*-nitrophenol. A variety of additives with acidic protons were investigated for the reduction of 2,6-diacetylpyridine **1**, and *p*-nitrophenol was found to be the most effective (Figure 1).

The reduction worked in the presence of other proton sources. Thiophenol (PhSH) was found to be only slightly less effective than *p*-nitrophenol. The reduction was less effective with additives such as pentafluorophenol (PFP), 1,1,1,3,3,3-hexafluoro-2-propanol (HFP), and phenol (PhOH). 1,1,1,3,3,3-Hexafluoro-2-propanol (HFP) was just as effective as phenol (PhOH), which leads us to believe that the

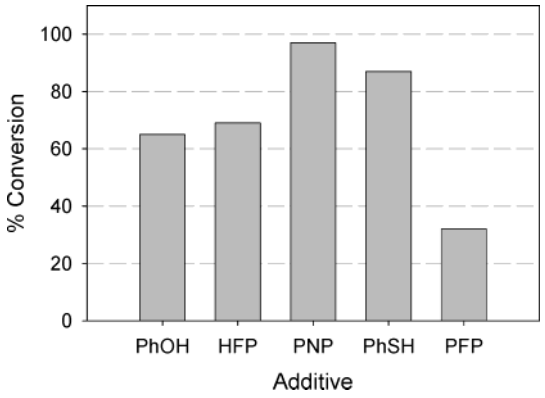
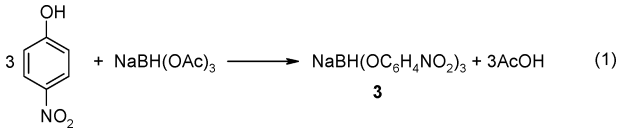


Figure 1. Effect of additives on the reduction of 2,6-diacetylpyridine with sodium triacetoxyborohydride in the presence of stoichiometric amounts of zinc trifluoromethanesulfonate in dichloromethane. Conversions were determined by ^{1}H NMR after 24 h. (PhOH, phenol; HFP, 1,1,1,3,3,3-hexafluoro-2-propanol; PNP, *p*-nitrophenol; PhSH, thiophenol; PFP, pentafluorophenol).

system is insensitive to the presence of aromatic rings but is affected by the acidity of the additive.

p-Nitrophenol reacts with sodium triacetoxyborohydride to produce tris(*p*-nitrophenoxy)borohydride **3** (eq 1). The complete substitution of the acetate groups with *p*-nitrophenoxy (OPNP) groups to produce the new borohydride species **3** is evident through ^{1}H NMR, where the acetate signal at 1.99 ppm is replaced by the acetic acid signal at 2.08 ppm after only 5 min at room temperature in dichloromethane (see Supporting Information). The ^{11}B NMR spectral analysis in methanol indicates the presence of a single species at (δ 18.6). Alcohols with enhanced acidity have been shown to react with sodium borohydride to generate tris(alkoxy)-borohydrides.[9] In contrast to the well-known disproportionation of alkoxyborohydrides, these tris(alkoxy)borohydrides, formed from acidic alcohols, are quite stable and resistant to any disproportionation.



In the absence of *p*-nitrophenol, no appreciable enantioselectivity was observed; therefore, we believe **3** to be important for the construction of the proposed active catalyst **4** (Scheme 1).

Molecular mechanics computation[10] of **1** coordinated to the proposed active catalyst (*R*,*R*)-**4** shows that the two *Re*-faces of **1** are blocked by the tris-(alkoxy)borohydride groups of **4** (see Supporting Information for a graphic illustration).

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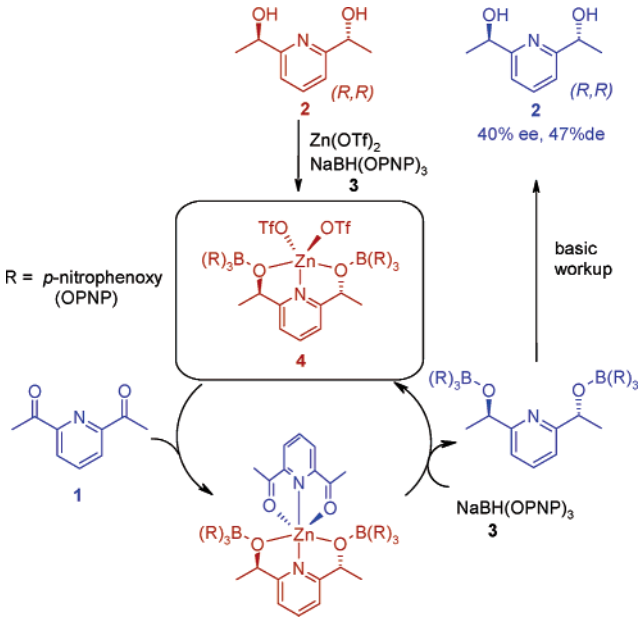
(10) Molecular mechanics computation was performed using HyperChem 5.0 from HyperCube, Inc., Gainesville, Florida. Octahedral geometry was assumed for the Zn(II) complex.

Scheme 1. Proposed Catalytic Rationale



The active catalyst **4** is only slightly soluble in dichloromethane, and the system operates under heterogeneous conditions. The ^{1}H NMR data obtained through an investigation of the system in a homogeneous medium (Figure 2) indicates that an initial coordination of the diol **2** to zinc is followed by the reaction to borohydride **3** to form the proposed active species **4**. The reaction to borohydride **3** is assisted by zinc, which increases the acidity of the diol in complex **4**.

In summary, we have described a new autocatalytic asymmetric system that generates two chiral centers through the reduction of 2,6-diacetylpyridine. The C_2-symmetric diol **2** was shown to interact with the metal and the reducing agent to produce what is believed to be the active catalyst **4**. The reaction employs a novel reducing system, which is generated in situ from sodium triacetoxyborohydride and *p*-nitrophenol. Detailed mechanistic studies of the described system are ongoing.

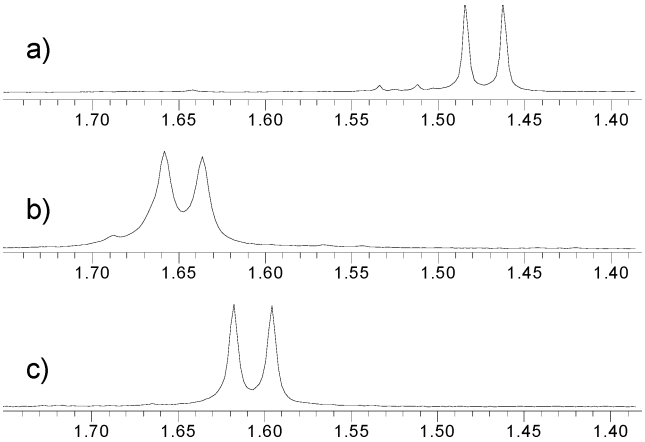


Figure 2. ^{1}H NMR of **2** in d_4-methanol. The doublet represents the $-CH_3$ of the diol. (a) Compound **2**. (b) **2**−zinc complex. (c) **2**−zinc complex after reaction with NaBH(OPNP)$_3$ **3**.

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Supporting Information Available: Detailed experimental procedures, including ^{1}H and ^{11}B NMR spectra, HPLC analysis of compound **2**, and a graphic representation of the modeled active complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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