Asymmetric Catalysis

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Chiral Phosphoric Acid Catalyzed Peroxidation of Imines**

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Peroxide-containing compounds are a class of biologically important targets, many of which possess antitumor, antibacterial, and antimalarial activities.[1] For example, the peroxide-containing natural product artemisinin (qinghaosu) has been shown to be a highly effective antimalarial drug.[2] The chiral peroxide moiety in this natural product was proven to be essential for the high antimalarial potency.[2] For this reason, the development of stereoselective methods and strategies for the preparation of chiral peroxides has become considerably important to the practitioners of chemical and pharmaceutical synthesis. However, catalytic syntheses of chiral peroxides is still a challenging goal to synthetic chemists.[3–5] Despite these challenges, the groups of Deng[6] and List[7] independently reported the use of a chiral base-catalyzed enantioselective peroxidation of α,β-unsaturated ketones in 2008.

Chiral α-amino peroxide moieties, though somewhat rare, can be found in natural products. For example, verruculogen (Figure 1) contains an α-amino peroxide, and has been found

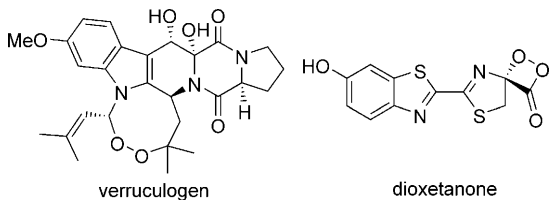
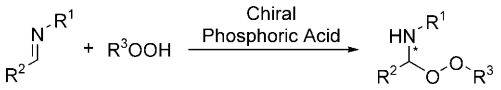


Figure 1. Natural products possessing a chiral α-amino peroxide.

to alter GABA receptor binding and inhibit the mammalian cell cycle.[1a] In addition, dioxetanone is a high-energy natural product containing a chiral α-amino peroxide found in the Japanese firefly.[8] To the best of our knowledge, there is no catalytic asymmetric method that can give direct access to chiral α-amino peroxides.[9]

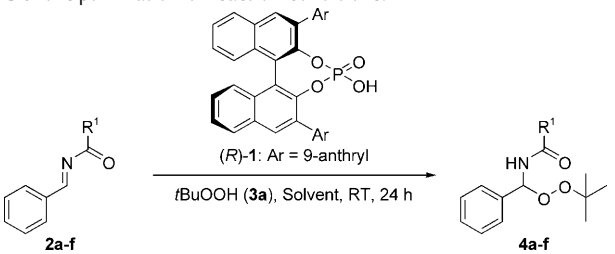
Chiral phosphoric acids have proven to be efficient catalysts for a large number of important enantioselective transformations.[10–11] So far most of the phosphoric acid catalyzed reactions have utilized carbon nucleophiles. Recently, our group and others reported on the addition of heteroatoms such as amines and alcohols, to imines catalyzed by chiral phosphoric acids.[12] Herein, we report the first example of a chiral phosphoric acid catalyzed addition of hydroperoxides to imines, thereby allowing the direct access to chiral α-amino peroxides in high yield and enantiomeric excess (Scheme 1).



Scheme 1. Catalytic synthesis of optically active α-amino peroxides.

Initial studies were conducted by examining the addition of *tert*-butyl hydroperoxide to imine **2a** in the presence of a chiral phosphoric acid. Catalyst screening revealed that phosphoric acid **1** was the most effective catalyst for the peroxidation of imine **2a** in terms of enantioselectivity.[13] With toluene as the solvent, the product was obtained in 88% yield and 75% *ee* (Table 1, entry 1). The reaction could also be conducted in CH_2Cl_2, THF, and EtOAc to give the desired product in high yields (Table 1, entries 2–4). Isopropyl acetate, a solvent having a variety uses in manufacturing, was found to be the best with respect to asymmetric induction (Table 1, entry 5). To additionally optimize the reaction

Table 1: Optimization of reaction conditions.[a]



Entry	Imine (R^1)	Solvent	Yield [%][b]	*ee* [%][c]
1	**2a** (Ph)	toluene	**4a**: 88	75
2	**2a**	CH_2Cl_2	**4a**: 88	79
3	**2a**	THF	**4a**: 86	47
4	**2a**	EtOAc	**4a**: 93	84
5	**2a**	*i*PrOAc	**4a**: 84	86
6	**2b** (4-$MeOC_6H_4$)	*i*PrOAc	**4b**: 83	90
7	**2c** (2-MeC_6H_4)	*i*PrOAc	**4c**: 92	84
8	**2d** (3-MeC_6H_4)	*i*PrOAc	**4d**: 83	88
9	**2e** (3-$MeOC_6H_4$)	*i*PrOAc	**4e**: 82	97
10	**2f** (3,5-$(MeO)_2C_6H_3$)	*i*PrOAc	**4f**: 81	96

[a] Reaction conditions: imine **2a–f** (0.1 mmol), hydroperoxide **3a** (0.2 mmol), (*R*)-**1** (5 mol%), solvent (0.6 mL) at room temperature. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase.

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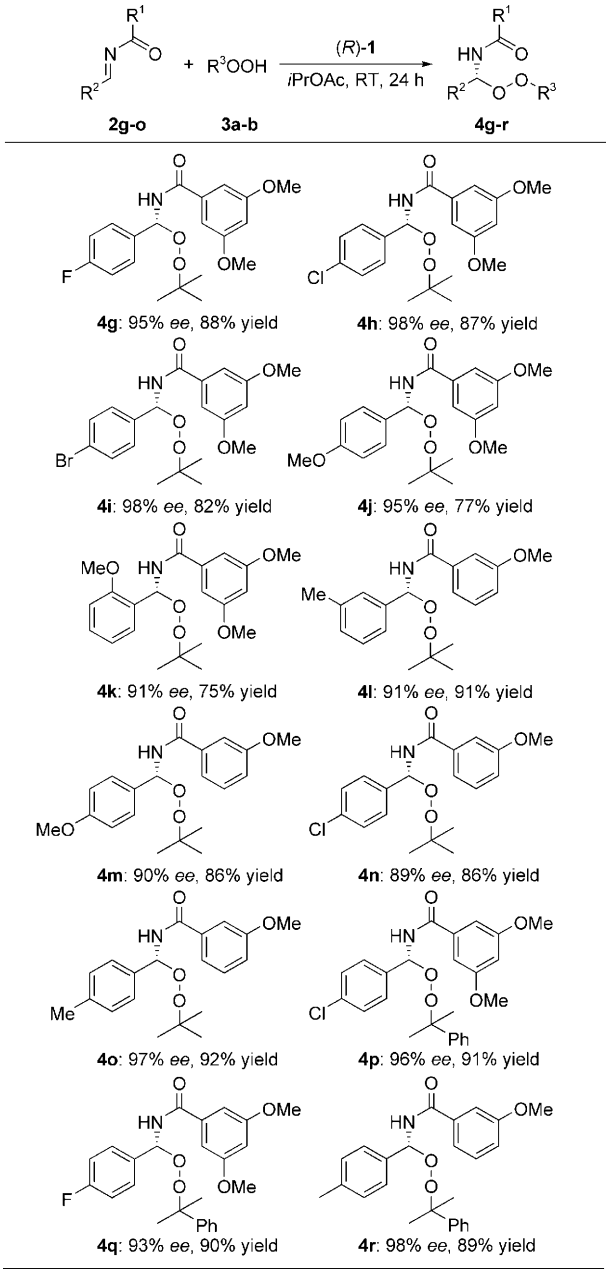
conditions, variation of protecting group on the nitrogen atom of the imine was investigated. As shown in Table 1, the enantiomeric excess increased with introduction of a methoxy group in the *para* position of phenyl ring (Table 1, entry 6). Placement of the same substituent in the *meta* position gave an even higher *ee* value (Table 1, entries 7–8). Installation of electron-rich groups in the *meta* position of the phenyl ring enhanced the *ee* value to 97% (Table 1, entry 9) and 96% (Table 1, entry 10). Two equivalents of *tert*-butyl hydroperoxide were used to ensure reaction completion and did not have a detrimental effect on the enantioselectivity or reaction efficiency. Notably, prolonged reaction times did not lead to a decrease in optical purity. This suggests that retro-addition leading to subsequent product racemization through an iminium ion was not observed.



Scheme 2. Substrate scope for the chiral phosphoric acid catalyzed enantioselective peroxidation of imines. Reaction conditions: imine **2g–o** (0.1 mmol), hydroperoxide **3a–b** (0.2 mmol), (*R*)-**1** (5 mol%), *i*PrOAc (0.6 mL) at room temperature. The reported yields are for the isolated product, and the reported *ee* values were determined by HPLC analysis using a chiral stationary phase.

With the optimized conditions in hand, we started to investigate the substrate scope for the asymmetric peroxidation of imines. The representative results are summarized in Scheme 2. To our delight, catalyst **1** gave excellent results for the reaction of a wide range of different imines with hydroperoxides. With 3,5-dimethoxybenzoyl as a protecting group, electron-withdrawing substituents (F, Cl, and Br) in the *para* position (**4g**, **4h**, and **4i**) were all shown to be excellent substrates for the peroxidation reaction. Likewise, electron-donating substituents in the *para* and *ortho* positions (**4j** and **4k**) also provided excellent asymmetric induction. With 3-methoxylbenzoyl as the protecting group, substrates having electron-withdrawing and electron-donating groups led to highly enantioselective products (**4m** and **4n**). When cumene hydroperoxide was used as a nucleophile, products **4p, 4q**, and **4r** were obtained with high enantioselectivity.

The absolute configuration of the peroxide product was determined to be (*R*)-**4i** by single-crystal X-ray diffraction analysis of compound **4i** (Figure 2).[14] Configurations of other products were assigned by analogy.

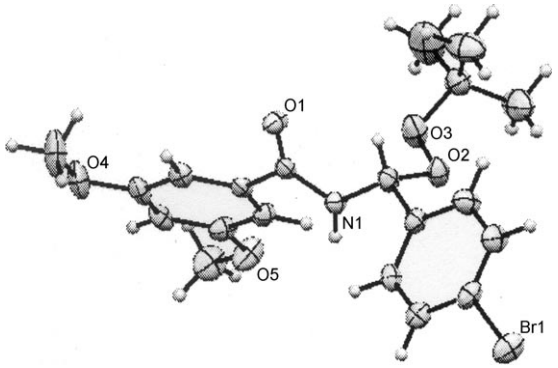


Figure 2. ORTEP representation of the X-ray structure of Compound (*R*)-**4i**. The thermal ellipsoids are shown at 50% probability.

We believe the bifunctional nature of the chiral phosphoric acid is responsible for concurrent activation of both the nucleophile and the electrophile through hydrogen-bonding interactions (Figure 3). These hydrogen-bonding interactions presumably serve to create a chiral environment, which allows for high selectivity during the addition of the peroxide to the activated imine.

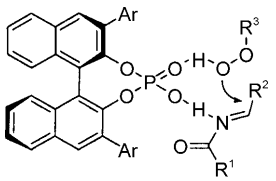


Figure 3. Proposed transition state for the chiral phosphoric acid catalyzed peroxidation of imines.

In summary, we have successfully discovered a novel catalytic enantioselective peroxidation of imines using a chiral phosphoric acid. This approach provides direct access to optically active α-amino peroxides with high enantioselectivities. Additional investigation into the expansion of the reaction scope and synthetic utility, with the aim of developing more enantioselective transformations (novel chiral oxidizing reagents), reaction methodologies, and applications to total synthesis, are currently underway in our laboratory and will be reported in due course.

Experimental Section

General procedure: The imine **2** (0.1 mmol) and catalyst (*R*)-**1** (5 mol%) were placed in a flame-dried reaction tube. Dry isopropyl acetate (0.6 mL) was added to the mixture. The reaction mixture was stirred for 5 min, and then hydroperoxide **3** (0.2 mmol) was added and the mixture was stirred for an additional 24 h at RT. The reaction mixture was directly subjected to silica gel column chromatography (hexanes/ethyl acetate 10:1) to give the pure product **4**.

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[13] Please see the Supporting Information for a table of chiral phosphoric acids that were screened.

[14] CCDC 775266 ((*R*)-**4i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

