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Activation of H_2O_2 by Chiral Confined Brønsted Acids: A Highly Enantioselective Catalytic Sulfoxidation

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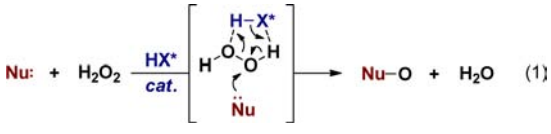
Supporting Information

ABSTRACT: Confined chiral Brønsted acids are shown to catalyze asymmetric oxidations of sulfides to sulfoxides with hydrogen peroxide. The wide generality and high enantioselectivity of the developed method compare even to the best metal-based systems and suggest utility in other asymmetric oxidations.

Enantioselective catalytic oxidations, in particular those involving oxygen atom transfer, have propelled the development of asymmetric catalysis during the last several decades.[1] Both enzymes and synthetic catalysts containing a metal as the active principle are commonly employed to facilitate this reaction class.[1,2] Organocatalysts represent an attractive alternative, and several systems have been developed.[3] The nature of the terminal oxidant is often crucial for the efficiency of oxidation reactions, and typical oxygen-transfer reagents include alkyl hydroperoxides, iodosobenzene, peroxycarboxylic acids, hypochlorite, and oxone.[1] Despite significant efforts to utilize H_2O_2 in asymmetric oxidation catalysis,[1,2] only a few general systems work well with this abundant, environmentally benign, atom-economical, and relatively safe oxidant. In asymmetric organocatalysis, H_2O_2 has been employed in epoxidations of α,β-unsaturated carbonyl compounds,[3b,4] Baeyer–Villiger reactions,[5] and oxidations catalyzed by ketones, iminium salts, or carboxylic acids.[3a,c] All of these reactions rely on the nucleophilic properties of H_2O_2, forming covalent adducts with electrophilic substrates or catalysts. We envisioned an alternative scenario in which H_2O_2 could be electrophilically activated toward nucleophilic substrates with a chiral Brønsted acid catalyst (eq 1):



Such a noncovalent activation mode has previously been used in non-enantioselective oxidation reactions,[6] including an alkyl hydrogen sulfate-catalyzed sulfoxidation.[7] However, the potential of this approach in asymmetric catalysis has not been recognized.[22] Here we demonstrate its successful utilization in a highly enantioselective and general oxidation of sulfides to sulfoxides that is catalyzed by a confined chiral Brønsted acid.

Chiral sulfoxides are widely used as intermediates, auxiliaries, and ligands in modern organic synthesis[8] and constitute important biologically active compounds, including several marketed pharmaceuticals.[9] Since the first enantioselective catalysts for the oxidation of sulfides were reported in 1984 by the groups of Kagan[10] and Modena,[11] who used modified Sharpless epoxidation catalysts, several elegant metal-based asymmetric sulfoxidation reactions have been developed.[12−14] Challenges to such methods include attainment of broad substrate scope and elimination of potential product contamination with sulfone overoxidation byproduct or residual metal impurities.[15] Among metal-free methods, high enantioselectivity has been achieved with chiral imine or oxaziridine reagents and catalysts,[16] but these systems are less general.[6,17] In view of the importance of optically pure sulfoxides, a general, metal-free, and highly enantioselective catalytic sulfoxidation reaction is highly desirable.

In accordance with our concept in eq 1, we initially investigated asymmetric sulfoxidation reactions with BINOL-derived phosphoric acid catalysts.[18] Indeed, a catalytic amount of phosphoric acid **4a** promoted the oxidation of phenyl methyl sulfide (**1a**) to sulfoxide **2a** with an aqueous 35% solution of H_2O_2, although the enantiomeric ratio (e.r.) was low (e.r. 63:37) and some overoxidation to sulfone **3a** was observed (Table 1, entry 1). Encouraged by this initial result, we performed an extensive screening of phosphoric acid catalysts (entries 2 to 9). Unfortunately, none of these well-investigated catalysts provided significantly improved enantioselectivity, although essentially perfect selectivity for the monooxidation product could be achieved in several cases (entries 2, 3, and 7−9). Catalyst **4g** with 4-^{t}BuC$_6$H$_4$ substituents gave the best enantiomeric ratio of 78:22, but further increasing the size of the para substituent on the phenyl ring resulted in slightly decreased stereoselectivity (entries 7 and 8). **STRIP** (**5**), a phosphoric acid based on the SPINOL backbone, proved equally unsuccessful (entry 9).[19] A solvent screening with catalyst **4g** also did not provide an improvement, although CCl_4 was revealed as an equally useful solvent as cyclohexane (see the Supporting Information).

In asymmetric Brønsted acid catalysis, the bifunctional activation of both the electrophile and the nucleophile, which preorganizes the substrates, is commonly assumed to be crucial for high enantioselectivity.[18c,d] We hypothesized that such preorganization is lacking in our system because of the absence of specific interactions of the sulfide with the phosphate catalyst. In the present reaction, both Brønsted acidic and basic sites of the catalyst are suggested to be involved in the activation of hydrogen peroxide only (eq 1). Consequently, the approach of the nucleophile to the catalyst−electrophile

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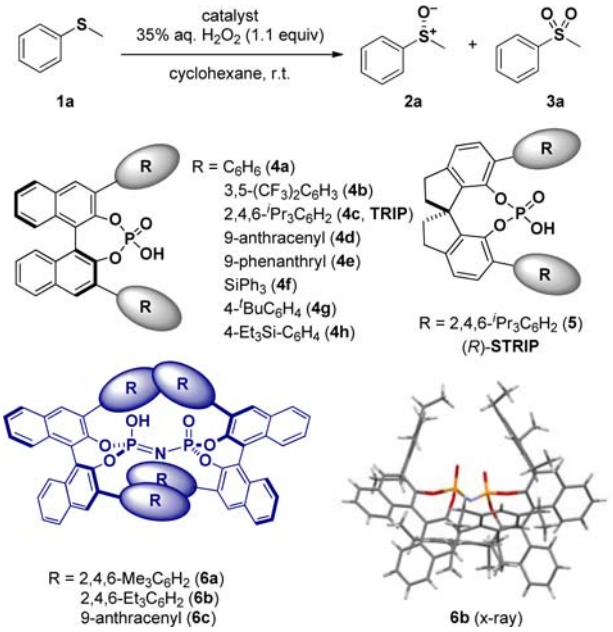
Table 1. Evaluation of Different Brønsted Acid Catalysts



entry	catalyst	t (h)	conv. (%)[a]	**3a** (%)[a]	e.r.
1	**4a** (5 mol %)	24	80	12	63:37
2	**4b** (5 mol %)	24	80	–	69:31
3	**4c** (5 mol %)	24	38	–	58:42
4	**4d** (5 mol %)	24	76	24	64:36
5	**4e** (5 mol %)	24	86	20	70:30
6	**4f** (5 mol %)	24	53	10	44:56
7	**4g** (5 mol %)	24	71	–	78:22
8	**4h** (5 mol %)	24	75	–	76:24
9	**5** (5 mol %)	15	38	–	58:42
10	**6a** (2 mol %)	24	90	–	92:8
11	**6b** (2 mol %)	24	80	–	99:1
12	**6c** (2 mol %)	24	85	<5	99:1
13[b,c]	**6b (2 mol %)**	**2**	**>99**	–	**99:1**
14[b,c]	**6b** (1 mol %)	10	>99	–	98.5:1.5
15[b,c,d]	**6b** (0.1 mol %)	72	75	–	95:5

[a]0.1 mmol scale, determined by GC–MS. [b]With $MgSO_4$. [c]With 1.05 equiv of 35% aq. H_2O_2. [d]0.5 mmol scale.

complex is governed largely by steric control. However, because of the open cone geometry of phosphoric acid catalysts, steric interactions with the sulfide may be insufficient for effective enantiodiscrimination. We recently developed highly sterically demanding Brønsted acids based on a C_2-symmetric imidodiphosphate anion for the activation of small and unbiased molecules.[20] A distinctive feature of these catalysts is the confinement of the active site within a deep chiral pocket. We therefore hypothesized that with the use of such confined Brønsted acids, H_2O_2 could be activated in a well-defined and narrow position within a chiral cavity (see the Supporting Information for a plausible model). This in turn would restrict the number of possible trajectories of the incoming sulfide nucleophile and thereby increase the enantioselectivity by limiting the diversity of productive transition states.

To our delight, confined imidodiphosphoric acids **6a–c** did indeed enable the highly enantioselective electrophilic oxidation of sulfide **1a** with H_2O_2 (Table 1, entries 10–12). An excellent e.r. of 99:1 was observed with catalysts **6b** and **6c** (entries 11 and 12). It is noteworthy that imidodiphosphoric acid catalysts **6** also exhibited significantly higher reactivity than phosphoric acids, and the catalyst loading could be reduced to 2 mol %. The reaction efficiency could be further improved by adding $MgSO_4$ to remove water, which is both present in aqueous hydrogen peroxide and also formed in the reaction. Thus, the reaction time was shortened from 24 h to only 2 h and only 1.05 equiv of hydrogen peroxide was required (entry 13). Water has a detrimental effect on the reaction rate, presumably as a result of competition with hydrogen peroxide for binding to the catalyst. The catalyst loading could be further reduced to 1 mol % without erosion of the enantioselectivity, and even a catalyst loading of 0.1 mol % gave a high e.r. of 95:5 (entries 14 and 15). CCl_4 and toluene were also found to be suitable solvents for this reaction, although slightly lower enantioselectivity (e.r. 97.5:2.5) was observed in toluene (see the Supporting Information).

The reaction scope was examined next using a series of representative substrates (Table 2). A remarkably broad range of aryl methyl sulfides could be converted to the corresponding sulfoxides in high yields with excellent chemo- and enantioselectivity. Various electron-rich substrates, including methoxy-substituted sulfide **2b**, and electron-poor substrates with nitro or cyano groups were equally well tolerated (entries 2–6). Excellent enantioselectivity was preserved even when varying a *p*-, *m*-, and *o*-chloro substituent on the aromatic ring (entries 7–9). Substrates with larger alkyl groups instead of methyl could also be oxidized with high enantioselectivity, although a small amount of sulfone (5–9%) was observed (entries 10 and 11). A high e.r. of 97.5:2.5 was achieved with vinyl sulfide **2l** (entry 12). Remarkably, high yields and enantioselectivities could be achieved even with simple dialkyl thioethers (entries 13 and 14). Sulfoxide **2n** substituted with a methyl group and a simple linear aliphatic group was obtained with an enantiomeric ratio of 95.5:4.5 (entry 14).

The synthetic value of our method was demonstrated by the enantioselective synthesis of the nonsteroidal anti-inflammatory drug sulindac, which has recently found additional utility in cancer treatment (Scheme 1).[21] The oxidation of sulfide **7** with confined acid catalyst **6b** was performed in CCl_4 because of the solubility of the substrate, and the reaction proceeded with excellent enantioselectivity. Following the hydrolysis of the ester intermediate, (*R*)-sulindac was obtained in 95% overall yield from sulfide **7** with an e.r. of 99:1. As a further demonstration of the utility of our reaction, a large-scale sulfoxidation of sulfide **7** was performed, yielding 3 g of the product in 97% yield with an e.r. of 97.5:2.5.

In summary, a novel oxidation system based on a chiral confined Brønsted acid catalyst and aqueous H_2O_2 has been developed. Imidodiphosphoric acid catalyst **6b**, which presumably binds hydrogen peroxide inside its chiral cavity, was found to catalyze an efficient sulfoxidation reaction of sulfides. To the best of our knowledge, the obtained levels of enantioselectivity are the highest reported to date for organocatalytic sulfoxidations[6] and rival those of the best metal-catalyzed variants.[10–15]

Further exploration of our new chiral confined Brønsted acid motif in general and especially in other asymmetric oxidation reactions is currently in progress in our laboratories.

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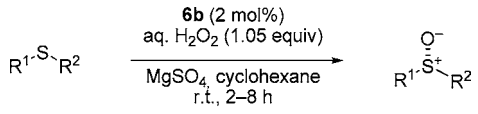
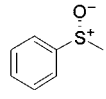
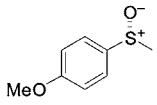
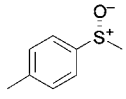
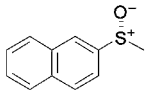
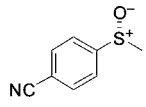
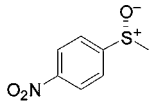
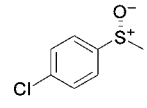
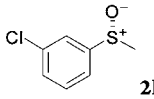
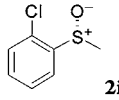
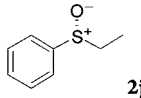
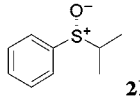
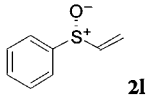
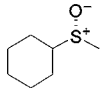
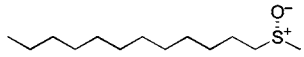
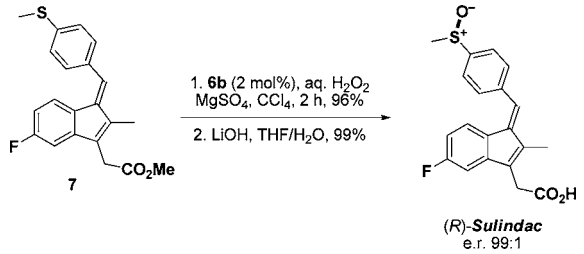
Table 2. Substrate Scope of Asymmetric Sulfoxidation



entry	product	yield[a]	e.r.
1	 **2a**	98%	99:1
2	 **2b**	96%	97.5:2.5
3	 **2c**	98%	98:2
4	 **2d**	98%	99:1
5	 **2e**	92%	97.5:2.5
6	 **2f**	95%	99.5:0.5
7	 **2g**	91%	98.5:1.5
8	 **2h**	95%	99.5:0.5
9	 **2i**	99%	99:1
10[b]	 **2j**	90%	95:5
11[c]	 **2k**	89%	92.5:7.5
12	 **2l**	91%	97.5:2.5
13[d]	 **2m**	96%	97:3
14[d,e]	 **2n**	96%	95.5:4.5

[a]Isolated yields on a 0.1−0.2 mmol scale. [b]5% sulfone observed by ^{1}H NMR analysis. [c]9% sulfone. [d]In CCl_4 at 0 °C. [e]2% sulfone.

Scheme 1. Enantioselective Synthesis of Sulindac



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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