

Novel Catalytic Asymmetric Sulfoxidation in Water Using the Hypervalent Iodine Reagent Iodoxybenzene

Hirofumi TOHMA, Shinobu TAKIZAWA,
Hironori MORIOKA, Tomohiro MAEGAWA, and
Yasuyuki KITA*

Graduate School of Pharmaceutical Sciences, Osaka University,
1-6 Yamada-oka, Suita, Osaka 565-0871, Japan.

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A new catalytic asymmetric oxidation of sulfides to sulfoxides in water using the hypervalent iodine(V) reagent iodoxybenzene (PhIO₂) has been developed. This methodology is distinctly different from the previously reported use of cyclodextrins or biological catalysts and provides a new route to asymmetric sulfoxidation in water.

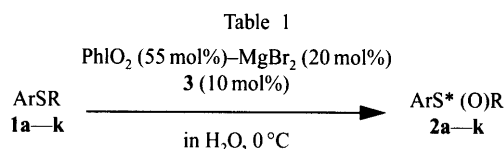
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
The recent demand for eco-friendly chemical processes has fueled the development of several clean and practical oxidation reactions and encourages further development of high-yielding, clean, safe, economical, and highly stereoselective oxidation methods. As a reaction medium, water is both economical and environmentally benign and has been applied to a variety of oxidation reactions.¹⁾ With regard to asymmetric oxidation of sulfides to sulfoxides in water, only a limited number of examples including the use of cyclodextrin derivatives,²⁾ chiral micelles,³⁾ or biological catalysts⁴⁾ exist. Although both biological catalysts and the use of cyclodextrins sometimes give sulfoxides with high enantioselectivities in water, these methods lack practicality and generality due to their low to moderate optical yields and high substrate specificity. Therefore we attempted to develop an

alternative chemical method with higher versatility compared with the previous methods for asymmetric sulfoxidation. As a continuation of our studies on hypervalent iodine reagents which have mild reactivity, low toxicity, and high versatility,^{5,6)} we recently achieved a novel catalytic asymmetric oxidation of sulfides to sulfoxides *via* cetyltrimethylammonium bromide (CTAB)-reversed micelles⁷⁾ (toluene–H₂O) using iodoxybenzene (PhIO₂).⁸⁾ Here we report a new and efficient catalytic activation of PhIO₂ in water using catalytic amounts of both MgBr₂ and (+)-dibenzoyl-D-tartaric acid **3** to yield chiral sulfoxides quantitatively with moderate optical yields.

In this study, we first examined the asymmetric oxidation of *p*-tolyl methylsulfide **1a** using our reported micellar conditions (PhIO₂–CTAB–**3**) in water. However, only low optical yield (18% ee [enantiomeric excess]) of *p*-tolyl methylsulfoxide **2a** was obtained, while the reaction proceeded quantitatively. Since we have recently found that the addition of a catalytic amount of KBr significantly activates hypervalent iodine reagents in water,⁹⁾ we tested other water-soluble additives such as alkali metal, alkali earth metal, and other metal salts in the presence of 10 mol% of **3** as a chiral source. Consequently, the addition of bromide salts effectively catalyzed the hypervalent iodine(V) sulfoxidation regardless of the type of metal cation. Therefore we chose MgBr₂, the most economical and safest metal bromide, for further studies, since it also showed a slightly enhanced ee value among the bromides tested (LiBr [43% ee], NaBr [42% ee], MgBr₂ [47% ee], CaBr₂ [46% ee], BaBr₂ [45% ee], ZnBr₂ [33% ee], YbBr₃ [38% ee], MgX₂ [X: Cl, OAc, ClO₄ {0–19 % yields, <15% ee}]).

In order to enhance the optical yield of **2a**, we examined the reaction using a variety of oxidants, chiral sources, and reaction conditions. In the presence of MgBr₂ (20 mol%) and **3** (10 mol%), common water-soluble oxidants such as H₂O₂ and cumene hydroperoxide completed the reaction immediately with no asymmetric induction, and sodium hypochlorite (NaOCl) only yielded *p*-tolyl methylsulfone. On the other



Entry	Substrate		Time (h)	Yield (%)	% ee ^{a)} (config.) ^{b)}	[α] _D ²⁴ (°)
	Ar	R				
1	4-MePh	Me (1a)	24	quant.	59 [R]	+101.7 (c=0.47, CHCl ₃)
2	3-MePh	Me (1b)	24	quant.	63 [R]	+74.8 (c=0.76, MeOH)
3	2-MePh	Me (1c)	48	95	60 [R]	+146.8 (c=1.03, acetone)
4	4-NO ₂ Ph	Me (1d)	48	quant.	60 [R]	+77.7 (c=1.67, CHCl ₃)
5	3-NO ₂ Ph	Me (1e)	64	quant.	61 [R]	+58.0 (c=0.21, CHCl ₃)
6	4-MeOPh	Me (1f)	64	84	63 [R]	+83.8 (c=0.98, CHCl ₃)
7	4-CNPh	Me (1g)	30	97	56 [R]	+66.1 (c=1.09, EtOH)
8	Ph	Me (1h)	36	quant.	60 [R]	+102.0 (c=0.64, CHCl ₃)
9	Ph	Et (1i)	48	quant.	51 [R]	+107.8 (c=0.44, acetone)
10	Ph	(CH ₂) ₂ OH (1j)	72	quant.	43 [R]	+91.2 (c=1.07, acetone)
11		 (1k)	48	quant.	52 [R]	–129.6 (c=0.53, acetone)

a) Determined by HPLC analysis employing a Daicel Chiralcel OD, OJ, or Chiralpak AD. b) Absolute configurations were established by comparison of the sign of [α]_D to values reported in the literature.

* To whom correspondence should be addressed.

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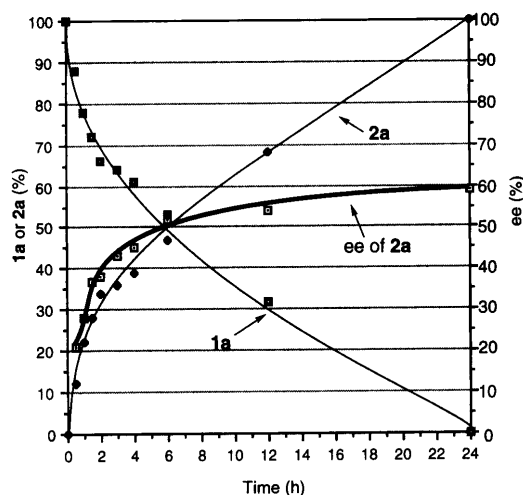


Fig. 1

hand, the best optical yield (47% ee) was observed using the normally unreactive PhIO_2 which is nearly insoluble in water in the absence of chiral activator **3**, while only low ee values were observed using the more reactive iodine reagents such as $\text{PhI}=\text{O}$ (9% ee), (diacetoxyiodo)benzene (5% ee), and iodosobenzoic acid (38% ee), which could be activated by MgBr_2 even in the absence of **3**. Next, we optimized the chiral sources in the reaction. So far, the best chemical and optical yields have been obtained using 10 mol% of commercially available (+)-dibenzoyl-D-tartaric acid **3**. The use of other tartaric acids or chiral sources such as various carboxylic acids, a sulfonic acid, an *N*-protected amino acid, and a phosphonic acid did not improve the ee of **2a**.¹⁰ Interestingly, the reaction temperature affects the ee of **2a**. That is, the ee value of **2a** was enhanced up to 59% ee at 0 °C although the reaction took longer to complete. Under these reaction conditions, we performed asymmetric oxidation of various sulfides.¹¹ The results are listed in Table 1. Table 1 shows that the reaction proceeds quantitatively with moderate optical yields, regardless of the substrate used.

A time profile of the oxidation of **1a** with 0.55 equivalent of PhIO_2 is depicted in Fig. 1. The remarkable enhancement of the ee value of **2a** observed at the initial step is surprising since there is no kinetic resolution derived from overoxidation to the sulfone and also because $\text{PhI}=\text{O}(\text{III})$, which was formed during the course of the reaction, only gave a low optical yield as described above. Probably the hydrophobic effect brings the reactants together to promote the *in situ* formation of the stereo-controlled reactive intermediates from $\text{PhIO}_2(\text{V})$, $\text{PhI}=\text{O}(\text{III})$, and the chiral tartaric acid **3**. However, the mechanism of asymmetric induction is still unclear. Although the optical yields of sulfoxides are not excellent so

far, we have opened up a new and facile route for asymmetric sulfoxidation in water. The optimization of optical yields and further application of this system are now underway.

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- 10) The ee values when using other chiral sources are as follows: di(2-MeO)benzoyl-L-tartaric acid (34% ee), di(2-toluoyl)-L-tartaric acid (14% ee), dipivaloyl-L-tartaric acid (13% ee), di(2-naphthoyl)-D-tartaric acid (24% ee), (S)-(+)- α -methoxyphenylacetic acid (14% ee), (+)-10-camphorsulfonic acid (0% ee), *N*-phthaloyl-L-glutamic acid (16% ee), and (S)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (0% ee).
- 11) Typical experimental procedure: A mixture of (+)-dibenzoyl-D-tartaric acid **3** (7.2 mg, 0.02 mmol), MgBr_2 (7.4 mg, 0.04 mmol), and PhIO_2 (26.0 mg, 0.11 mmol) in water (5.0 ml) was stirred for 5 min at room temperature. To the stirred mixture, sulfide (**1**) (0.20 mmol) was added dropwise at 0 °C and then stirred until completion of the reaction at 0 °C. The reaction mixture was extracted with AcOEt, dried over Na_2SO_4 , filtered, and evaporated. The residue was purified by column chromatography ($\text{SiO}_2/\text{CH}_2\text{Cl}_2$ -acetone=4:1) to give pure sulfoxide (**2**), the ee of which was determined by HPLC. Absolute configurations were assigned by comparison of the sign of the specific rotation with data in the literature.^{4,8)}