JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
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Catalytic Asymmetric Oxidation of *N*-Sulfonyl Imines with Hydrogen Peroxide–Trichloroacetonitrile System

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Supporting Information

ABSTRACT: An efficient and highly enantioselective Payne-type oxidation of *N*-sulfonyl imines is developed. The reaction exhibits broad substrate generality and unique chemoselectivity based on the combined use of hydrogen peroxide and trichloroacetonitrile under the catalysis of *P*-spiro chiral triaminoiminophosphorane.

Organic peroxy acids are undoubtedly one of the most common and widely applicable types of oxidants in organic synthesis.[1] While their competent reactivity as electrophilic as well as nucleophilic oxidizing agents is routinely appreciated in synthetic operations, selectivity control, particularly absolute stereocontrol, in oxygen atom-transfer from the peroxy acid is not a trivial task primarily because of its high reactivity indivisible from its thermal instability and potentially explosive nature. On the other hand, hydrogen peroxide is relatively stable and abundant, but its reactivity as an oxidant is usually insufficient for direct use in the oxidation of simple organic molecules without an appropriate activator.[2] Accordingly, a system that enables the catalytic generation of reactive peroxy acids or their equivalents from hydrogen peroxide would provide an attractive platform for pursuing stereochemical control in the oxidations with peroxy acids as the source of an active oxygen atom. However, efforts toward the development of catalytic asymmetric protocols based on this strategy are very limited.[3] The seminal studies reported by the Miller group nicely demonstrated the feasibility of the in situ derivatization of a chiral carboxylic acid to the corresponding peroxy acid by using stoichiometric amount of carbodiimide and an aqueous solution of hydrogen peroxide; highly enantioselective catalytic oxidations of olefins were achieved under the catalysis of a small peptide having an aspartic acid residue.[3a,b,d] Meanwhile, the control of an in situ-generated achiral peroxy acid by a chiral molecular catalyst appears to be a promising alternative and yet the successful implementation of this approach is entirely unknown. This is partially because the carboxylic acid inevitably formed during the oxidation would make it intractable for the catalyst to selectively activate the peroxy acid over the structurally similar acidic side product. In this context, we became interested in the Payne oxidation, in which a peroxy imidic acid is generated from a nitrile and hydrogen peroxide by the use of excess base, and a primary amide is eliminated as a nonacidic side product.[4,5] Although the applicability of the Payne oxidation system to various reactions such as epoxidation has been well documented, its actual synthetic potential has been rather overlooked; the catalytic asymmetric variant has never been developed probably due to the lack of suitable chiral base catalysts. Here, we disclose the first catalytic asymmetric Payne-type oxidation of *N*-sulfonyl imines under the catalysis of *P*-spiro chiral triaminoiminophosphorane of type **1**,[6−9] featuring high efficiency, broad substrate scope, and unique chemoselectivity.[10,11]

The inspiration for developing an asymmetric Payne oxidation using a catalytic quantity of chiral base arose from the strong basicity of chiral triaminoiminophosphorane **1** and the anion-recognition ability of its conjugate acid **1**·H.[10] As a model reaction to substantiate this possibility, we chose the oxidation of *N*-sulfonyl imines.[12] The catalytic enantioselective oxidation of *N*-sulfonyl imines was recently pioneered by Jørgensen using a cinchona alkaloid-derived catalyst in combination with *m*-chloroperoxybenzoic acid (*m*-CPBA) as an oxidant,[12a] and Yamamoto also demonstrated the effectiveness of a chiral hafnium(IV) complex–cumenhydroperoxide

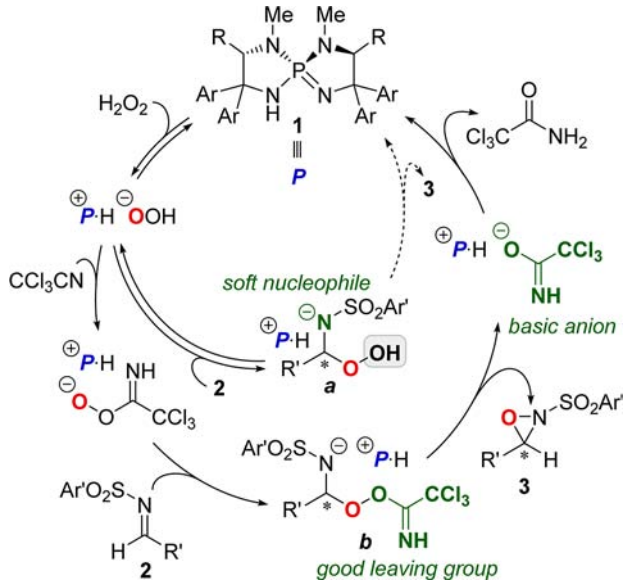


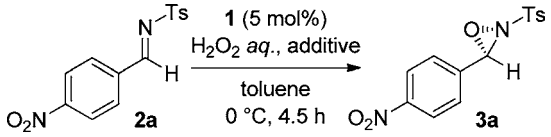
Figure 1. Plausible reaction mechanism for the asymmetric Payne-type oxidation of *N*-sulfonyl imine **2** under the catalysis of chiral triaminoiminophosphorane **1**.

Received: April 8, 2013
Published: May 16, 2013

dx.doi.org/10.1021/ja403491j | J. Am. Chem. Soc. 2013, 135, 8161−8164

system.[12b] Nevertheless, the full potential of this reaction has yet to be realized in terms of both stereoselectivity and general applicability. Our approach relied on the catalytic generation of chiral aminophosphonium hydroperoxide **1**·HOOH from **1** and H_2O_2 in the presence of trichloroacetonitrile as the requisite activator (Figure 1). This chiral hydroperoxide would undergo rapid addition to either *N*-sulfonyl imine **2** or trichloroacetonitrile. However, even if **1**·HOOH adds to **2** in a stereocontrolled manner, the process is thought to be reversible, and the ring closure from the intermediary peroxyhemiaminal **a** to oxaziridine **3** would be sluggish owing to the soft character of the sulfonylamide ion and the poor leaving ability of the hydroxide ion. On the other hand, the addition of **1**·HOOH to trichloroacetonitrile would generate the aminophosphonium peroxyimidate **1**·HOOC(=NH)CCl_3 as an active oxidant, which would enantioselectively react with **2** to form the peroxyhemiaminal intermediate **b**. Since the amidate ion behaves as a good leaving group, swift conversion of **b** into **3** would take place with concomitant production of the corresponding aminophosphonium amidate **1**·$H_2NC(=O)CCl_3$. The amidate ion would be basic enough to abstract a proton from aminophosphonium ion **1**·H to regenerate iminophosphorane **1**, thus completing the catalytic cycle. The viability of this mechanistic blueprint was assessed by two related experiments. When aqueous H_2O_2 was introduced to a solution of *N*-tosyl 4-nitrobenzaldimine **2a** and chiral iminophosphorane **1a** (5 mol%) in toluene at 0 °C, **2a** was smoothly consumed, but only a trace amount of the desired oxaziridine **3a** was detected by crude ^{1}H NMR analysis (Table 1, entry 1). In sharp contrast, **3a** was quantitatively obtained by

Table 1. Structural Optimization of Catalyst 1[a]



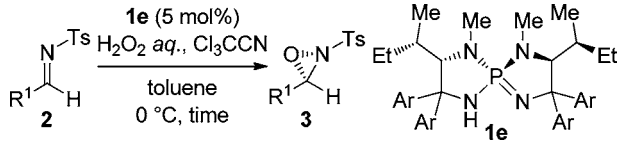
entry	1 (R, Ar)	additive	yield[b] (%)	ee[c]
1	**1a** (^{i}Pr, Ph)	none	trace	–
2	**1a** (^{i}Pr, Ph)	Cl_3CCN	99	68
3	**1b** (^{i}Pr, 4-MeC_6H_4)	Cl_3CCN	88	44
4	**1c** (^{i}Pr, 4-ClC_6H_4)	Cl_3CCN	83	74
5	**1d** (^{i}Pr, 3,5-$Cl_2C_6H_3$)	Cl_3CCN	86	94
6	**1e** (^{s}Bu, 3,5-$Cl_2C_6H_3$)	Cl_3CCN	89	98
7[d]	**1e** (^{s}Bu, 3,5-$Cl_2C_6H_3$)	Cl_3CCN	96	98

[a]Unless otherwise noted, reactions were performed on 0.1 mmol scale with 1.2 equiv of 35% aqueous solution of H_2O_2, 1.2 equiv of Cl_3CCN, and 5 mol% of **1** in toluene (2.0 mL) at 0 °C. [b]Isolated yield. [c]Enantiomeric excess was analyzed by chiral stationary phase HPLC. Absolute configuration was assigned according to the literature data.[12a] [d]Reaction was conducted on 5.0 mmol scale with 1 mol% of **1e** for 24 h.

conducting the reaction in the presence of trichloroacetonitrile under otherwise identical conditions, albeit with moderate enantiomeric excess (entry 2). These results strongly suggested the operation of the Payne-type oxidation mechanism.[13] On the basis of this initial yet important information, we examined the effect of the structure of **1** on the enantioselectivity. As shown in Table 1, the introduction of electron-deficient aromatics to the diazaphosphacycles was beneficial, and a critical improvement in the enantioselectivity was attained with **1d** bearing 3,5-dichlorophenyl groups (entries 2–5). Through additional evaluation of the parent amino acid structure, iminophosphorane **1e**, derived from L-isoleucine, was identified to be the optimal catalyst, and **3a** was isolated in 89% yield with 98% ee (entry 6).[14] It is worthy to add that the present oxidation is scalable as the reaction with 1.5 g of **2a** under the influence of 1 mol% of **1e** reached completion by simply extending the reaction time to 24 h to afford **3a** with similar degree of selectivity (entry 7).

The scope of this new protocol was then investigated, and representative results are summarized in Table 2. In general, the

Table 2. Substrate Scope (Ar = 3,5-$Cl_2C_6H_3$)[a]



entry	R^1 (2)	time (h)	yield[b] (%)	ee[c]	3
1	Ph (**2b**)	2.5	90	95	**3b**
2	2-FC_6H_4 (**2c**)	4	83	95	**3c**
3	2-MeC_6H_4 (**2d**)	2.5	86	96	**3d**
4	3-$MeOC_6H_4$ (**2e**)	3.5	99	95	**3e**
5	3-BrC_6H_4 (**2f**)	2	84	97	**3f**
6	4-MeC_6H_4 (**2g**)	4.5	91	95	**3g**
7	4-ClC_6H_4 (**2h**)	1.5	89	96	**3h**
8	3-furyl (**2i**)	4	96	93	**3i**
9	Me_3C (**2j**)	2	85	98	**3j**
10	cyclo-hexyl (**2k**)[d]	1	91	98	**3k**
11	Me_2CHCH_2 (**2l**)[d,e]	1	92	95	**3l**
12	$Ph(CH_2)_2$ (**2m**)[d,e]	0.5	87	96	**3m**

[a]Unless otherwise noted, reactions were performed on 0.1 mmol scale with 1.2 equiv of 35% aqueous solution of H_2O_2, 1.2 equiv of Cl_3CCN, and 5 mol% of **1e** in toluene (2.0 mL) at 0 °C. [b]Isolated yield. [c]Enantiomeric excesses were analyzed by chiral stationary phase HPLC. Absolute configurations of **3** were determined according to the literature data[12a] except for **3e**, **3i**, **3l**, and **3m**. [d]Reaction was conducted at room temperature in dichloromethane (2.0 mL). [e]*N*-Mesitylenesulfonyl ($MesSO_2$) imine was used instead of *N*-Ts imine.

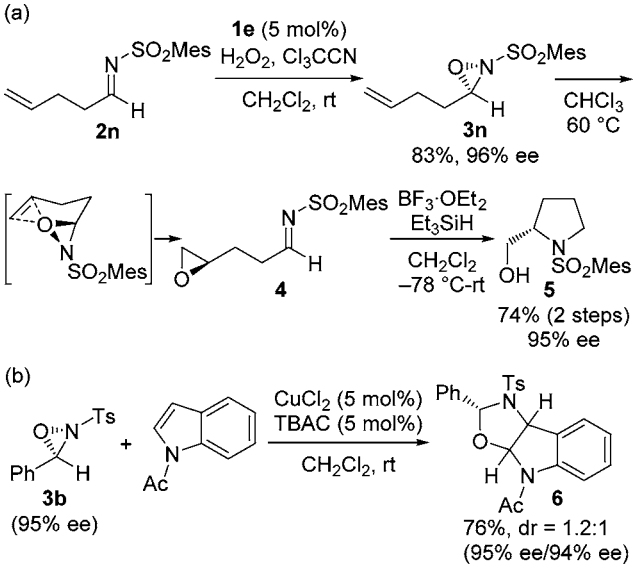
use of 5 mol% of **1e** and each 1.2 equivalents of aqueous H_2O_2 and trichloroacetonitrile was sufficient to achieve a smooth reaction, giving **3** in high yield with excellent enantioselectivity. For aromatic *N*-sulfonyl imines, this method tolerated the incorporation of both electron-withdrawing and electron-donating substituents arbitrarily positioned on the aromatic nuclei (entries 1–7). In addition, the 3-furaldehyde-derived imine **2i**, possessing a potentially oxidizable heteroaromatic, was converted into the corresponding enantioenriched oxaziridine **3i** without any difficulties (entry 8). Aliphatic *N*-sulfonyl imines also appeared to be good electrophilic partners; the employment of dichloromethane as a solvent at ambient temperature turned out to be essential for selective oxidation except for substrates having tertiary alkyl substituents (entries 9–12). It should be noted that the bulky *N*-mesitylenesulfonyl ($MesSO_2$) protecting group was crucial for attaining high chemical yields in the reactions of primary aldimines without detrimental effect on the selectivity profile (entries 11 and 12).[15]

A distinct advantage of the present catalytic system was highlighted by the highly chemo- and enantioselective oxidation of imines with electron-rich double bonds, and fruitful derivatization of the resulting oxaziridines. For instance,

dx.doi.org/10.1021/ja403491j | J. Am. Chem. Soc. 2013, 135, 8161–8164

under the suitably optimized conditions, *N*-sulfonyl imine **2n**, derived from 4-pentenal, was converted to the corresponding oxaziridine **3n** in 83% yield with 96% ee, leaving the olefin moiety intact (Scheme 1a). The inherent ability of the

Scheme 1. Derivatization of Chiral Oxaziridines 3



oxaziridine as an organic oxidant was then harnessed for intramolecular oxygen transfer at 60 °C in chloroform to afford epoxy imine **4**, probably via a cyclic transition state.[16−20] The subsequent Lewis acid-promoted reduction of the imine functionality with triethylsilane led to a subsequent intramolecular cyclization to furnish pyrrolidine methanol **5** in good yield. The conservation of enantiomeric purity throughout this process was confirmed by chiral stationary phase HPLC analysis of **5**. Moreover, in conjunction with the recent progress in methodology for significantly enhancing the synthetic relevance of oxaziridines as versatile intermediates,[21−23] Yoon's protocol was successfully applied to the ready transformation of **3b** (95% ee) into tricyclic indoline derivative **6** without any loss of enantiomeric excess (Scheme 1b).[22j]

In conclusion, we have developed a highly enantioselective Payne-type oxidation of *N*-sulfonyl imines based on the combined use of H_2O_2 and trichloroacetonitrile under the catalysis of chiral *P*-spiro triaminoiminophosphorane. This method exhibited high efficiency and unique chemoselectivity, and provided reliable access to structurally diverse, optically pure oxaziridines. The present study demonstrates the viability of catalytically generating and controlling organic peroxy acids by chiral molecular catalysts and the significant potential of this system for selective oxidations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. 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.

■ ACKNOWLEDGMENTS

This work was supported by NEXT program, a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT, Program for Leading Graduate Schools "Integrative Graduate Education and Research Program in Green Natural Sciences" in Nagoya University, Grants of JSPS for Scientific Research, and the Asahi Glass Foundation. R.T. acknowledges JSPS for financial support.

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