Charge-Transfer Effect on Chiral Phosphoric Acid Catalyzed Asymmetric Baeyer-Villiger Oxidation of 3-Substituted Cyclobutanones Using 30% Aqueous H_2O_2 as the Oxidant†

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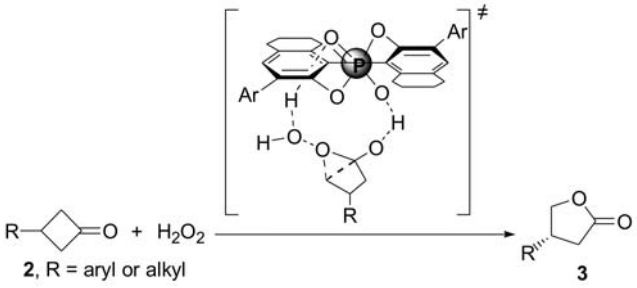
The intermolecular charge-transfer effect has been employed for the first time as a modulating approach to affect the enantioselectivity in asymmetric catalysis by taking the chiral phosphoric acid catalyzed asymmetric Baeyer-Villiger oxidation of 3-aryl cyclobutanones as the reaction prototype. It was found that the electron acceptor additives were able to effectively tune the enantioselectivity via donor-acceptor interaction with the catalyst and up to 9% enhancement of *ee* value was observed in a favorable case.

Keywords asymmetric catalysis, Baeyer-Villiger oxidation, Bronsted acid, charge-transfer effect, hydrogen peroxide, organocatalysis, phosphoric acid

Introduction

In our previous report[1] on the asymmetric Baeyer-Villiger oxidation[2] of 3-substituted cyclobutanones (**2**) with 30% aqueous H_2O_2 catalyzed by the BINOL (1,1'-binaphthyl-2,2'-diol)-derived chiral phosphoric acids (**1**) (Scheme 1), it was found that the 3,3'-substituents (Ar group) of the catalyst plays a key role in enantioselectivity control.[3] A prominent feature of the catalyst with high asymmetric induction is that the backbone of chiral phosphoric acid bears fused conjugated aromatics such as pyrenyl groups, which are rigid, planar, and electron-rich in nature. On the other hand, some BINOL derivatives have also been reported to function as electron donor units to form intermolecular charge-transfer complexes with various electron acceptors.[4] However, the use of such kind of effect for tuning the enantioselectivity in asymmtric catalysis has never been reported to the best our knowledge. Inspired by these facts, we envisaged that an appropriate electron-deficient molecule might influence the micro-environment of the catalyst through intermolecular charge-transfer interaction with the binaphthyl backbone of catalyst and its electron rich Ar groups at 3,3'-positions, and as a result, to further fine-tune the enantioselectivity of the catalysis. In the present work, we will report our results of investigations on the first use of charge-transfer effect[5] as a modulating approach to affect the enantioselectivity in asymmetric catalysis by taking asymmetric Baeyer-Villiger oxidation of 3-aryl cyclobutanones catalyzed by chiral phosphoric acids as the reaction prototype.

Scheme 1 BINOL-derived chiral phosphoric acid-catalyzed enantioselective B-V reaction of 3-substituted cyclobutanones



Results and discussion

It has been observed in our previous report that chiral phosphoric acid **1a** featuring electron-rich pyren-1-yl groups at the 3,3'-positions of the backbone cata-

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lyzed the BV oxidation of **2a** in up to 71% *ee* at room temperature.[1] The investigation of impact of steric and electronic properties of the 3,3'-substituents and the effect of the backbone of phosphoric acid scaffold on the enantioselectivities of the reaction shows that fine tuning of the chiral environment around phosphoric acid is critical for the enantioselectivity of the reaction.[1,2] We speculated that in the case of chiral phosphoric acid catalysts bearing electron-rich aromatic motifs on their backbones (*e.g.* pyren-1-yl), charge-transfer complex formation by self-assembly with an electron-deficient molecule (such as tetracyanobenzene) would result in a subtle change in the chiral environment nearby the reactive site, and hence may lead to a variation in the enantioselectivity of the catalysis (Figure 1). On the basis of working hypothesis shown in Figure 1, we decided to employ a variety of electron acceptor molecules (**A1**—**A7**, Figure 2) as additives for examining their impact on the phosphoric acid **1a** catalyzed B-V reaction of **2a** with 30% H_2O_2 as the terminal oxidant at room temperature.

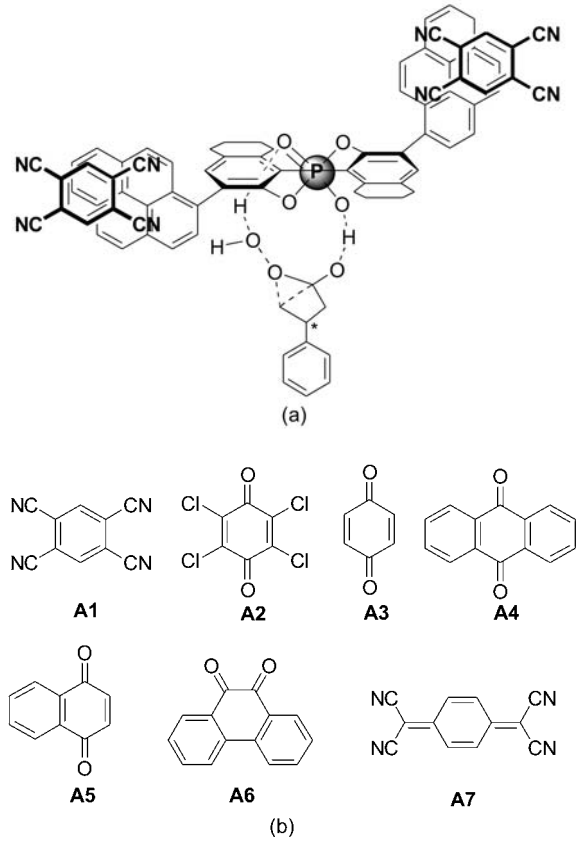


Figure 1 (a) Schematic representation for the hypothesis of donor-acceptor interaction on enantioselective control of the catalysis by formation of charge-transfer complex. (b) Electron acceptor additives employed for affecting the enantioselectivity of asymmetric B-V reaction catalyzed by chiral phosphoric acid **1a**.

Indeed, intensely colorful solutions developed immediately upon the mixing of catalyst **1a** with the acceptor **A** in chloroform. For examples, both catalyst **1a** and acceptor **A1** or **A7** are colorless in $CHCl_3$, however, an orange or dark green solution was obtained, respectively, when catalyst **1a** and electron acceptor additive **A1** or **A7** were mixed in chloroform (Figure 2). This clearly indicated the charge-transfer interaction exists between **1a** and **A1** or **A7**.

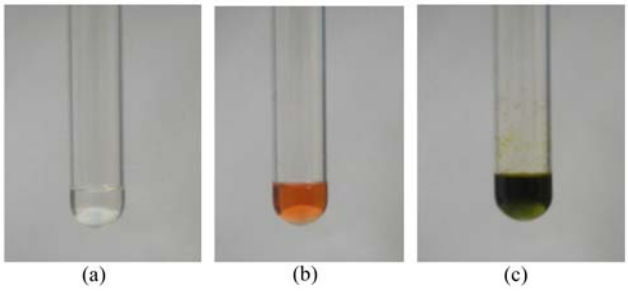


Figure 2 (a) **1a** in $CHCl_3$, (b) **1a** and **A1** in $CHCl_3$, (c) **1a** and **A7** in $CHCl_3$.

To further estimate this charge-transfer interaction in a molecular level, the ^{1}H NMR spectra of catalyst **1a**, **A1** and their mixture were measured in $CDCl_3$. As shown in Figure 3, the signal of **A1** at δ 8.26 shifted to δ 6.45 as a broad singlet after mixing with catalyst **1a** in a molar ratio of 2∶1. This apparent up-field shift of the signal for acceptor is obviously caused by the electron transfer from electron rich catalyst **1a** to electron-poor acceptor additive **A1**. Although the UV absorption spectrum of catalyst **1a** in $CHCl_3$ does not undergo evident change after mixing with **A1** (Figure 4a), the maximum fluorescence emmision band of **A1** completely disappeared after combination with catalyst **1a** in $CHCl_3$, indicating a strong fluorescence quenching effect of **1a** on **A1**. All the spectral evidence clearly indicated the charge transfer interaction is indeed present in the system, which might provide an excellent opportunity for reaction optimization via intermolecularly charge-transfer interaction between the catalyst and the additive.

As expected, the charge-transfer interaction indeed resulted in a remarkable effect on the enantioselectivity of the reactions performed at room temperature, as evidenced by the results shown in Table 1. The reaction of **2a** in the presence of 20 mol% of **A1** with 10 mol% of **1a** as the catalyst in chloroform at room temperature affords the product with 99% yield in 76% *ee* (Table 1, Entry 2), which is obviously higher than those without additive under otherwise identical experimental conditions (Table 1, Entry 1).[1] Under the otherwise identical conditions, the impact of a variety of additives **A1**—**A7** was further examined on the control of enantioselectivity in the catalysis of B-V oxidation of **2a** in chloroform at room temperature, leading to the nearly quantitative formation of lactone **3a** with an enhancement of *ee* values from 71% (Entry 1) up to 78% (Entries 2—4, 8—13). Among the solvents screened for the **1a**/**A1** combination, chloroform turns out to be the best in terms of both the catalytic efficiency and enantioselectivity (Entries 5—7 vs .2).

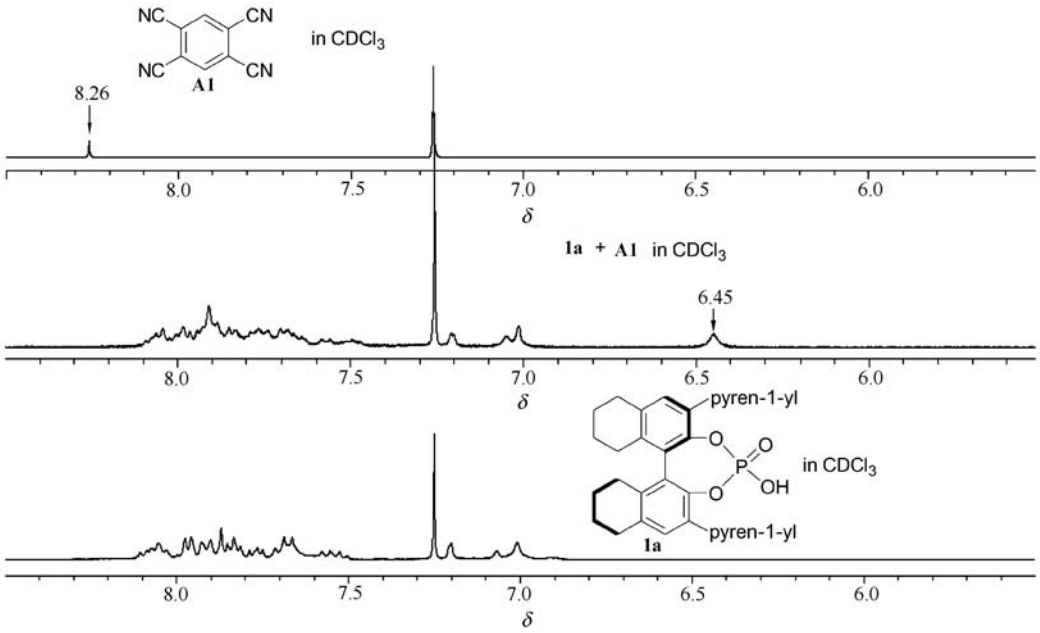


Figure 3 Comparison of ^{1}H NMR spectra of **A1**, **1a** and **1a**+**A1** in $CDCl_3$.

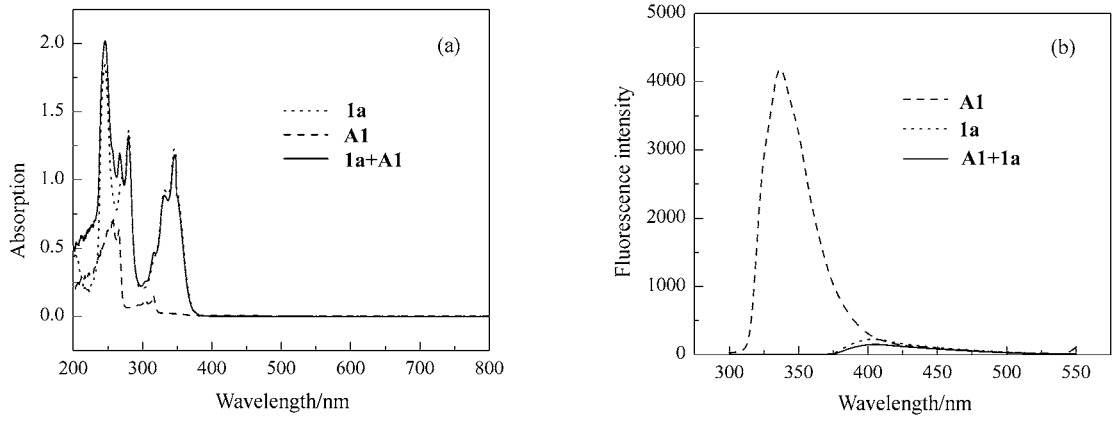


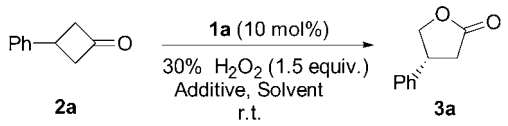
Figure 4 (a) Comparison of UV absorption spectra of **1a**, **A1** and **1a**+**A1**; (b) comparison of fluorescence emission spectra of **1a**, **A1** and **1a**+**A1** (excitation wavelength of 275 nm).

An important advantage of the strategy using electron-acceptor additives is that the enantioselectivity can be fine-tuned by simply changing the catalyst/additive combinations without additional synthesis, which has never been explored previously to the best of our knowledge.[6] In an effort to further evaluate the potential of the donor-acceptor intereaction for the stereocontrol, a variety of chiral phosphoric acid catalysts[7] with different fused-ring aromatic substituents were examined in combination with **A3** in the asymmetric B-V oxidation of **2a**. As shown in Table 2, the *ee* values of **3a** can be enhanced appreciably (up to 9%) relative to that of using phosphoric acid **1e** alone by appropriate combinations of **A3** and **1e** at room temperature (Entry 5). Surprisingly, the effect diminished (or essentially disappeared) as the reaction was carried out at a much lower temperature. As shown in Table 3, for **1a**-catalyzed B-V reactions of 3-aryl substituted cyclobutanones performed at −40 ℃, there is no much difference in *ee* values for the reactions performed in the presence or absence of the electron-acceptor additive **A1**. Although the exact reason is still not clear at the present stage, it is indeed reflecting the complexity in the control of the stereoselectivity in the catalysis of this type reaction.[3]

Conclusions

In summary, we have clearly demonstrated that the intermolecular charge-transfer effect can be used as an effective strategy for tuning the enantioselectivity of the asymmetric cataysis, as shown in asymmetric BV oxidation of 3-aryl cyclobutanones performed at room temperature catalyzed by chiral phosphoric acid. Up to 9% enhancement of *ee* value was observed in a case with the combined use of the chiral phosphoric acid **1a** catalyst and an appropriate electron-acceptor additive. It

Table 1 Additive effect in the phosphoric acid **1a** catalyzed asymmetric B-V oxidation of 3-phenyl cyclobutanone **2a**[a]



Entry	Additive/mol%	Solvent	Time/h	Yield[b]/%	*ee*[c]/%
1	None	$CHCl_3$	12	99	71
2	**A1** (20)	$CHCl_3$	12	99	76
3	**A1** (10)	$CHCl_3$	12	99	76
4	**A1** (40)	$CHCl_3$	12	99	76
5	**A1** (20)	DCM	12	88	69
6	**A1** (20)	DCE	12	88	72
7	**A1** (20)	Toluene	12	93	53
8	**A2** (20)	$CHCl_3$	12	99	75
9	**A3** (20)	$CHCl_3$	12	99	78
10	**A4** (20)	$CHCl_3$	12	98	75
11	**A5** (20)	$CHCl_3$	12	99	72
12	**A6** (20)	$CHCl_3$	12	99	75
13	**A7** (20)	$CHCl_3$	11	99	75

[a] The reaction was carried out at room temperature with [**2a**]=0.1 mo/L and 1.5 equiv. 30% H_2O_2 to give the lactone **3a**. [b] The yield of isolated product. [c] The enantiomeric excess of **3a** was determined by HPLC analysis on a chiral column (Chiralpak AS-H).

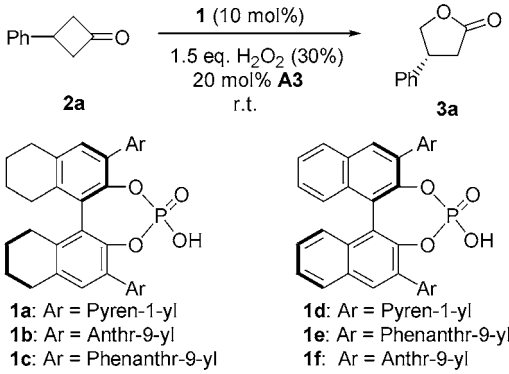
is noteworthy that this work represents the first example of unequivocal demonstration on the use of the donor-acceptor interaction for fine-tuning the enantioselectivity in the area of the asymmetric catalysis to the best of our knowledge. This conceptually new strategy might stimulate future efforts to explore its new application in other catalytic systems.

Experimental

General methods

NMR spectra were recorded on a Varian Mercury 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) or Varian 400-MR (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometer in $CDCl_3$. Chemical shifts are expressed in δ with TMS as an internal standard (δ=0) for ^{1}H NMR data. Coupling constants, *J*, are listed in hertz. ^{13}C NMR data are reported in terms of chemical shift (δ) with $CDCl_3$ (δ=77) as internal standard. EI-MS and HRMS-EI data were obtained on the instrument Shimadzu GCMS-QP2010 and Waters Micromass, GCT respectively. UV and fluorescence spectra were recorded on a CARY 100 Conc. UV-Visible spectrophotometer and a F-4500 FL spectrophotometer respectively. HPLC analysis was carried out on a JASCO PU 2089 or JASCO 1589 instrument. Unless stated otherwise, all solvents were purified and dried according to standard methods prior to use.

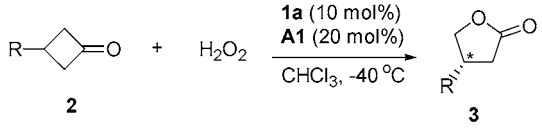
Table 2 Chiral phosphoric acids catalyzed asymmetric B-V reaction of 3-phenyl cyclobutanone in the presence of electron acceptor **A3**[a]



Entry	Catlyst	Time/h	Yield[b]/%	*ee*[c]/%
1	**1a**	12	99	78 (71)
2	**1b**	24	80	51 (50)
3	**1c**	24	90	67 (65)
4	**1d**	24	83	65 (57)
5	**1e**	24	86	63 (54)
6	**1f**	24	96	46 (44)

[a] The reaction was carried out at room temperature with [**2a**]=0.1 mol/L and 1.5 equiv. 30% H_2O_2 to give the lactone **3a**. [b] The yield of isolated product. [c] The enantiomeric excess of **3a** was determined by HPLC analysis on a chiral column (Chiralpak AS-H), the data in the parentheses were obtained in the absence of additive under the otherwise identical experimental conditions.

Table 3 Chiral phosphoric acid **1a** catalyzed asymmetric B-V reaction of 3-phenyl cyclobutanone in the presence of electron acceptor **A1**[a]



Entry	R in **3**	Time/h	Yield[b]/%	*ee*[c]/%
1	C_6H_5 (**a**)	18	88	90 (88)
2	4-MeC_6H_4 (**b**)	24	95	93 (93)
3	4-BrC_6H_4 (**c**)	24	99	83 (83)
4	4-ClC_6H_4 (**d**)	24	99	82 (82)
5	4-FC_6H_4 (**e**)	24	99	86 (84)
6	2-Nphthyl (**f**)	24	91	87 (86)
7[d]	C_6H_5 (**a**)	18	99	84 (88)
8[e]	C_6H_5 (**a**)	28	99	88 (88)

[a] All the reactions were carried out at −40 ℃ with [**2**]=0.1 mol/L and 1.5 equiv. 30% H_2O_2. [b] The yield of isolated product. [c] The enantiomeric excesses of **3** were determined by HPLC analysis on a chiral column. The data in the parentheses were obtained in the absence of any additive under the otherwise identical conditions. [d] and [e] Additives **A3** and **A7** were used, respectively, in the reactions.

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General procedure for asymmetric B-V reaction of 3-arylcyclobutanones catalyzed by chiral phosphoric acid in the presence of electron acceptor A1—A7

A 5-mL Schlenk tube was charged with **1** (0.01 mmol), additive **A** (0.02 mmol), and $CHCl_3$ (1 mL). The mixture was stirred at r.t. for 30 min before 3-arylcyclobutanone **2** (0.1 mmol) and 30% H_2O_2 (17 μL, 1.5 equiv.) were added, respectively. The resulting mixture was stirred for 12—24 h at the defined temperature. The residual hydrogen peroxide was quenched with an aqueous solution of Na_2SO_3, and the lactone product **3** was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (*V*/*V* = 6/1) as the eluent. The enantiomeric excess was determined by HPLC on a Chiralcel AS-H column.

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