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Photoswitchable Chiral Phase Transfer Catalyst

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ABSTRACT: Azo-crown ether-based photoswitching chiral phase transfer catalysts have been developed to control the catalytic activity by photoirradiation. Azobenzene binaphthyl crown ether (ABCE) can switch its reactivity and selectivity through structural transformation of the crown ether moiety induced by E/Z photoisomerization of azobenzene. (*Z*)-ABCE promoted enantioselective alkylation of the glycine Schiff base to afford chiral amino acid derivatives in good yields with high enantiomer ratios. In contrast, (*E*)-ABCE hindered the reaction progress under the same conditions.

KEYWORDS: photoresponsive chiral molecule, crown ether, azobenzene, enantioselective organocatalysis, phase transfer catalyst

photoswitchable catalyst, involving a catalytically active A site and a photoresponsive unit, can be used to iteratively modulate catalytic activity through reversible switching of steric and electronic properties with photoisomerization using light as a clean external stimulus. Because photoswitchable catalysts are unique, many efforts have been made to develop photoswitchable organo- and organometallic catalysts.¹ Photoswitchable chiral catalysts allow the switching of reactivity and enantioselectivity under photoirradiation.² It is crucial to introduce a photoresponsive unit to the chiral skeleton and appropriately position each unit to achieve a high selectivity and significant photomodulation of the reaction outcome. For highly sophisticated catalytic systems, multistep preparation and expensive reagents are often required. Among the photoresponsive units, azobenzene, an easily available and well-known photochromic molecule, rapidly and reversibly switches the E/Z isomer under exposure to UV or visible light, resulting in significant changes in its dipole moment and conformation.³ Azo-crown ether,⁴ consisting of azobenzenes and crown ethers, is one of the most important photoswitchable supramolecules. Shinkai et al. developed various elegant azo-crown ethers such as the butterfly crown ether^{4c} and macrocycle units containing azobenzene and crown ether,^{4d} which can switch their geometry, extraction, and coordination ability with alkali metals through the photoisomerization of azobenzene units (Figure 1A). As a pioneering report on photocontrol of the catalytic activity of an azo-crown ether, in 2003, Cacciapaglia et al. reported the ethanolysis of anilides using a butterfly crown ether.^{5a} Inspired by these reports on the unique properties and catalytic activities of azocrown ethers, we focused on azo-crown ether as a photoresponsive unit. Despite many examples of azobenzenecontaining achiral catalysts,^{1j,5} there is only one report on chiral photoswitchable catalysts employing azobenzene (salen complexes for asymmetric sulfoxidation).²¹

In this work, to introduce the functionalities of both the azocrown ether and a chiral unit to a catalytic molecule, a chiral crown ether consisting of BINOL and an azobenzene framework was designed (Figure 1B). We envisioned that an azobenzene binaphthyl crown ether (ABCE) with an appropriate ring structure can control the reactivity and enantioselectivity as a chiral phase transfer catalyst (PTC)⁶ through geometry modulation attributed to the reversible photoisomerization of azobenzene. To verify our catalyst, we demonstrated light-controlled reactivity of the enantioselective reaction,^{2C,h} which is still less explored compared to the effect of photocontrol over the stereochemical outcome.

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(A) Previous work Uν Vis or A The E/Z photoisomerization of the azobenzene unit on the azo-crown ether modulates etry, extraction, and coordination ability. (B) This work azo-crown ether (photoswitch) commercially available photoresponsive and chiral units short-step synthesis easy tuning of crown ether structure work as a phase transfer catalyst (PTC) -derived crown ether (chiral unit) UV Vis or ∆ m, n = 0, 1 or 2 (E)-ABCE (Z)-ABCE ⇒ photoisomerization of azobenzene unit change of crown ether geometry photoswitchable modulation of reactivity and selectivity for enantioselective reactions

Figure 1. (A) Previously reported azo-crown ether: early reports^{4c,d} and catalytic application.^{5a} (B) This work: ABCE as a photoswitchable chiral PTC.

We commenced our study by establishing a general procedure and a library of ABCE 4. ABCEs 4a-4f were synthesized from BINOL or 3,3'-disubstituted BINOL 1 in three steps: (a) alkylation and (b) tosylation, followed by (c) a ring-closing reaction with the corresponding dihydroxyazobenzene (Scheme 1). Then, we performed photoisomerization of the representative ABCE 4a by UV-vis spectroscopy as shown in Figure 2A,B. As expected, UV irradiation at 365 nm rapidly decreased the $\pi \rightarrow \pi^*$ band with a slight increase of the $n \rightarrow \pi^*$ transition for the formation of the Z isomer of 4a. Visible light irradiation at 405 nm reversibly led to the E isomer of 4a. Moreover, we quantified the photostationary states of 4a by ¹H NMR analysis in toluene- d_8 . Before UV irradiation, the E/Z ratio was calculated to be 84:16 on the basis of the azobenzene-associated proton signals (Figure 2C). UV irradiation (5 min, 365 nm) promoted photoisomerization from the *E* to *Z* isomer, leading to E/Z = 12.88 (Figure 2D). Reversible photoisomerization from Z to E was observed, and E/Z = 68/32 was obtained under exposure to visible light at 405 nm (Figure 2E).^{8,9}

To investigate the catalytic activity of the photoswitchable chiral PTC with or without UV, we applied ABCE **4** to the enantioselective alkylation reaction of glycine Schiff base **5a** with 4-chlorobenzyl bromide **6a** in toluene, affording unnatural amino acid precursor **7a** under the modified reaction conditions reported previously (Table 1).^{6d,h} Gratifyingly, ABCE **4a** (1 mol %) switched reactivity, affording the desired product **7a** in 75% yield, 92:8 er under UV irradiation during the reaction, and 11% yield, 92:8 er in the absence of UV (entries 1 and 2).^{10,11} Using shorter-chained ABCE **4b**, **7a** was obtained in 45% yield and 58:42 er at 365 nm, and the reaction hardly proceeded without UV irradiation (entries 3 and 4). The use of longer-chained ABCE **4c** afforded higher yields and the opposite enantiomer of **7a** under UV irradiation, albeit



4b (R = H; m = n = 0) **4e** (R = H; m = n = 1) **4c** (R = H; m = n = 2) **4g** (R = H; m = 0; n = 1) **4h** (R = H; m = 1; n = 2)

"Reaction conditions: (a) 2-(2-iodoethoxy)ethanol, 2-iodoethanol, or 2-(2-(2-iodoethoxy) ethoxy)ethanol (3.0 equiv), K_2CO_3 (4.0 equiv), 60 °C, DMF; (b) TsCl (2.5 equiv), Et₃N (4.0 equiv), DMAP (20 mol %), 0 °C to rt, DCM; (c) 2,2'- or 3,3'-dihydroxy azobenzene (1.05 equiv), Cs_2CO_3 (3.3 equiv), dibenzo-18-crown-6 (33 mol %), 80 °C, DMF.

with low enantioselectivities (52:48 and 46:54 er) (entries 5 and 6). The reaction catalyzed by 4d bearing phenyl groups at the 3,3'-position of the binaphthyl unit exhibited a lower yield and er (entries 7 and 8). When 3,3'-diiodinated ABCE 4e was used, the switching reaction rate was moderate (67% yield vs 29% yield), probably owing to the weak coordination of the iodo group with potassium cations (entries 9 and 10).¹² In addition, the enantioselectivity of 7a dropped from 81:19 to 64:36 er without photoirradiation. When we employed ABCE 4f derived from 3,3'-dihydroxyazobenzene, the desired product was obtained in 42% and 26% yields with no enantioselectivity under UV and dark conditions, respectively (entries 11 and 12).¹³ In the absence of PTC 4, a trace amount of the desired product was detected (entries 13 and 14).

Under the reaction conditions shown in Table 1, we examined the photomodulating reactivity of enantioselective alkylation using a variety of benzyl bromides **6** in the presence of ABCE **4a** (Table 2). Other para-substituted substrates **6b** (Ar = 4-BrC₆H₄) and **6c** (Ar = 4-MeC₆H₄) were tolerable, providing the corresponding alkylated products **7b** and **7c** in 61% and 54% yields with 90:10 and 86:14 er, respectively, under UV irradiation (entries 3 and 5). In contrast, non-UV irradiation significantly suppressed these transformations, recovering the corresponding substrates (entries 4 and 6). Likewise, when we used meta-substituted benzyl bromides **6d** and **6e** (**6d**: Ar = 3-ClC₆H₄; **6e**: Ar = 3-BrC₆H₄) as a substrate, these reactions accelerated to afford the corresponding products **7d** and **7e** in higher yields than those obtained under the dark condition (**7d**: 77% yield and 86:14 er; **7e**: 69%

Scheme 1. Synthesis of ABCE 4^{a}



Figure 2. Changes in the UV–vis spectra (in $CHCl_3$, 100 μ M) and ¹H NMR spectra (in toluene- d_8 , 8 mM) of **4a** upon photoirradiation.

Table 1. Screening of ABCE 4^{a}

		ABCE 4 (1 m	nol %)	CI
	+	toluene, 0 °C	$\frac{\text{equiv}}{2, 6 \text{ h}} N$	COO ^t Bu
5a	Br 6a (3 equiv)		Ph	⊃h 7a
entry	ABCE (wavelength)	E/Z ratio	yield (%) ^b	er ^c
1	4a (365 nm)	12:88	75 (75)	92:8
2	4a (no light)	84:16	11	92:8
3	4b (365 nm)	12:88	45	58:42
4	4b (no light)	91:9	trace	
5	4c (365 nm)	15:85	59	52:48
6	4c (no light)	88:12	80	46:54
7	4d (365 nm)	13:87	65	66:34
8	4d (no light)	93:7	trace	
9	4e (365 nm)	11:89	67	81:19
10	4e (no light)	92:8	29	64:36
11	4f (365 nm)	6:94	42	50:50
12	4f (no light)	85:15	26	50:50
13	- (365 nm)		trace	
14	 – (no light) 		trace	

^{*a*}Reaction conditions: **5a** (0.2 mmol), **6a** (0.6 mmol), KOH (1.0 mmol), and ABCE **4** (1 mol %) in toluene (0.5 mL) at 0 °C. ^{*b*}1,3,5-Trimethoxybenzene was used as an internal standard. Isolated yield is shown in parentheses. ^{*c*}Enantiomeric ratio was determined by HPLC analysis (DAICEL Chiralpak IE).

yield and 86:14 er) (entries 7–10). Using 2-methyl-benzyl bromide **6f**, the UV-mediated reaction smoothly proceeded to

Table 2. Evaluation of Photo-Controlled Reactivity of	
Enantioselective Alkylation of 5a with 6 Using ABCE 4a ⁴	L

N	[_] COO ^t I	Bu _Ar	AB0 solid	CE 4a (1 mol d KOH (5 eq	%) uiv)	Ar
Ph ^{//} P	h	+ Br	tolu	uene, 0 °C, ti	me Ń	COO ^t Bu
					Ph´ `P	h
5a		6a-g (3 equi	v)		7	a-g
entry	6	Ar	light	time (h)	yield (%)	er ^d
1	6a	4-ClC ₆ H ₄	UV	6	75 ^b	92:8
2					11 ^c	92:8
3	6b	4-BrC ₆ H ₄	UV	7	61 ^b	90:10
4					trace ^c	
5	6c	4-MeC ₆ H ₄	UV	6	54 ^b	86:14
6					trace ^c	
7	6d	3-ClC ₆ H ₄	UV	5	77 ⁶	86:14
8					10 ^c	90:10
9	6e	$3-BrC_6H_4$	UV	7	69 ^b	86:14
10					trace ^c	
11	6f	$2-MeC_6H_4$	UV	4	71 ^b	85:15
12					trace ^c	
13	6g	C ₆ H ₅	UV	4	63 ^b	80:20
14					trace ^c	

^{*a*}Reaction conditions: **5a** (0.2 mmol), **6** (0.6 mmol), KOH (1.0 mmol), and ABCE **4a** (1 mol %) in toluene (0.5 mL) at 0 $^{\circ}$ C. ^{*b*}Isolated yield. ^{*c*}1,3,5-Trimethoxybenzene was used as an internal standard. ^{*d*}Enantiomeric ratio was determined by HPLC analysis.

afford the corresponding product 7f in 71% yield and 85:15 er (entry 11). Sterically less bulky benzyl bromide **6g** was converted into the alkylated product 7g in 63% yield and 80:20 er (entry 13). In the absence of UV, trace amounts of products 7f and 7g were detected by TLC monitoring and crude ¹H NMR analysis (entries 12 and 14).

To gain further insights into the control over the reactivity of the enantioselective alkylation of 5a with 6a under photoirradiation, kinetic studies were performed using photoresponsive ABCE 4a (Figure 3). While UV-treated 4a



Figure 3. Reaction profile of 5a and 6a promoted by (A) 1 mol % of ABCE 4a (4 mM) (orange: in the dark; blue: under photoirradiation at 365 nm); (B) photoacceleration of the reaction using ABCE 4a (4 mM) under the dark followed by UV (365 nm) irradiation.

indicated a higher reactivity over nonphotoirradiated conditions (7a: 75% vs 11% yield) (Figure 3A), no acceleration was observed when using 18-crown-6 as a nonphotoresponsive crown ether under photoirradiation (see Figure S7). Considering these results, we can rule out the possibility of thermal- and photoactivation of substrates by LED irradiation. The reaction rate would increase due to the geometry transformation of the crown ether ring on 4a induced by photoisomerization of azobenzene.¹⁴ The Z isomer of 4a would be highly suitable for the alkylation reaction of 5a with 6a over the E isomer. Next, acceleration and deceleration of the enantioselective alkylation of **5a** with **6a** were examined in the presence of **4a** by switching wavelengths during the reaction process. It is noted that the reaction was accelerated by switching the *E* to *Z* isomer by UV irradiation after 1 h in the dark (**7a**: 68% vs 11% yield) (Figure 3B). Furthermore, visible light irradiation at 405 nm moderately decelerated the alkylation within the course of the reaction after 1 h under UV light (**7a**: 58% vs 71% yield)^{15,16} (see Figure S8).

In conclusion, we demonstrated chiral BINOL-derived azocrown ethers control the reactivity for the enantioselective alkylation reaction of glycine Schiff base with benzyl bromides as a photoswitchable PTC with and without UV irradiation. The alkylation reaction was accelerated and decelerated by in situ photoisomerization of the catalyst at different wavelengths. Further investigations of the mechanism of switching reactivity in more detail and applications of the photoswitchable PTCs to modulate stereoselectivity are being carried out in our group.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c00057.

Compound characterization data; HPLC chromatograms; experimental procedures; spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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(8) Potoirradiation for 5 min was enough to reach the photostationary states (see Figure S3). The photostationary states did not change at the same concentration as the reaction ([4a] = 4 mM). The half-life of Z-4a was 158 h (in toluene, 20 °C) (see Figure S6). Heating in toluene at 80 °C restored the isomerization ratio of 4a to E/Z = 84:16.

(9) The reversible photoisomerization of **4a** occurred smoothly in the presence of KOH (see Figures S4 and S5). ESI-HRMS supported **4a** forms in a 1:1 complex with potassium cation (positive ion mode, calculated for $C_{40}H_{36}KN_2O_6^+$: 679.2205; observed: 679.2206) (see Figure S2).

(10) When thermally isomerized **4a** (E/Z = >95/5 at 100 °C in toluene, before adding KOH, **5a**, and **6a**) was applied to the reaction, a trace amount of the product **7a** was obtained (<5%).

(11) The absolute configuration of the product 7a was determined by the comparison of the optical rotation with the reported value. See Wen, S.; Li, X.; Lu, Y. Enantioselective Alkylation of Glycine Imine Promoted by Amino-Acid-Derived Phosphonium Salts. *Asian J. Org. Chem.* **2016**, *5*, 1457–1460.

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(13) The ABCE 4g (R = H; m = 0; n = 1) and 4h (R = H; m = 1; n = 2) were also prepared and applied to the enantioselective alkylation of 5a and 6a. The reaction using 4g and 4h afforded the desired product 7a in 62% and 77% yields with 70:30 and 51:49 er under UV irradiation, respectively, while the reaction was significantly suppressed to provide a trace amount of the product without photoirradiation.

(14) We presumed that the different reaction rate between the E and Z isomers of **4a** was probably caused by the different extraction ability of solid KOH. The Z isomer of **4a** can efficiently form a catalytic active species owing to the stronger extraction ability of the potassium cation over the E isomer. This hypothesis would be supported by DFT studies (see Figure S9). However, we cannot rule out the possibility that the steric difference between both the isomers modulated the reactivity of the nucleophilic substitution reaction process.

(15) The reaction was not completely turned off due to the moderate photoisomerization from the *Z* to *E* isomer of **4a** at 405 nm. Although other wavelengths of LED and solvents were examined, they were ineffective for the photoisomerization from the *Z* to *E* isomer of **4a** (see Tables S1 and S2). Functionalization on the azobenzene moiety for the stabilization of the *E* isomer or the destabilization of the *Z* isomer would sharply control the reactivity under UV and visible light.

(16) The range of er for product 7a was between 90:10 and 92:8 after photoacceleration and deceleration.