Light-controlled pKa Value of Chiral Brønsted Acid Catalysts in Enantioselective Aza-Friedel–Crafts Reaction

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Light-controlled pKa Value of Chiral Brønsted Acid Catalysts in Enantioselective Aza-Friedel–Crafts Reaction

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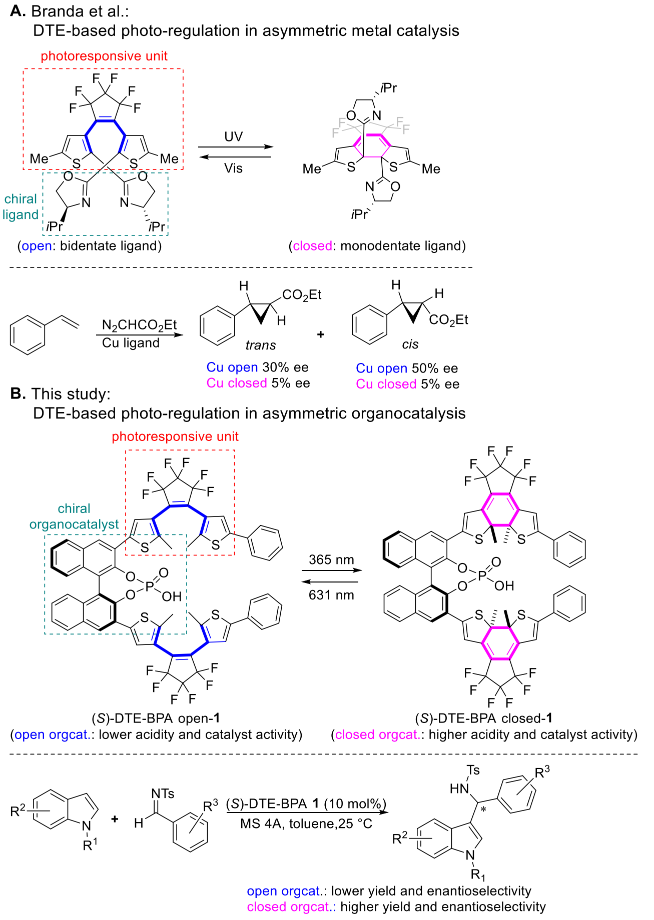
Bis(dithienylethene)-based BINOL-derived phosphoric acid (DTE-BPA) has been developed as a light-controlled chiral organocatalyst for the first time. The photoinduced modulation of the reactivity and selectivity via the open/close isomerization of DTEs scaffold led to the superior light-controlled ability on the enantioselective aza-Friedel–Crafts reaction of aldimines with indoles. DFT studies revealed that photoisomerization is accompanied by a shift of 1.1 pKa units between the open and closed isomers.

The boundless potential offered by a photoswitchable catalyst for the non-invasive dynamic control over both catalytic activity and selectivity encouraged researchers to produce new creative designs bearing various photoresponsive units.[1] Among them, considerable attention has been given to diarylethene candidates such as DTEs,[2] because of their exceptional photochromic properties, i.e., high quantum yield, prompt photoresponsiveness, high fatigue resistance, and excellent thermal stability (P-type photochromism)[3] in both isomeric forms.[4] The difference in rigidity between the open and closed isomers of DTEs has been exploited for light-driven molecular recognition.[5] In 1988, Irie group discovered the photochromic properties of DTEs.[6] After their discovery, the applications of DTEs as photoswitchable scaffolds have been widely explored.[7] In 2005, Branda et al. reported only one example of DTE-based photoregulation in asymmetric metal catalysis (Scheme 1A).[8a] Light-responsive regulation of the catalytic function was achieved by integrating the light-responsive DTE unit with the chiral oxazoline function between the monodentate and bidentate ligands. Following this seminal work, DTE-based metal catalysis using Karstedt's catalyst,[9] Cu,[10] Rh catalysts,[11] and DTE-based achiral organocatalysts with pyridines,[12] *N*-heterocyclic carbenes,[13] phenols,[14] imidazoles,[15] and pyridinium salts have been reported.[16] These studies on light-responsive DTEs encouraged us to explore dithienylethene photochromic skeletons for asymmetric organocatalysis. To the best of our knowledge, DTE-based asymmetric organocatalysts are yet to be reported. BINOL-derived phosphoric acid (BPA) catalysts exhibit unique structural and chemical features such as an acid/base dual function and, steric and electronic influence with substitution at the 3,3'-positions, leading to efficient enantioselective transformations.[17] Phosphoric acid-catalysed reactions have significant selectivity depending on the substituent at the 3,3'-positions of the binaphthyl core. Overly large substituents might completely stop reactions[18] or change the selectivity.[19]



Scheme 1 DTE-based photo-regulation in asymmetric catalysis.

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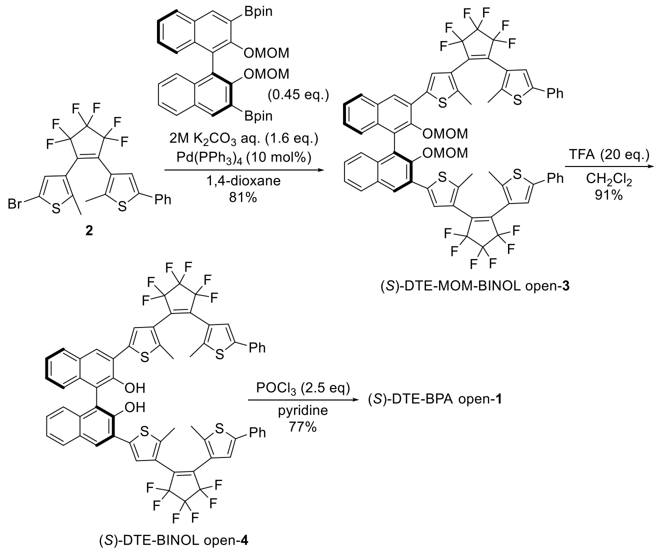
Therefore, the strategic design of photoresponsive catalysts for modulation is challenging. As part of our continuous effort to develop novel asymmetric light-controlled catalysis,[20] we assumed that the electronic differences between the two photoisomers of DTE, namely its open and closed forms, at the 3,3’-positions on BPAs might influence both the reactivity and selectivity on the organocatalytic transformations. As part of our continuous effort to develop novel asymmetric light-controlled catalysis,[20] we assumed that the electronic differences between the two photoisomers of DTE, namely its open and closed forms, at the 3,3’-positions on BPAs might influence both the reactivity and selectivity on the organocatalytic transformations.

Photocyclisation of DTE derivatives can also reversibly alter the acidity/basicity upon photoisomerization to form compounds with distinct electronic environments *via* π-conjugate acid/base system.[8b-d,21] For example, Lehn et al. reported a modulation approach to the acidity of phenol with 1.2 pK_a units that were photochemically adjusted between two temporally distinct forms of DTEs.[21a] Branda et al. demonstrated significant changes in the reactivity of DTE-based switchable acids/bases involving a central ethene unit.[8b-d] Another effective system for pH-gated photochromism using DTE derivatives was demonstrated by Hecht et al. for acid-base catalysis.[21e] Recently, Glorius et al. developed DTE-based *N*-heterocyclic imines as photoswitchable nitrogen superbases.[21f] However, the photomodulation of electronic properties has not been employed in asymmetric organocatalysis. Herein, the first synthesis of bis(dithienylethene)-based BINOL-derived phosphoric acid (DTE-BPA) as a chiral light-controlled organocatalyst has been presented. In this study, the photomodulation of the DTE-BPA was also conducted on the enantioselective aza-Friedel–Crafts (aza-FC) reaction of aldimines with indoles (Scheme 1B).



Scheme 2. Synthesis of bis(dithienylethene)-based (*S*)-1,1'-bi-2-naphthol (BINOL)-derived phosphoric acid ((*S*)-DTE-BPA open-**1**).

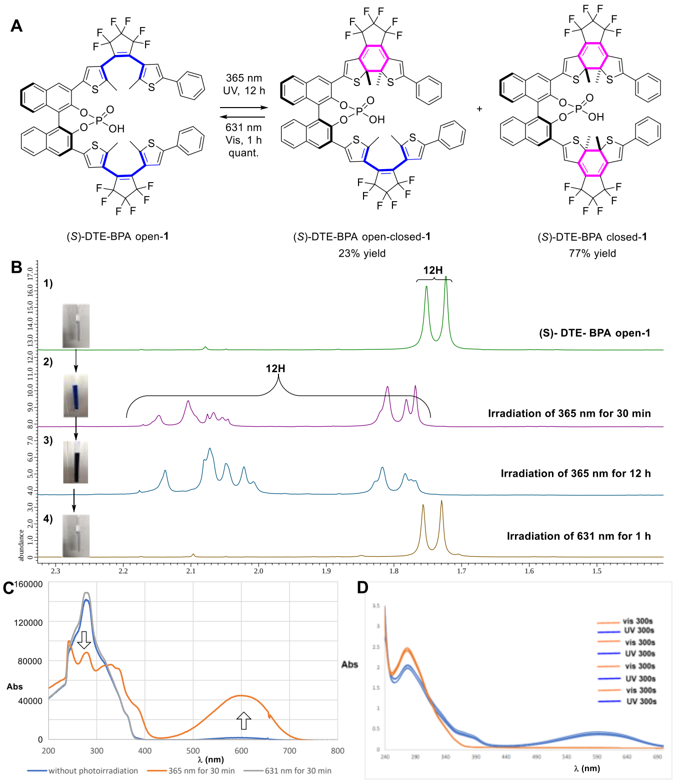
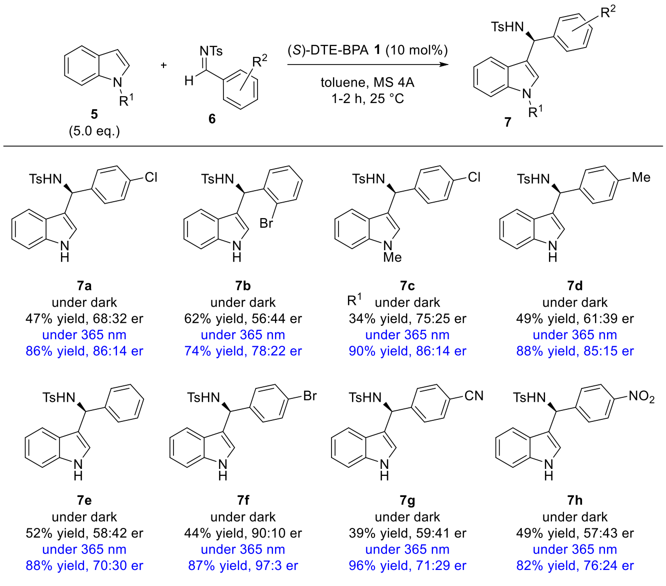


Figure 1 (A) The schematic representation of photochemical isomerization of (*S*)-DTE-BPA **1**. (B) ^{1}H-NMR ($CDCl_3$) photoisomerization experiment studies: 1) (*S*)-DTE-BPA-open-**1**, 2) mixture of (*S*)-DTE-BPA-open-**1** and (*S*)-DTE-BPA-closed-**1** (irradiation of 365nm to (*S*)-DTE-BPA-open-**1** for 30 min), 3) mixture of (*S*)-DTE-BPA-open-**1** and (*S*)-DTE-BPA-closed-**1** (irradiation of 365nm to (*S*)-DTE-BPA-open-**1** for 12 h), 4) (*S*)-DTE-BPA-open-**1** (irradiation of 631 nm to the mixture for 1 h). (C) UV/Vis spectral changes of (*S*)-DTE-BPA **1** upon UV (365 nm, 30 min) and visible light (631 nm, 30 min) irradiation in $CHCl_3$ (20 μM). (D) Fatigue resistance testing in $CHCl_3$ (40 μM).

The catalyst (*S*)-DTE-BPA open-**1** was synthesised from **2**[22] in three additional steps *via* Suzuki–Miyaura cross-coupling, removal of the MOM group, and phosphate ester formation (Scheme 2). Next, photochemical isomerisation between the thermally stable isomers of (*S*)-DTE-BPA **1** was studied using ^{1}H-NMR and UV/Vis spectroscopy (Figure 1). In the ^{1}H-NMR spectrum ($CDCl_3$) of (*S*)-DTE-BPA open-**1**, the protons of the methyl group of the methyl thiophene unit were detected at δ 1.76 and δ 2.01. After 30 min of irradiation by an LED light at the wavelength of 365 nm, the solution in the ^{1}H-NMR tube turned blue, and a new set of methyl signals in the ^{1}H-NMR spectrum appeared at δ 1.81 and δ 2.04–2.16, which are attributed to the mixture of (*S*)-DTE-BPA open-**1** (27%), open-closed-**1** (29%), and closed-**1** isomers (44%). Finally, irradiation at the same wavelength for 12 h reveals the full conversion of the open isomer (the signal at δ 1.76 and δ 2.01 disappeared) to a mixture of (*S*)-DTE-BPA closed-**1**/open-closed-**1** in a ratio of 77% to 23%. Reverse isomerisation (reverse ring opening process) was achieved under 631 nm visible-light irradiation for 1 h (Figure 1B). We also analysed the effects of solvents and wavelengths on the photostationary state (PSS) of (*S*)-DTE-BPA **1**. Solvent screening revealed that the use of toluene-d_8 improved the open-to-closed isomerisation of **1**, resulting in the maximum PSS ratio of (*S*)-DTE-BPA **1** (closed/open-closed = 77/23) after irradiation at 365 nm for 2 h (see ESI for details). The longer irradiation time and wavelength variation did not improve the PSS ratio. The photoisomerization of (*S*)-DTE-BPA **1** was also recorded using UV/Vis spectroscopy (20 μM, $CHCl_3$, Figure 1C). For the open form of (*S*)-DTE-BPA **1**, an intense absorption band appeared at 285 nm,[23] corresponding to the $\pi \rightarrow \pi^*$ transition in thiophene-cyclopentene junctions. Concomitantly, the intensity of the absorption band corresponding to the extended π-conjugated system (electrocyclic conrotatory ring closure) of (*S*)-DTE-BPA **1** after UV irradiation (365 nm, 12 h) decreased the band at 285 nm, and two new bands appeared in the UV/Vis spectrum at 370 and 600 nm.[24] At 315 nm, the isosbestic point confirmed stoichiometric product formation, suggesting that no significant by- products were formed during the photoisomerization of (*S*)-DTE-BPA **1**.[25] A subsequent photoirradiation with visible light at a wavelength of 631 nm for 30 min was sufficient to restore the initial UV/Vis spectrum (quantitative conversion). Furthermore, a solution of (*S*)-DTE-BPA **1** was cyclically irradiated with UV light at a wavelength of 365 nm and visible light at a wavelength of 631 nm to test its fatigue resistance. Minimal changes were observed in the UV/Vis spectra upon switching between the (*S*)-DTE-BPA open-**1** and closed-**1** states over several cycles (Figure 1D).

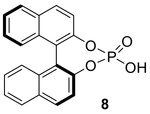
Since an enhanced acidity of the extended π-conjugation of (*S*)-DTE-BPA **1** was expected after photochemical isomerization, the catalytic activity modulation behavior and the asymmetric induction ability with and without photoirradiation were investigated. First, we examined the influence of the PSS ratio on the catalytic reactivity and selectivity of the aza-FC reaction of indole (**5a**) with aldimine **6**a.[26] For this purpose, the photoirradiation time (0−2 h) was varied to obtain different isomerisation ratios at 365 nm in toluene. As expected, (*S*)-DTE-BPA closed-**1** could be a more active catalyst the other isomers of **1** (Table S4, see supporting information),[27] and under photoirradiation at a wavelength of 365 nm, the reaction afforded 3-indolyl methanamine derivative **7a** in 86% isolated yield with enantiomer ratio (er) of 86:14.[26,28] In contrast, the reaction in the dark was sluggish, giving product **7a** in 47% yield with the lower er (68:32, Scheme 3). The higher acidity of the closed isomer of (*S*)-DTE-BPA **1** accounts for its increased reactivity under UV light irradiation. Additionally, photochemical isomerisation to the ring-closed form provides a suitable chiral environment for asymmetric induction.[29] The outcomes with 2-Br-phenyl *N*-tosylimine **6b** (R^2 = 2-Br) also suggested an enhanced reactivity (**7b**: 84% yield under 365 nm photoirradiation vs. 54% yield under dark conditions) and enantioselectivity (**7b**: 78:22 er under 365 nm photoirradiation vs. 56:44 er under dark conditions) with and without photoirradiation. When 1-Me-indole (**5**b: R^1 = Me) was employed with **6a** (R^2 = 4-Cl) in the presence of 10 mol% of catalyst **1**, a significant enhancement in the catalytic activity under photoirradiation was observed, affording the corresponding product **8c** in 90% yield with 86:14 er. In contrast, without photoirradiation, the yield and enantioselectivity of **7c** decreased to 34% and 68:32 er, respectively. Similar trends in the modulation were observed when other aldimines were used [**6d**: R^2= 4-Me, **6e**: R^2 = H, **6f**: R^2 = 4-Br, **6g**: R^2 = 4-CN, **6h**: R^2 = 4-NO_2], where both the reactivity and enantioselectivity were significantly enhanced upon light irradiation (Scheme 3).



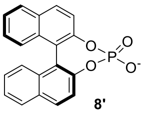
Scheme 3 Evaluation of the yield and enantiomer ratio (er) modulation on the aza-Friedel−Crafts reaction. Yield was determined by ^{1}H-NMR yield with 1,3,5-trimethoxybenzene as an internal standard. Er was determined by HPLC (DAICEL Chiralpak OD-H).

As a mixture of half- and fully-closed isomers is present after 365 nm photoirradiation, experimental measurements are unreliable for determining their acidity. Therefore, to understand the trend in the acidities of photoresponsive DTE-BPA **1** using DFT computational calculations (B3LYP/6-31+G(d)), the proton-exchange method[30] was utilized with respect to the experimental value of (*S*)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (**8**) as a reference acid ($pK_{a\ (DMSO,\ experimental)}$ = 3.37). The exchanged free energy in DMSO was determined using the following equation:

$$\Delta G^*_{exchange} = \Delta G^*_{gas,\ exchange} + \Delta G^*_{solv((S)\text{-}DTE\text{-}BPA\mathbf{1}(anion))} + \Delta G^*_{solv(\mathbf{8})} - \Delta G^*_{solv((S)\text{-}DTE\text{-}BPA\mathbf{1})} - \Delta G^*_{solv(\mathbf{8'})}$$



8 Reference acid



8' Reference anion

The ΔpK_a was then calculated using $\Delta pK_a = (\Delta G^*_{exchange,\ close} - \Delta G^*_{exchange,\ open})/RT\ln 10$, where R is the universal gas constant and T = 298.15 K. (See ESI for details). As an outcome of the aforementioned computational calculations with the selected most stable optimized geometries, a difference of 1.1 pK_a units was observed between the open and closed forms of the DTEs.

In summary, we have developed a novel chiral Brønsted acid, (*S*)-DTE-BPA**1** as a light-controlled organocatalysts for the first time. (*S*)-DTE-BPA**1** showed reversible isomerization in response to visible light. The DFT calculation of 1 indicated that the closed form has higher acidity (1.1 pk_a units) than that of the open form. Thus, by taking advantage of the photoswitchable properties of DTE units, we could control both the reactivity and selectivity of the aza-FC reaction. Future research should seek to improve the PSS ratio of the catalyst by modifying the photochromic backbone and expanding the range of reactions to create more versatile catalysts.

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Conflicts of interest

There are no conflicts to declare.

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