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Communication

Enantioselective [2 + 2] Photocycloaddition via Iminium Ions: Catalysis by a Sensitizing Chiral Brønsted Acid

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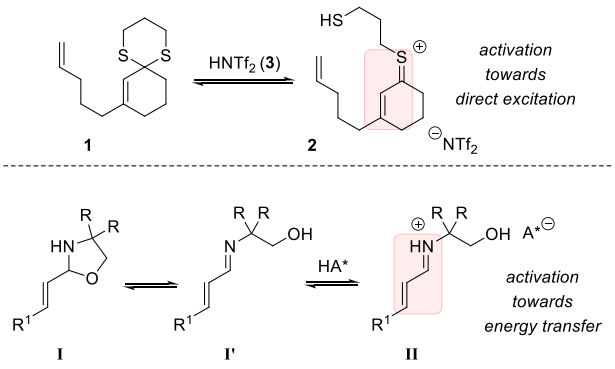
ABSTRACT: *N,O*-Acetals derived from α,β-unsaturated β-aryl substituted aldehydes and (1-aminocyclohexyl)methanol were found to undergo a catalytic enantioselective [2 + 2] photocycloaddition to a variety of olefins (19 examples, 54−96% yield, 84−98% *ee*). The reaction was performed by visible light irradiation (λ = 459 nm). A chiral phosphoric acid (10 mol %) with an (*R*)-1,1′-bi-2-naphthol (binol) backbone served as the catalyst. The acid displays two thioxanthone groups attached to position 3 and 3′ of the binol core via a *meta*-substituted phenyl linker. NMR studies confirmed the formation of an iminium ion which is attached to the acid counterion in a hydrogen-bond assisted ion pair. The catalytic activity of the acid rests on the presence of the thioxanthone moieties which enable a facile triplet energy transfer and an efficient enantioface differentiation.

Apart from their occurrence in nature,[1] cyclobutanes represent useful building blocks for synthetic applications[2] and serve as valuable scaffolds for the precise spatial location of functional groups, e.g. in drug design.[3] The intermolecular [2 + 2] photocycloaddition reaction between two different olefins represents one of the most straightforward methods to access this compound class.[4] Each carbon atom of the cyclobutane core can be stereogenic, which in turn requires control of the configuration within the ring system. Enantioface differentiation[5] arguably poses the most complex challenge in this context. Research efforts toward an enantioselective photochemical synthesis of cyclobutanes have increased in recent years, and the number of contributions is growing continuously.[6,7]

A key question that needs to be addressed in catalytic enantioselective [2 + 2] photocycloaddition chemistry relates to the selective excitation of a given substrate in a chiral environment. Since photochemical reactions occur rapidly after excitation, it is of pivotal importance that the substrate is bound to the catalyst once it is promoted to the reactive singlet or triplet state. A possible means to achieve this goal relies on the use of chiral Brønsted acids. If the acid catalyzes reversible formation of a species, which invites a selective excitation, the chiral counterion potentially controls the ensuing carbon−carbon bond forming process. The concept of chiral Brønsted acid catalysis is well established in thermal chemistry,[8] and there are also several elegant applications in photoredox catalysis.[5c,9] However, chiral Brønsted acids have so far not been successfully exploited to allow for an enantioselective intermolecular [2 + 2] photocycloaddition reaction.[10] We have now found that iminium ions, which are reversibly formed upon protonation of chiral *N,O*-acetals, serve as useful intermediates to promote an enantioselective reaction on the triplet hypersurface.

Previously, it was shown that thioacetals, such as compound **1**, are activated toward an intramolecular [2 + 2] photocycloaddition by protonation with strong acids (**3**, Tf = trifluoromethylsulfonyl) and by formation of thioniumions, such as **2** (Scheme 1).[10a] Unfortunately, the search for chiral acids that allow for a protonation of dithianes remained unsuccessful which is why other acetals were considered as potential precursors for a [2 + 2] photocycloaddition reaction. Pioneering work by Akiyama and co-workers on the Mannich reaction of aldimines derived from *ortho*-hydroxyaniline[11] inspired us to study *N,O*-acetals for this purpose. It was

Scheme 1. Previous Work on the Activation of Thioacetals by a Brønsted Acid and Current Study towards an Enantioselective [2 + 2] Photocycloaddition via Iminium Ions II (A*⁻: Chiral Anion)



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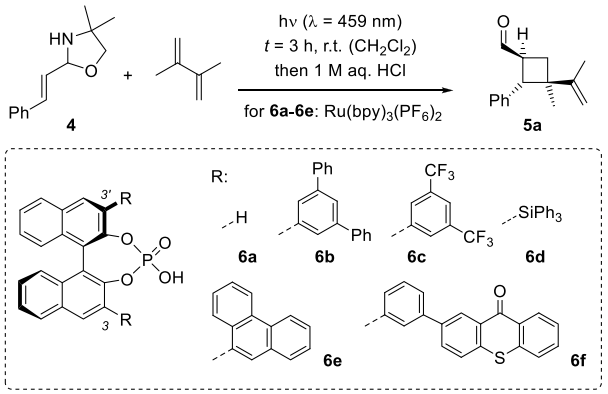
hypothesized that they deliver upon protonation a similar binding element as the aldimines. In addition, the propensity of iminium ions to undergo [2 + 2] photocycloaddition reactions via triplet energy transfer has been established recently.[12] Taken together, we considered *N,O*-acetals of the general structure **I** to be ideally suited to form iminium ions **II** which are activated toward energy transfer and display a suitable binding element to coordinate to a chiral counterion A^{*-}. The formation of the open-chain form **I′** was considered inconsequential because the triplet energy of imines[13] is higher than the triplet energy of the respective iminium ion (*vide infra*).

Preliminary work commenced with substrate **4**.[14] A dual catalysis approach was considered according to which the chiral acid would deliver the desired iminium ion pair and excitation would occur by energy transfer from a sensitizer. 2,3-Dimethylbutadiene was employed as the olefin component in the reaction. The intermediate product was hydrolyzed to deliver chiral cyclobutanecarbaldehyde **5a** displaying three contiguous stereogenic centers. Irradiation at λ = 459 nm was performed for a limited time period (3 h) to test the efficacy of the catalysts. Under these conditions, there was no background reaction in the absence of a catalyst. $Ru(bpy)_3(PF_6)_2$ (bpy = 2,2′-bipyridine) was used as the sensitizer (3 mol %) in combination with chiral phosphoric acids (20 mol %) **6a**–**6e** derived from (*R*)-1,1′-bi-2-naphthol (binol) (Scheme 2).

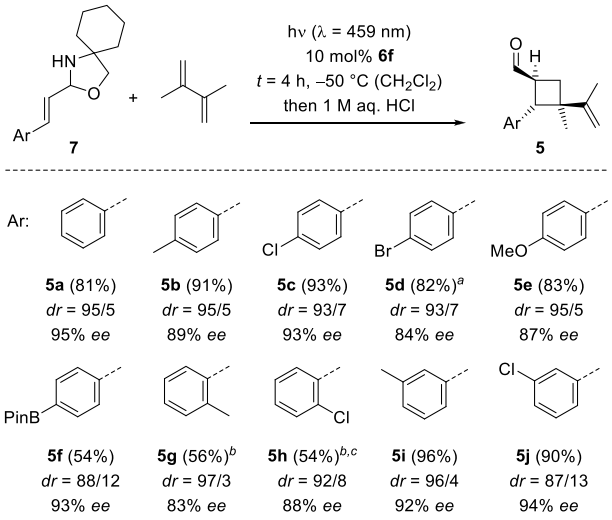
Scheme 2. Search for a Chiral Phosphoric Acid that Promotes the Enantioselective Intermolecular [2 + 2] Photocycloaddition of Substrate 4



Although a catalytic reaction was observed, the enantioselectivity did not exceed 34% *ee* (see the Supporting Information for details). A major breakthrough was achieved when phosphoric acid **6f** was employed as a *single* catalyst.

The acid displays two C_2-symmetrically positioned thioxanthone chromophores which capture long wavelength light (λ_{max} = 394 nm) and promote an energy transfer (triplet energy E_T = 235 kJ mol^{-1}, 77 K, CH_2Cl_2).[15,16] With this acid (10 mol %), the enantioselectivity of the [2 + 2] photocycloaddition rose to 66% *ee*. Further experiments addressed the role of the substituents in the 2-position of the used 2-aminoalcohol. A bridging cyclohexane unit was found to further improve the performance (52%, 70% *ee*). Gratifyingly, a decrease in the reaction temperature to −50 °C significantly improved the enantioselectivity. Under optimized conditions (Table 1), the *N,O*-acetal derived from cinnamic aldehyde and (1-aminocyclohexyl)methanol (**7a**, Ar = phenyl) produced in the presence of 10 mol % **6f** the desired cyclobutane **5a** in 81% yield and with 95% *ee*. A single diastereoisomer prevailed, and only traces of a second diastereoisomer were detectable (*dr* = diastereomeric ratio).

Table 1. Variation of the Aryl Group in the Catalytic Enantioselective [2 + 2] Photocycloaddition of *N,O*-Acetals Derived from Substituted Cinnamic Aldehydes



[a]Irradiation time *t* = 9 h. [b]Incomplete Conversion. [c]Irradiation time *t* = 16 h.

A variation of the *para*-substituent at the phenyl ring revealed that several useful functional groups were tolerated (products **5b**–**5f**). Of particular note is the boronate **5f** (pin = pinacolate) which opens several possibilities for further synthetic transformations[17] and which was generated in 93% *ee*. Yields and selectivities remained high without adaptation of the conditions except for the bromo-substituted product **5d** which required an extended irradiation time. A substituent in the *ortho*-position also retarded the reaction rate, and product yields were moderate (products **5g**, **5h**). The same substituents (methyl, chloro) in the *meta*-position, however, turned out to be fully compatible with the optimized conditions. Both products **5i** and **5j** were obtained in excellent yields and with high enantioselectivity. A limitation relates to substrates with acid sensitive hetaryl groups (2-furyl, 2-thiophenyl) which gave only low product yields. The absolute configuration of the products was assigned based on the known absolute configuration of compound **5a**.[12]

The acid catalyzed transformation allows to access cyclobutanecarbaldehydes by an enantioselective catalytic [2 + 2] photocycloaddition reaction, and its synthetic utility relies on the relative wide variety of olefin components which were successfully applied (Table 2). In all reactions of representative *N,O*-acetal **7a**, enantioselectivities exceeded 90% *ee*. Apart from styrenes (products **8b**, **8c**, **8g**), 1,3-enynes (products **8a** and **8f**) and 1,3-dienes (products **8d**, **8e**, **8h**, **8i**) underwent the [2 + 2] photocycloaddition cleanly and delivered 1,2,3-tristubstituted cyclobutanes with exquisite enantiocontrol. While the relative configuration between the phenyl group in 2-position and the formyl group at C1 is consistently *trans* in cyclobutanes **5** and **8**, the relative configuration between the stereogenic centers C2 and C3 is variable. NOESY experiments were employed to assign the relative configuration of the major and minor diastereoisomer.

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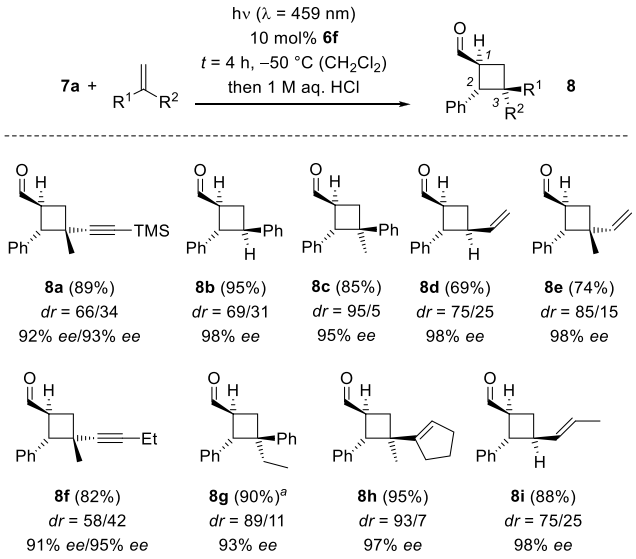
Table 2. Variation of the Olefin Component in the Intermolecular Enantioselective [2 + 2] Photocycloaddition of *N,O*-Acetal 7a



[a]Irradiation time t = 15 h.

NMR studies revealed that all *N,O*-acetals **7** existed as a mixture of the closed (**I**, Scheme 1) and the open (**I′**) form with a preference for the closed form (ca. 2/1). Upon protonation, the formation of the open protonated form **II** was indicated by a strong bathochromically shifted UV/vis absorption. However, the species is not competent[18] to undergo a [2 + 2] photocycloaddition upon irradiation at λ = 459 nm. Also in the presence of a chiral Brønsted acid, like compound **6e**, there was no reaction of substrate **7a** in the absence of a sensitizer.

In order to assess the triplet energy of the iminium ion, the imine of *para*-bromocinnamic aldehyde and (1-aminocyclohexyl)methyl methyl ether was prepared. Due to the heavy-atom effect[19] we hoped that a phosphorescence signal was detectable upon direct excitation under cryogenic conditions. Indeed, iminium ion **9** obtained from the imine by protonation with HBF_4 emitted a signal at 77 K (Figure 1) which differed

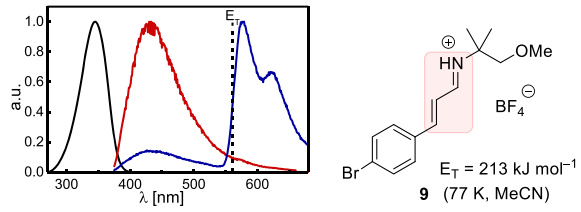


Figure 1. Absorption and luminescence spectra (λ_{exc} = 360 nm) of iminium ion **9** in MeCN. Colors: Absorption, black; fluorescence (rt), red; phosphorescence (77 K), blue. The energy of the (0,0) transition was calculated from the point of inflection at λ = 562 nm.

clearly from the respective fluorescence. From the emission in the short-wavelength regime, the triplet energy E_T was determined as 213 kJ mol^{-1}. The value is lower than E_T of compound **6f** (235 kJ mol^{-1}) enabling an exothermic energy transfer to the iminium ion. Interestingly, the imine from which the iminium ion **9** derived did not exhibit any phosphorescence despite the heavy atom present.

The enantioselectivity of the [2 + 2] photocycloaddition can be tentatively explained in analogy to a model proposed by Akiyama and co-workers for the addition to related prochiral iminium ions. They suggested a 1:1 complex **10** with the chiral phosphoric acid in which the aryl groups of the acid invite an attack from the *Re* face (Figure 2a).[11] If we assume a similar

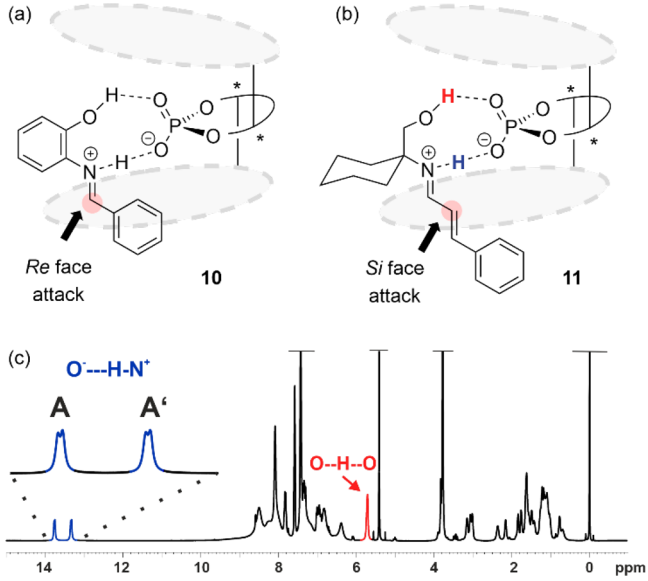


Figure 2. (a) Previously established model for the enantioselective addition to *N*-(*ortho*-hydroxyphenyl) substituted imines in their complex **10** with a chiral phosphoric acid (* = stereogenic center).[11] (b) Analogy-based model for the enantioface differentiation in complex **11** of phosphoric acid **6f** and the iminium ion derived from *N,O*-acetal **7a**. (c) ^{1}H NMR spectrum of a 1:1 mixture of **6c** and **7e** (1:1, 10 mM, CD_2Cl_2) at −93 °C and 600 MHz. Three different hydrogen bond signals with an integral ratio of ca. 1:1.1:2.1, corresponding to two conformational isomers of **11** were observed.

coordination of the iminium ions derived from compounds **7** and an extended s-*trans* conformation, the same enantioface differentiation should apply and it should account for an *Si* face attack in complex **11** (Figure 2b).

Extensive low temperature NMR studies on the complexes between acids **6c**, **6f** and substrates **7a**, **7b**, and **7e** validated the existence of a 1:1 complex as a hydrogen-bond assisted ion pair. For **6c**/**7e**, two distinct species **A** and **A′** were observed (see Figure 2c), differing in the conformation of the cyclohexane ring. For both species, the O$^-$---***H***-N$^+$ and O--***H***--O proton signals could be identified and unambiguously assigned as hydrogen bonded protons by the detection of *trans*-hydrogen bond scalar coupling via ^{1}H,^{15}N/^{31}P-HMBC and ^{1}H,^{1}H-COSY spectra.[20] Thus, the bidentate binding motif is clearly confirmed by the complete network of magnetization transfers. Moreover, the assigned ^{15}N, $^1H_\alpha$, and $^{13}C_\alpha$ chemical shifts of **A** and **A′** precisely match the expected values for a protonated iminium ion[21] and thus validate that the open protonated form **II** of the *N,O*-acetals is bound to the catalyst. Additionally, diffusion ordered spectroscopy (DOSY) NMR experiments confirmed that the observed species are monomeric and not higher aggregates. For complexes with catalyst **6f**, the identical O$^-$---**H**−N$^+$ hydrogen bond patterns were detected. In this case, additional hydrogen bonded species were observed, but the significant line broadening induced by rotational isomers of the catalyst and the flexibility

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of the substrate-backbone have so far prevented a further assignment. Decreasing the basicity of the substrate (**7e** > **7b** > **7a**) led to a downfield shift of the O---**H**−N^+ proton signal, which reflects an increasing hydrogen bond strength. In accordance with our previous results on the analysis of hydrogen bonding in chiral phosphoric acid/imine systems,[20] the observation confirms that the observed species are hydrogen-bond assisted ion pairs.

Phosphoric acid **6f** thus not only provides the required energy to promote the substrates to the triplet state but also guarantees the required enantioface differentiation. Remarkably, the enantioselective reactions display a higher degree of diastereoselectivity[22] than related reactions with achiral iminium ions which were used to prepare racemic cyclobutanes[12] for comparison. For example, the d.r. for the formation of product **8c** was 67/33 in the racemic case but 95/5 in the catalytic reaction. In the case of product **8e**, the relative configuration at C2/C3 was opposite (d.r. = 85/15) to the racemic series (d.r. = 30/70). It is therefore conceivable that the iminium ion remains bound to the phosphoric acid after initial C−C bond formation and that the acid influences the simple diastereoselectivity.

In summary, an enantioselective [2 + 2] photocycloaddition reaction has been accomplished which delivers cyclobutanecarbaldehydes **5** and **8** in high yields and with excellent *ee*. Key to the success of the reaction is the use of a chiral phosphoric acid **6f** that displays two C_2-symmetrically arranged thioxanthone substituents for energy transfer. The association of the iminium ion to the phosphoric acid warrants further studies to shed light on the enantioface differentiation and to elucidate its potential role in the second carbon−carbon forming step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c05240.

Experimental procedures, analytical data and NMR spectra for all new compounds, GLC and HPLC traces of all products, detailed NMR analysis of 1:1 catalyst−substrate complexes (PDF)

NMR data for compounds **4**, **5h**, **5j**, **7a**−**7j**, **8b**, **8g**, **8i**, **9**, **S1**−**S5**, **S9**, **S10**, **S12**, **S15**, **S17**−**S19** (ZIP)

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Author Contributions

#F.P. and Y.S. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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