Enantioselective [2+2] Photocycloaddition Reactions Mediated by a Sensitizing Chiral Phosphoric Acid

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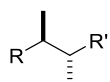
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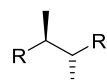
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In this thesis, the relative configuration of racemates is represented by straight lines (bold or hashed). The absolute configuration of enantiomerically pure or enriched compounds is represented by wedge-shaped lines (bold or hashed).

ABSTRACT

The [2+2] photocycloaddition reaction is the most important photochemical transformation to date as it facilitates the formation of cyclobutane cores – a motif found in natural products and pharmaceuticals – with up to four new stereogenic centers. In the last decade, many classes of catalysts have been developed to target enantiocontrol and access chiral cyclobutane derivatives. However, chiral phosphoric acid catalysts – while they have already demonstrated their high potential in ground state chemistry – have not been exploited in enantioselective [2+2] photocycloaddition reactions. In this thesis, the synthesis of a novel chiral phosphoric acid catalyst bearing two thioxanthone substituents in the *C*-3/*C*-3' position which promote energy transfer and simultaneously induce enantioface differentiation is reported. The catalyst was successfully employed in the intermolecular [2+2] photocycloaddition reaction of cyclic enone carboxylic acids with a variety of alkenes (6 examples, up to 56% yield, up to 85% *ee*). Furthermore, the catalyst's applicability could be extended to *N,O*-acetals derived from cinnamaldehyde. Upon protonation, cinnamoyl *N,O*-acetals formed the respective eniminium ions which underwent a triplet sensitized, enantioselective [2+2] photocycloaddition reaction to afford cyclobutane carbaldehydes in high yields and excellent enantioselectivities (19 examples, 54-96% yield, 84-98% *ee*).

KURZZUSAMMENFASSUNG

Die [2+2]-Photocycloaddition erweist sich bis heute als die wichtigste photochemische Reaktion, da sie unter anderem die Bildung von synthetisch wertvollen Cyclobutan-Fragmenten mit bis zu vier neuen Stereozentren ermöglicht. Im letzten Jahrzehnt wurden viele Katalysatoren zur gezielten Stereokontrolle entwickelt, um chirale Cyclobutan-Derivate zugänglich zu machen. Obwohl chirale Phosphorsäuren in einer Vielzahl von thermischen Transformationen bereits Anwendung fanden, wurde ihr Potential zur asymmetrischen Induktion in [2+2]-Photocycloadditionen bisher noch nicht ausgeschöpft. Zu diesem Zweck wurde in der vorliegenden Arbeit eine chirale Phosphorsäure mit zwei Thioxanthon-Substituenten in *C*-3/*C*-3' Position zur Photosensibilisierung und gleichzeitigen enantiofacialen Differenzierung synthetisiert. Dieser neuartige Katalysator wurde erfolgreich in der intermolekularen [2+2]-Photocycloaddition von cyclischen Enoncarbonsäuren mit einer Auswahl an Alkenen eingesetzt (6 Beispiele, bis zu 56% Ausbeute, bis zu 85% *ee*). Außerdem konnte der Anwendungsbereich des Katalysators auf *N,O*-Acetale von Zimtsäurealdehyden ausgeweitet werden. Nach Protonierung bildeten diese die entsprechenden Eniminium-Ionen, welche eine Triplett-sensibilisierte, enantioselektive [2+2]-Photocycloaddition zu Cyclobutancarbaldehyden mit hohen Ausbeuten und Enantiomerenüberschüssen eingingen (19 Beispiele, 54-96% Ausbeute, 84-98% *ee*).

LIST OF ABBREVIATIONS

Ac	acyl
Ar	aryl
BArF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINOL	1,1'-bi-2-naphthol
bpy	2,2'-bipyridine
cat.	catalyst
Cbz	benzyloxycarbonyl
CD	circular dichroism
conv.	conversion
CPA	chiral phosphoric acid
CPME	cyclopentyl methyl ether
Cy	cyclohexyl
DFT	density functional theory
DME	1,2-dimethoxyethane
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridyl
EnT	energy transfer
Et	ethyl
equiv.	equivalents
EWG	electron withdrawing group
HA	*Brønsted* acid
HAT	hydrogen atom transfer
HE	*Hantzsch* ester
*i*Pr	isopropyl
ISC	intersystem crossing
Me	methyl
NMR	nuclear magnetic resonance
PC	photocatalyst
PCET	proton-coupled electron transfer
Ph	phenyl
ppy	2-phenylpyridyl
*p*TsOH	*para* toluenesulfonic acid
rt	room temperature
S_1	first excited singlet state

SPINOL   1,1'-spirobiindane-7,7'-diol

TADDOL   α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol

TDS   thexyldimethylsilyl

Tf   trifluoromethanesulfonyl

VAPOL   2,2'-diphenyl-4-biphenanthrol

CONTENTS

1. INTRODUCTION

"Modern civilization is the daughter of coal [...]. Modern man uses it with increasing eagerness and thoughtless prodigality for the conquest of the world [...]. So far, human civilization has made use almost exclusively of fossil solar energy. Would it not be advantageous to make better use of radiant energy?" – Ciacomo Ciamician[1] (1912)

At the beginning of the last century, Italian chemist *Ciacomo Ciamician* already recognized the potential of light as a sustainable and abundant energy source as well as a powerful tool for the construction of complex molecular frameworks in organic synthesis.[2-3] In 1908, he and *Silber* discovered the first intramolecular [2+2] photocycloaddition reaction[4] when they observed the formation of carvone camphor (**1**) after exposing (+)-carvone to sunlight over the period of one year (Figure 1).[5]
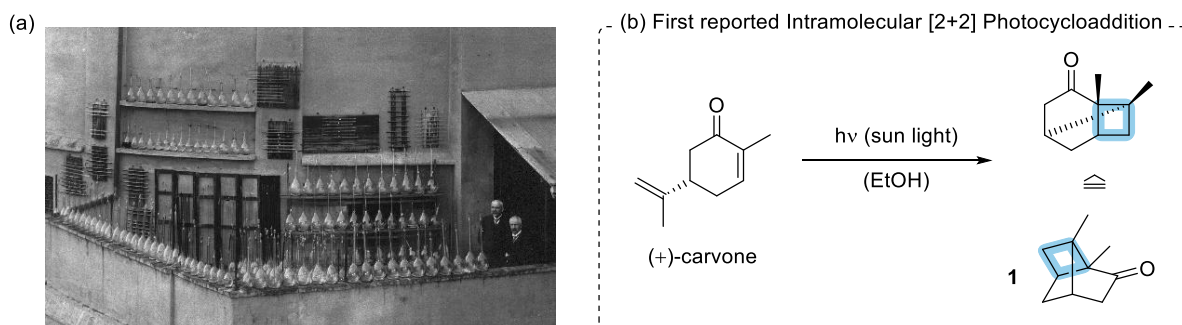
Figure 1. (a) *Ciamician* and *Silber* next to their photochemical experiments on the balcony of the Chemical Institute of the University of Bologna, Italy.[6] (b) Conversion of (+)-carvone to carvone camphor (**1**) representing the first reported intramolecular [2+2] photocycloaddition reaction of a cyclic enone.[5] Cyclobutane is marked in blue.

Confirmation of the constitution and configuration of **1** by *Büchi* and *Goldman*[7] in 1957 and the advancement in artificial light sources[8] and photochemical equipment[9-10] led to a resurgence of interest in the synthetic value of the [2+2] photocycloaddition reaction over the last decades. Notably, [2+2] photocycloaddition reactions enable the construction of valuable cyclobutane derivatives via the simultaneous formation of two new carbon-carbon bonds and up to four stereogenic centers.[11]

Chiral cyclobutanes are an interesting structural motif often found in bioactive natural products[12-14] such as (+)-grandisol[15] (**2**) and meroterpenoid **3**[16] (Figure 2a). Due to their conformational rigidity,[17-18] cyclobutanes are also privileged structural motifs in drug design. They can be found, for example, in the protease inhibitor Boceprevir[19] (**4**) that is used in the treatment of hepatitis C, or in dihydro-5*H*-naphthyridine **5**,[20] a clinical candidate for the treatment of autoimmune diseases (Figure 2b). In addition, cyclobutanes are prone to undergo facile ring expansion or cleavage reactions due to their inherent ring strain, thus enabling the

synthesis of a variety of structurally complex molecules (see Figure 2c for an example).[21-22] Therefore, the synthesis of chiral cyclobutane derivatives by [2+2] photocycloaddition is of great interest for the scientific community.
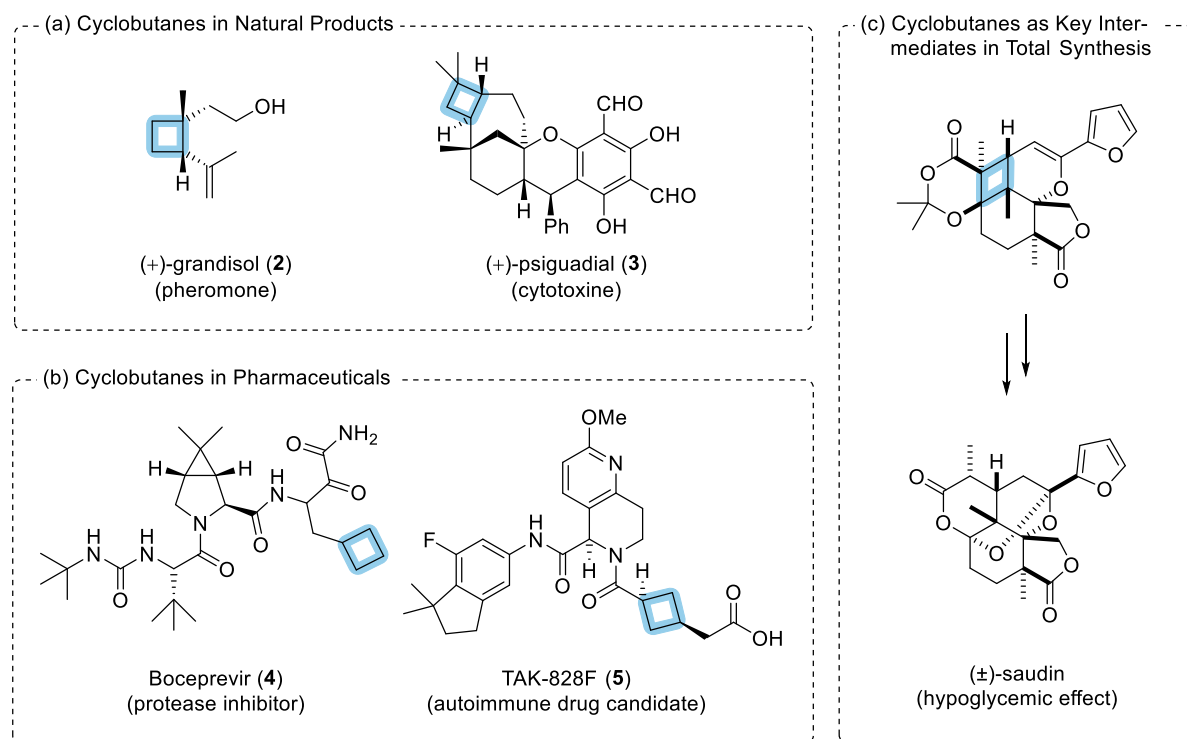
Figure 2. (a) Naturally occurring chiral cyclobutanes (+)-grandisol (**2**) and (+)-psiguadial (**3**). (b) Cyclobutane moieties in pharmaceuticals such as Boceprevir (**4**) and TAK-828F (**5**). (c) *De Mayo* ring expansion of a photochemically generated cyclobutane in the synthesis of (±)-saudin. Cyclobutane is marked in blue.

In the last two decades, asymmetric organocatalysis has become a powerful tool for the construction of such complex molecular skeletons and its importance has been emphasized by awarding the Nobel Prize in Chemistry 2021 to *Benjamin List*[23] and *David W. C. MacMillan*[24] "*for the development of asymmetric organocatalysis*". By now, organocatalysis has successfully merged with photocatalysis[25] and the synergy has proven quite fruitful in recent years.[26] In regard to asymmetric [2+2] photocycloaddition reactions, considerable accomplishments have been made with the rise of small organic molecule catalysts such as secondary amine **6**[27] and lactam **7** (Figure 3a).[28] However, the application of 1,1'-bi-2-naphthol (BINOL)[29-30]-derived chiral phosphoric acid[31-32] (CPA) catalysis, that has demonstrated its versatility in ground state organic synthesis and whose evolution has been particularly driven by *List* and coworkers,[33] has so far not been exploited to its full potential in photochemical transformations (Figure 3b).
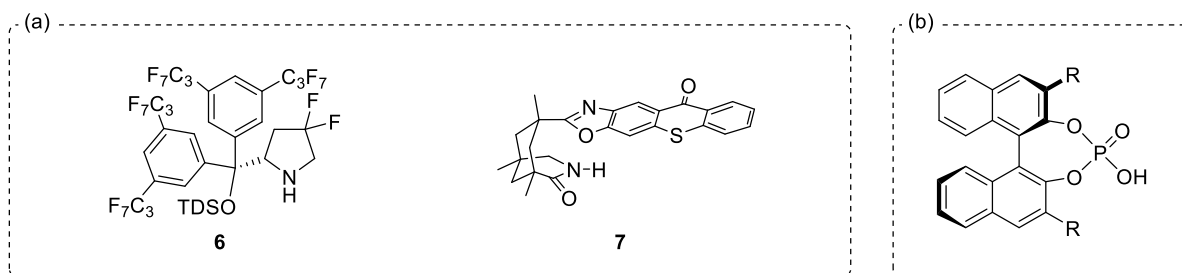
Figure 3. Established catalysts **6** and **7** (a) next to BINOL-derived chiral phosphoric acids (b) as potential catalysts for enantioselective [2+2] photocycloaddition reactions.

The scope of the presented work is to concisely discuss previous methods for asymmetric induction in [2+2] photocycloaddition reactions. It then serves to elaborate on recent advances in the application of chiral phosphoric acids for the construction of chiral cyclobutane cores and in other photochemical reactions. At the end, the development of a novel chiral phosphoric acid sensitizer and its application in the enantioselective [2+2] photocycloaddition of β-carboxyl-substituted cyclic enones and cinnamoyl *N,O*-acetals will be described.

2. ENANTIOSELECTIVE PHOTOCATALYSIS

Photocatalysis enables – based on changes in polarizability, bond strengths or spin multiplicity – complex synthetic transformations that are not accessible from the ground state.[34-35] Rendering a photocatalytic transformation enantioselective remains a challenging endeavor due to the short life-time, high reactivity and weak inter- and intramolecular interaction of photogenerated intermediates.[36]

In the following thesis, it will be distinguished between three approaches to achieve enantioselectivity in photochemical transformations (Figure 4):

(a) Firstly, exclusive use of a non-photoactive, chiral catalyst can lead to a substrate-catalyst complex causing a change in the photophysical properties, e.g. a bathochromic shift in absorption, of the substrate thus enabling its selective *direct excitation.*

(b) The second approach encompasses a *dual catalytic system* that merges an achiral photocatalyst with a chiral transition metal or organocatalyst. While the former is responsible for photoactivation of the substrate, the latter evokes asymmetric induction.

(c) The third approach comprises a *single catalyst* combining a photoactive moiety within a chiral scaffold. The substrate can be bound in close proximity to the photoactive moiety and thus be selectively excited within a chiral environment.
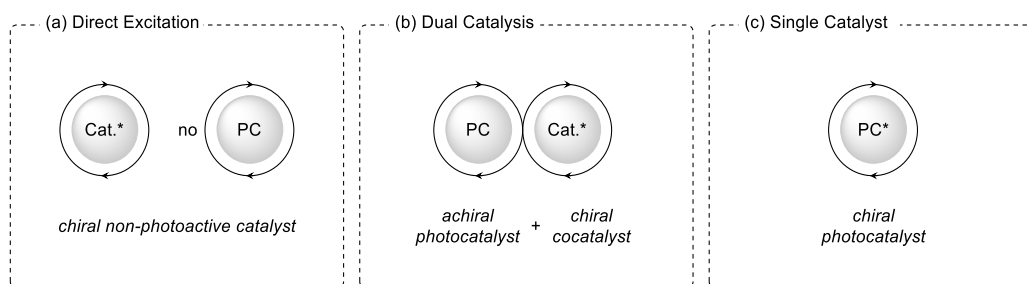
Figure 4. Different approaches to achieve asymmetric induction in photochemical transformations. PC = photocatalyst. cat. = catalyst. * = chiral.

Based on these three approaches, established photocatalytic systems for enantioselective [2+2] photocycloaddition reactions will be addressed in Chapter 2.1. Furthermore, recent advances in the application of chiral phosphoric acid catalysis in enantioselective [2+2] photocycloaddition reactions as well as other photochemical transformations will be discussed in Chapter 3.1 and 3.2, respectively.

2.1. Enantioselective Photocatalysis in [2+2] Photocycloaddition Reactions

By now, a variety of photocatalysts has been successfully employed in enantioselective [2+2] photocycloaddition reactions. While chiral *Lewis* acids[37-40] have found ample use in the synthesis of chiral cyclobutanes,[11] they will not be subject of discussion in this chapter. Instead, the focus will be on *Brønsted* acid and secondary amine organocatalysts as well as hydrogen-bonding catalysts.

2.1.1. Direct Excitation

Analogous to *Lewis* acids, *Brønsted* acids can influence the photophysical properties of a particular compound. In the 1960s, *Zalewski* and *Dunn* observed the absorbance of crotonaldehyde to be significantly red-shifted upon protonation with sulfuric acid ($\lambda_{max} = 230$ nm $\rightarrow$ 256 nm). An increase in the molar extinction coefficient for the protonated species was also detected ($\varepsilon = 15600$ M^{-1} cm^{-1} $\rightarrow$ 20400 M^{-1} cm^{-1}).[41-42] Subsequently, photochemical *E/Z* isomerizations[43-45] and rearrangements[46] of quantitatively protonated α,β-unsaturated carbonyl compounds were studied comprehensively by the group. Nevertheless, it took another 20 years to translate the concept of chromophore activation by *Brønsted* acids into an approach towards enantioselective catalysis.

In 2014, *Sibi, Sivaguru* and coworkers exploited the fact that coumarin can be activated upon binding to a *Brønsted* acid towards selective direct excitation. By employing the atropoisomeric thiourea catalyst **8** (10 mol%) the intramolecular [2+2] photocycloaddition of 4-alkenyl-substituted coumarin **9** by direct excitation ($\lambda = 350$ nm) proceeded enantioselectively (**9**→**10**, Figure 5).[27, 47]
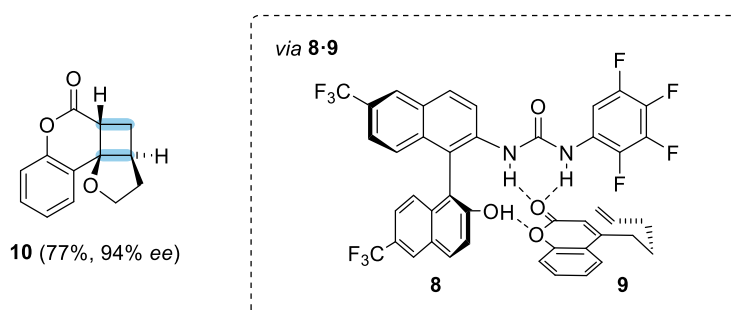

Figure 5. Chiral cyclobutane **10** synthesized via catalyst-substrate complex **8·9** in the intramolecular [2+2] photocycloaddition of **9**. Newly formed bonds are marked in blue.

The authors propose a three-point binding of coumarin **9** to chiral thiourea **8** (see **8·9** in Figure 5) ensuring enantioface differentiation. Binding of the substrate not only leads to a bathochromic shift but also to an increased intersystem crossing (ISC) rate and prolonged lifetime of the excited species.[48] Therefore, the bound substrate can be selectively excited and furnish cyclobutane **10** in high enantioselectivity (94% *ee*).

2.1.2. Dual Catalysis

In a dual catalytic approach, our group attempted to employ achiral thioxanthone[49] as triplet sensitizer in combination with chiral bisthiourea[50-51] **11** as cocatalyst in the enantioselective [2+2] photocycloaddition of 2,3-dihydropyridone-5-carboxylate **12** (**12→13**, Figure 6).[52] However, efforts towards a catalytic version failed and bisthiourea **11** (50 mol%) had to be employed as chiral template to achieve good enantioselectivity. The authors suggest a nonsymmetric[53] binding of the substrate (see **11·12** in Figure 6) in which the other thiourea moiety acts as a shield and invites a *Si* face attack of the olefin tether yielding tricyclic product **13** in good enantioselectivity (75% *ee*). Introducing a covalent linkage between thioxanthone and the chiral thiourea backbone led to a bifunctional catalyst that, however, did not show any promising enantioface differentiation in photochemical transformations.[54]
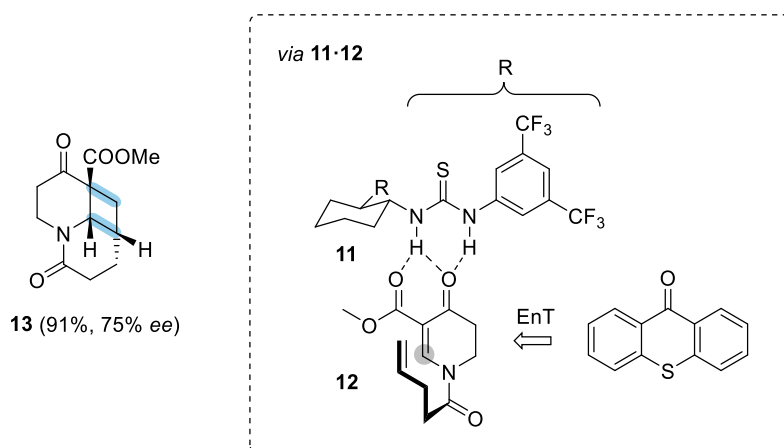
Figure 6. Chiral cyclobutane **13** synthesized via catalyst-substrate complex **11·12** in the intramolecular [2+2] photocycloaddition of **12** under triplet sensitization of thioxanthone. Newly formed bonds are marked in blue. EnT = energy transfer. Me = methyl.

Apart from noncovalent activation as seen in the previous examples, the reversible formation of iminium ions and enamines also offers the possibility to modulate the reactivity of carbonyl compounds. This concept has been especially exploited in ground state organocatalysis[55-57] by *List*[23] and *MacMillan*[24] for which they have been awarded the 2021 Nobel prize in chemistry. Since their initial publications, the research field has flourished tremendously, often referred to as the "asymmetric aminocatalysis gold rush".[58]

2.1. ENANTIOSELECTIVE [2+2] PHOTOCYCLOADDITIONS

In 2008, *MacMillan* and *Nicewicz* were the first to merge asymmetric enamine catalysis with photoredox catalysis, resulting in an efficient α-alkylation of aldehydes.[25] Pioneering work on the first excited singlet state (S_1) photochemistry of iminium ions,[59] however, commenced even earlier with studies by *Mariano* and coworkers at the beginning of the 1980s.[60-61] Regarding their photophysical properties, eniminium ions can be selectively excited because their ππ* absorption is bathochromically shifted compared to the respective α,β-unsaturated aldehydes.[62] Furthermore, they display a very high oxidation potential in the S_1 state.[63] Based on these properties, *Melchiorre* and coworkers have developed several enantioselective radical addition reactions with chiral proline-derived pyrrolidines as catalyst.[63-64]

The first [2+2] photocycloaddition reactions of eniminium ions were reported by *Mariano* and coworkers and proceeded on the singlet hypersurface.[65-66] Eniminium perchlorates derived from cyclic 3-alkenyl enones and pyrrolidine were shown to give tricyclic photoproducts upon direct irradiation (λ > 250 nm). The group was, moreover, able to render the transformation enantioselective by employing a C2-symmetric pyrrolidine as chiral auxiliary (**14→15**, Figure 7a).
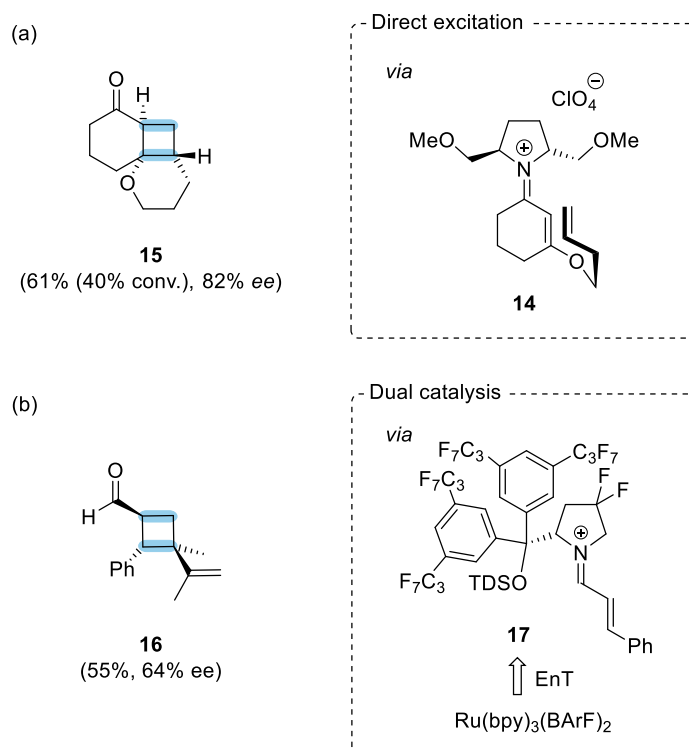
Figure 7. (a) Chiral cyclobutane **15** synthesized by direct excitation of stoichiometrically formed chiral iminium ion **14**. (b) Chiral cyclobutane **16** synthesized by energy transfer from Ru(bpy)3(BArF)2 to catalytically formed chiral iminium ion **17**. Newly formed bonds are marked in blue. conv. = conversion. TDS = hexyldimethylsilyl. Ph = phenyl.

Irradiation of chiral eniminium ion **14** (λ > 250 nm) led to photoproduct **15** in 61% yield (40% conversion) and 82% *ee* after hydrolysis.

In 2018, our group showed that the triplet energy of eniminium ions is lower than that of the respective α,β-unsaturated carbonyl compounds and that [2+2] photocycloaddition reactions can thus proceed by energy transfer from a suitable photosensitizer.[67] Although yields remained moderate, our group was indeed able to access cyclobutane carbaldehyde **16** employing catalytic amounts of chiral pyrrolidine **6** (20 mol%) that formed iminium ion **17** with cinnamaldehyde *in situ* (**17**→**16**, Figure 7b). Compound **17** was then prone to energy transfer by ruthenium catalyst Ru(bpy)₃(BArF)₂ (bpy = 2,2-bipyridine, BArF = tetrakis[3,5-bis(trifluoro-methyl)phenyl]borate).[68]

2.1.3. Single Catalyst

Using a single chiral photocatalyst that combines a photoactive moiety with a functional group for substrate binding is another attractive strategy for the asymmetric induction in [2+2] photocycloaddition reactions. In 2003, *Krische* and coworkers accessed cyclobutane **18** in low enantioselectivity employing chiral benzophenone **19** as catalyst (**20**→**18**, Figure 8).[69] It was shown that the pyridine moiety is essential for hydrogen bonding of lactam **20** and that the benzophenone moiety acts as a steric shield resulting in a preferred attack from the *Re* face of the substrate.

Figure 8. Cyclobutane **18** synthesized via catalyst-substrate complex **19·20** in an intramolecular [2+2] photocycloaddition. Newly formed bonds are marked in blue.

Simultaneously, our group developed a chiral sensitizer which incorporates the 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one skeleton[70] as a rigid chiral backbone and xanthone[71] as the photosensitizing unit.[72] Catalyst **21** (10 mol%) successfully furnished cyclobutane *ent*-**18** in high enantioselectivity (**20**→*ent*-**18**, Figure 9).[73] In recent years, our group, furthermore, synthesized catalyst **7** bearing a thioxanthone moiety which successfully expanded the application to visible-light mediated [2+2] photocycloaddition reactions.[28] Until now, catalysts **21** and **7** have been used in the enantioselective [2+2] photocycloaddition

reaction of a multitude of substrates[74-76] and in several other photochemical transformations[77-82] as well.[83]

Figure 9. Cyclobutane *ent*-**18** synthesized via catalyst-substrate complex **21·20** in an intramolecular [2+2] photocyclo-addition. Newly formed bonds are marked in blue.

In 2017, *Yoon* and coworkers reported the chiral-at-metal iridium complex **Λ-22** that functions both as a sensitizer and hydrogen bonding template in the enantioselective conversion of quinolone **23** (**23**→**24**, Figure 10).[84] Coordination of the substrate occurs through hydrogen bonding to the pyrazole moiety while the pyridyl group acts as a steric shield leading to enantioface differentiation. Substrate **23** was converted into cyclobutane **24** in high enantioselectivity (91% *ee*) under visible-light irradiation with a catalyst loading of only 1 mol%. The group later expanded the concept to the intermolecular [2+2] photocycloaddition of 3-alkoxyquinolones with maleimides.[85]
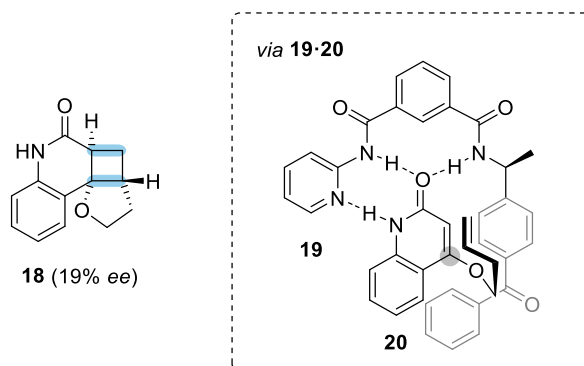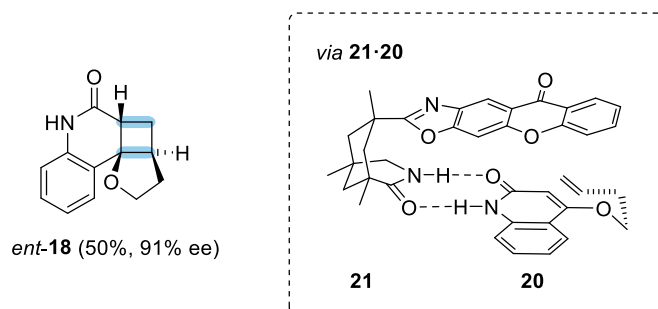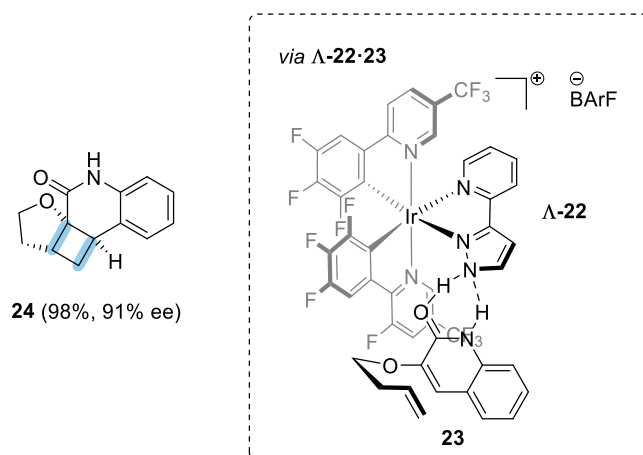

Figure 10. Cyclobutane **24** synthesized via catalyst-substrate complex **Λ-22·23** in an intramolecular [2+2] photocyclo-addition. Newly formed bonds are marked in blue.

3. Chiral Phosphoric Acids as Versatile Catalysts in Enantioselective Transformations

Since pioneering work by Akiyama[31] and Terada[32] in 2004, chiral phosphoric acids derived from axially chiral BINOL[29-30] have emerged as highly efficient and versatile catalysts for a plethora of synthetic transformations.[86-91]

Their catalytic potential can be accredited to the following properties (Figure 11): (a) They are easily accessible and stable towards oxidation and hydrolysis. (b) They exhibit a bifunctional character bearing both *Brønsted* acidic and *Lewis* basic site. (c) They display a rigid chiral backbone with restricted conformational flexibility. (d) Substituents in the *C*-3/*C*-3' position create a well-defined, tunable binding cavity within a chiral environment.
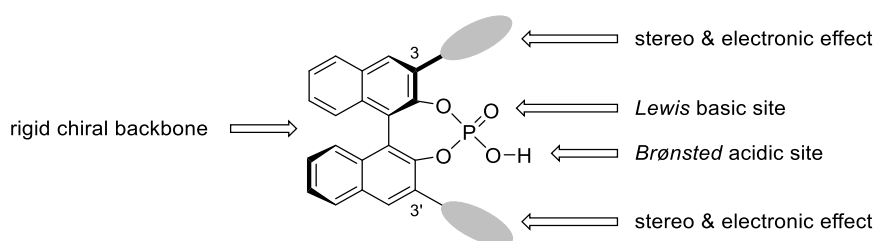
Figure 11. Schematic structure of BINOL-derived chiral phosphoric acid catalysts.

As of now, chiral phosphoric aicds have been successfully applied in a wide range of asymmetric reactions such as transfer hydrogenations,[92-93] reductive aminations,[94] *Mannich* type reactions[31-32, 95] or *Strecker* reactions.[96-98]

Alongside the disclosure of novel catalytic transformations, their immediate success also prompted the development of a repertoire of structurally diverse catalysts. As shown in Figure 12, the catalysts can differ in (a) substituents in *C*-3/*C*-3' position, (b) chiral backbone and (c) *Brønsted* acid moiety.

(a) Different substituents are easily introduced in *C*-3/*C*-3' position in order to tune steric bulk and electronics of the catalyst and thus increase the enantioface differentiation in a particular reaction (e.g. **CPA 1-3**).[99-102]

(b) Alternative chiral backbones derived from H8-BINOL,[103] VAPOL,[104-105] TADDOL[106-107] and SPINOL[108-109] were developed to modify geometrical parameters, e.g. dihedral angle, of the active site (e.g. **CPA 4-9**).

(c) Alternative functional groups such as *N*-triflyl phosphoramides,[110] disulfonimides[111-112] and bis(sulfuryl)imides[113] were introduced to increase the acidity[114-116] and activate particular substrates which were previously not accessible (e.g. **CPA 10**).
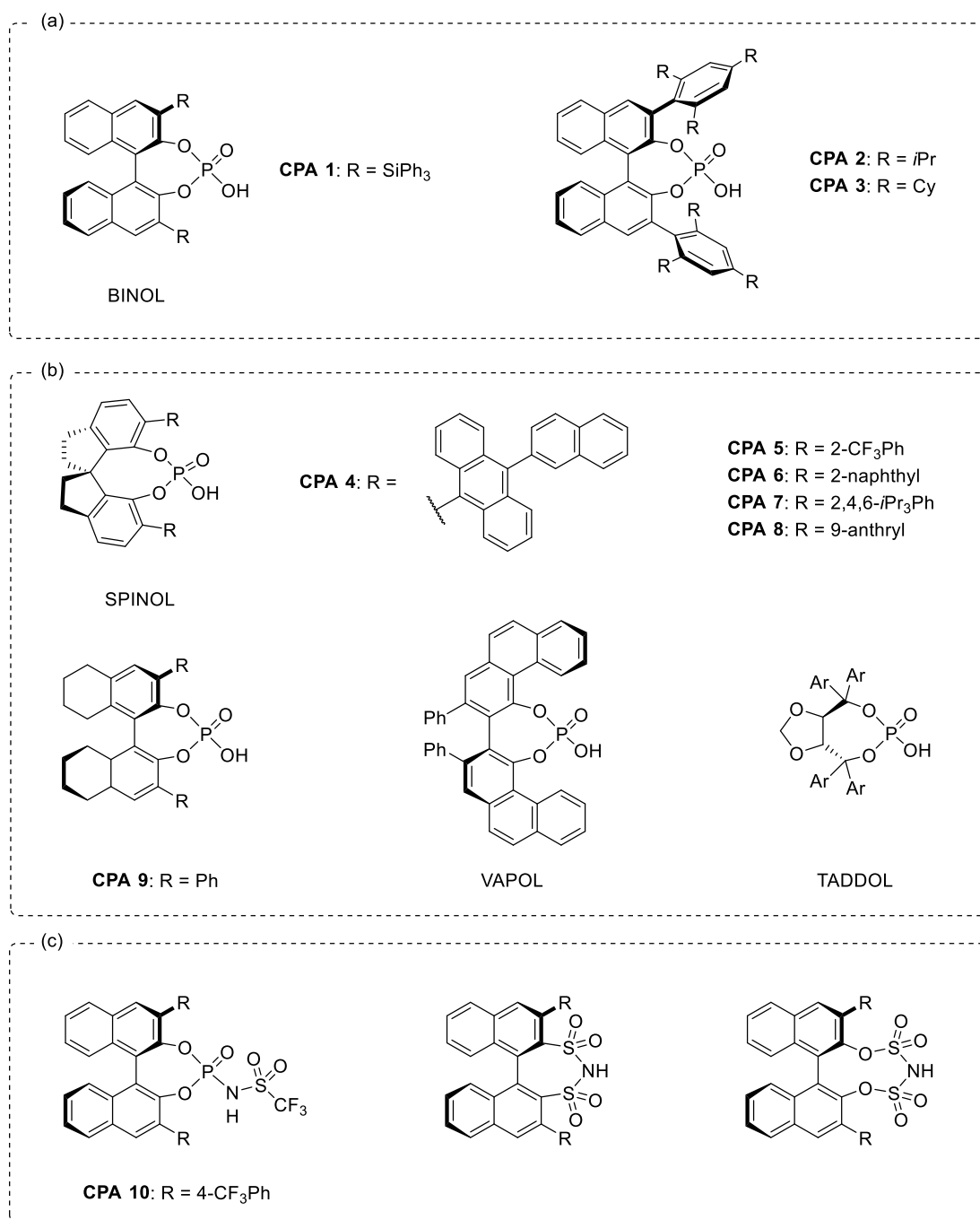
Figure 12. (a) Selection of BINOL-derived chiral phosphoric acid catalysts with different substituents in *C*-3/*C*-3' position. *i*Pr = isopropyl. Cy = cyclohexyl. (b) Selection of H8-BINOL, VAPOL, TADDOL and SPINOL-derived chiral phosphoric acid catalysts. VAPOL = 2,2'-diphenyl-4-biphenanthrol. SPINOL = 1,1'-spirobiindane-7,7'-diol. TADDOL = α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol. (c) Selection of BINOL-derived *N*-triflyl phosphoramide, disulfonimide and bis(sulfuryl)imide catalysts.

While chiral phosphoric acid catalysis is well established in thermal chemistry, its application in photocatalysis was limited at the beginning of this study and there were no reports on its successful application in enantioselective [2+2] photocycloaddition reactions.

3.1. Chiral Phosphoric Acids in [2+2] Photocycloaddition Reactions

In the following chapter, recent attempts towards the enantioselective cyclobutane formation by [2+2] photocycloaddition reactions employing chiral phosphoric acids as the key tool for asymmetric induction will be discussed.

3.1.1. Direct Excitation

As illustrated in Chapter 2.1, *Brønsted* acids can activate a particular chromophore analogous to *Lewis* acids[38] by reducing the singlet excited state energy. As the catalyst-bound substrate absorbs at a longer wavelength, it can be selectively excited by judicious choice of the irradiation wavelength.

In 2020, *Takagi* and *Tabuchi* used **CPA 9** in a direct excitation strategy for the intramolecular [2+2] photocycloaddition of quinolones **25**. While the reaction did not proceed with catalytic amounts of *Brønsted* acid, employing **CPA 9** as a stoichiometric template furnished cyclobutanes **26** in moderate to high enantioselectivities (up to 92% *ee*) (**25→26**, Scheme 1).[117]
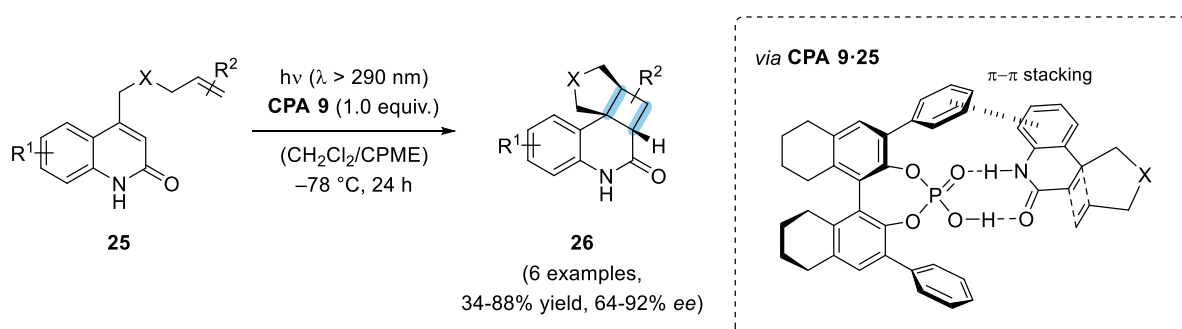
Scheme 1. Intramolecular [2+2] photocycloaddition of 4-alkenyl quinolones **25** with phosphoric acid **CPA 9** as chiral template. Newly formed bonds are marked in blue. CPME = cyclopentyl methyl ether.

Nnuclear magnetic resonance (NMR) studies suggested the formation of a 1:1 complex between substrate **25** and **CPA 9**, fixating the substrate in a chiral environment through bidentate hydrogen bonding of the lactam moiety (see **CPA 9·25** in Scheme 1). Furthermore, density functional theory (DFT) calculations indicated that π–π interactions between the phenyl ring on **CPA 9** and quinolone **25** significantly contributed to the enantioface differentiation leading to a bottom face attack of the olefin moiety. While **CPA 9** did not show any effect on the photophysical properties of **25** and thus could not be applied catalytically, the methodology, nevertheless, substantiates the potential of lactams as possible binding motif for chiral phosphoric acid catalysts.

In 2021, *Yoon* and coworkers demonstrated that **CPA 10** can activate *C*-cinnamoyl imidazole derivatives **27** towards direct excitation in the intermolecular [2+2] photocycloaddition with styrene derivatives (**27→28**, Scheme 2).[118] Upon combining colorless solutions of **CPA 10** and imidazole **27**, the mixture turned noticeably yellow and a bathochromic shift in absorption was overserved corroborating the hypothesis that the relative energy of the singlet excited state of the substrate is decreased upon protonation. In addition to altering the absorption properties of **27**, **CPA 10** then provided a stereodifferentiating environment for the enantioselective [2+2] photocycloaddition. The procedure tolerated a variety of electron rich and poor β-aryl substituents and products **28** were isolated with high yields and excellent enantioselectivities (up to 99% *ee*).
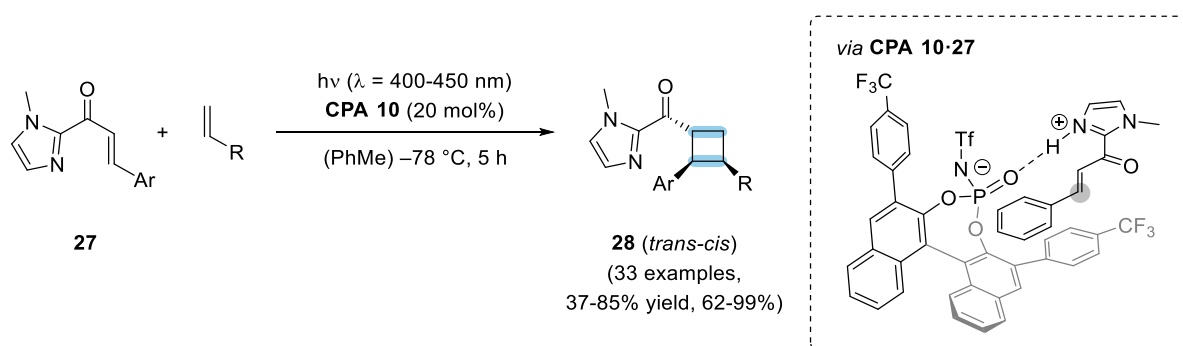
Scheme 2. Intermolecular [2+2] photocycloaddition of *C*-cinnamoyl imidazoles **27** via substrate-catalyst complex **CPA 10·27**. Newly formed bonds are marked in blue. Ar = aryl. Tf = trifluoromethanesulfonyl.

Interestingly, the reported methodology gives access to *trans-cis* fused chiral cyclobutanes while the racemic reaction favors formation of *trans-trans* diastereoisomers. This result indicates that the diastereoselectivity of the acid-catalyzed reaction is a product of catalyst control. Furthermore, *Yoon* and coworkers isolated the substrate-CPA complex and determined its structure by X-ray crystallography. The complex displayed a hydrogen bond between the protonated imidazolium ion and the phosphoramide oxygen of **CPA 10** (see **CPA 10·27** in Scheme 2). Moreover, the *Re* face of the bound substrate is open to an attack by styrene which is in accordance with the experimentally observed absolute configuration of cyclobutanes **28** and suggests that the crystal structure could be similar to the catalytically active complex in solution.

3.1.2. Dual Catalysis

As shown, *Brønsted* acids can activate a chromophore through a bathochromic shift in its absorption. In addition, *Leermakers* and coworkers showed that *Brønsted* acids can decrease the triplet energy and prolong the triplet lifetime of carbonyl compounds.[119] The triplet energy of benzophenone was observed to be significantly decreased in acidic media

(E_T = 277 kJ mol^{-1}) compared to non-polar solvents (E_T = 307 kJ mol^{-1}) with a concomitant 200-fold increase in its excited state lifetime (0.005 s → 1.03 s). Building up on these findings, *Yoon* and coworkers reported the racemic intermolecular [2+2] photocycloaddition of *C*-cinnamoyl imidazole **27** enabled by *Brønsted* acid catalyzed triplet energy transfer.[120] Formation of cyclobutane *rac*-**29** with styrene under visible light irradiation was only observed when both Ru(bpy)$_3$Cl$_2$ (2.5 mol%) as photosensitizer and *para* toluenesulfonic acid (*p*TsOH) as co-catalyst were employed. These findings underline the possibility to employ chiral phosphoric acids in order to deliberately decrease the triplet energy of a particular substrate, thus, making it prone to energy transfer from an external photosensitizer.

3.2. CHIRAL PHOSPHORIC ACIDS IN OTHER PHOTOCHEMICAL TRANSFORMATIONS

3.2.1. Dual Catalysis

Whereas investigations into the use of chiral phosphoric acids in [2+2] photocycloaddition chemistry remain scarce, their application in electron transfer catalysis has seen a significant growth in recent years.[26, 40, 121-123] In electron transfer catalysis, the formation of the reactive key intermediates proceeds through oxidation or reduction of the substrate by the excited state photocatalyst. After single electron transfer, the resulting radical species can be intercepted under the influence of the chiral phosphoric acid for subsequent enantioselective bond formations.

The first application of chiral phosphoric acids in enantioselective electron transfer catalysis was reported by *Knowles* and coworkers in 2013. They successfully employed catalyst **CPA 1** with [Ir(ppy)$_2$(dtbpy)]PF$_6$ (ppy = 2-phenylpyridyl, dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridyl) as photoredox catalyst in the asymmetric intramolecular *aza*-pinacol cyclization of hydrazones **29** (**29→30**, Scheme 3).[124] A proton-coupled electron transfer (PCET) process was proposed to form ketyl radical **31** which interacts with the chiral counterion of **CPA 1** thus enabling enantioface differentiation. Subsequent cyclization and hydrogen atom transfer (HAT) from *Hantzsch* ester (HE) furnishes cyclic products **30** in good yields and excellent enantioselectivities (up to 95% *ee*).
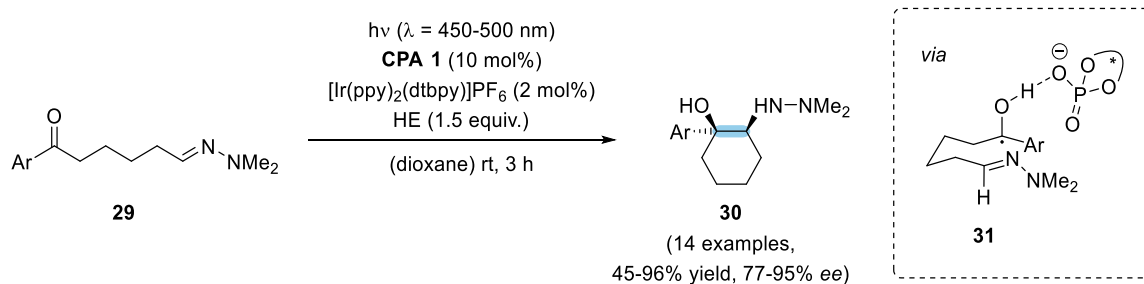
Scheme 3. Intramolecular *aza*-pinacol cyclization of hydrazones **29** by *Knowles* and coworkers. Newly formed bonds are marked in blue.

Following the years after this initial report by *Knowles* and coworkers, noteworthy attempts[125-126] at successfully combining chiral phosphoric acid and electron transfer catalysis have been made, ultimately culminating in a significant contribution by *Phipps* and coworkers in 2018. They accomplished the enantioselective *Minisci*-type addition of α-amino alkyl radicals to pyridines and quinolines employing a dual catalytic system of photocatalyst [Ir(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ and chiral phosphoric acids **CPA 2** or **CPA 3** (Scheme 4).[127] The iridium catalyst initiates radical generation by electron transfer assisted decarboxylation

of redox active phthalimide esters **32**, while **CPA 2** or **CPA 3** facilitates radical addition via hydrogen bond interaction between protonated azaarenes **33** and the generated α-amino alkyl radicals. As shown by *Phipps* and *Goodman* the reaction follows the *Curtin-Hammett* principle. Consequently, the enantiodetermining step is, in fact, not the radical addition, which is fast and reversible, but rather the irreversible deprotonation of radical cation **34**.[128] Based on DFT calculations and experimental studies, they propose a deprotonation mechanism in which the carbonyl oxygen atom of the *N*-acetyl group – which in turn is activated by the chiral phosphoric acid – acts as an internal base. Deprotonation by an external quinoline molecule, dissociation from the chiral phosphoric acid catalyst and single-electron oxidation results in formation of products **35**.
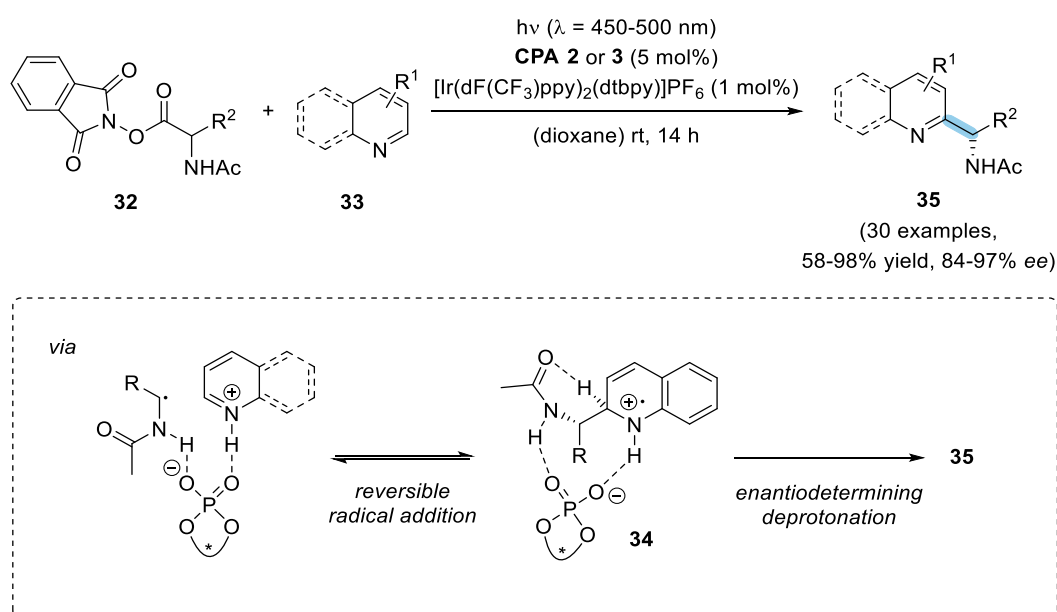
Scheme 4. *Minisci*-type addition of α-amino alkyl radicals to pyridines and quinolines catalyzed by chiral phosphoric acid **CPA 2** or **CPA 3**. Newly formed bonds are marked in blue. Ac = acyl.

Soon after *Phipps'* initial report, *Jiang*'s group reported a closely related study on the enantioselective *Minisci*-type addition of redox active ester **36** to isoquinolines **37** employing the dicyanopyrazine-derived chromophore (DPZ) photosensitizer **38** in combination with chiral SPINOL-derived phosphoric acid **CPA 4** (**36**→**39**, Scheme 5a).[129] *Zheng* and *Studer* later expanded this protocol for the synthesis of valuable chiral γ-amino-acid derivatives **40** by an enantioselective three-component radical cascade reaction of quinolines or pyridines with enamides and α-bromo carbonyl compounds (**33**→**40**, Scheme 5b).[130]
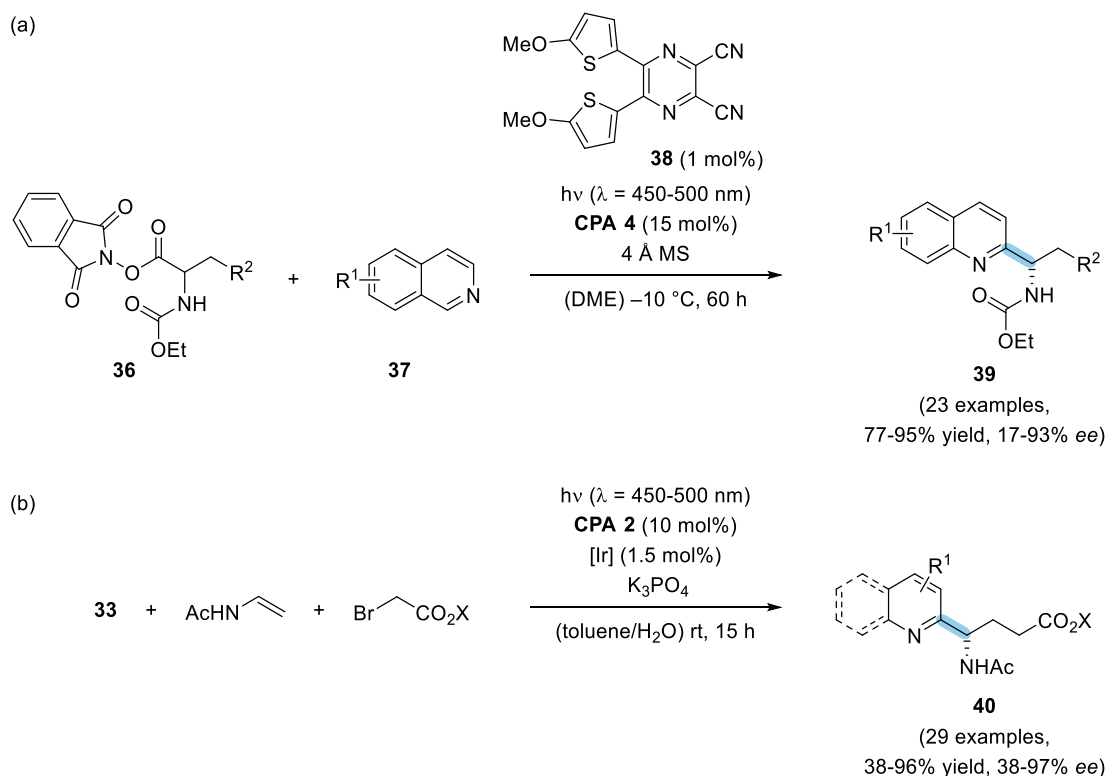
Scheme 5. (a) Enantioselective *Minisci*-type addition by *Jiang* and coworkers. (b) Enantioselective three-component radical cascade reaction by *Zheng* and *Studer*. Newly formed bonds are marked in blue. Et = ethyl. DME = 1,2-dimethoxyethane. [Ir] = [Ir(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$.

In 2018, *Jiang* and coworkers disclosed the conjugate addition/enantioselective protonation of *N*-aryl glycines **41** to α-branched 2-vinylazaarenes **42** using **38** together with SPINOL-derived chiral phosphoric acids **CPA 5** or **CPA 6** (**41**→**43**, Scheme 6a).[131] In 2019, they also adopted the catalytic protocol for the formation of γ-substituted pyridines **44** by addition of prochiral ketone and imine derivatives **45** to vinylpyridines **46** (**45**→**44**, Scheme 6b).[132]

Ever since, *Jiang* and coworkers continued to explore the potential of chiral phosphoric acids in electron transfer catalysis. They successfully applied the catalytic system of DPZ and chiral phosphoric acids to radical cross coupling reactions of α-bromoketones,[133] 3-chlorooxindoles[134] and 1,2-diketones,[135] *Povarov* reactions,[136] a cascade aerobic oxidation/semipinacol rearrangement[137] and reductions of azaarene-based ketones.[138-139]
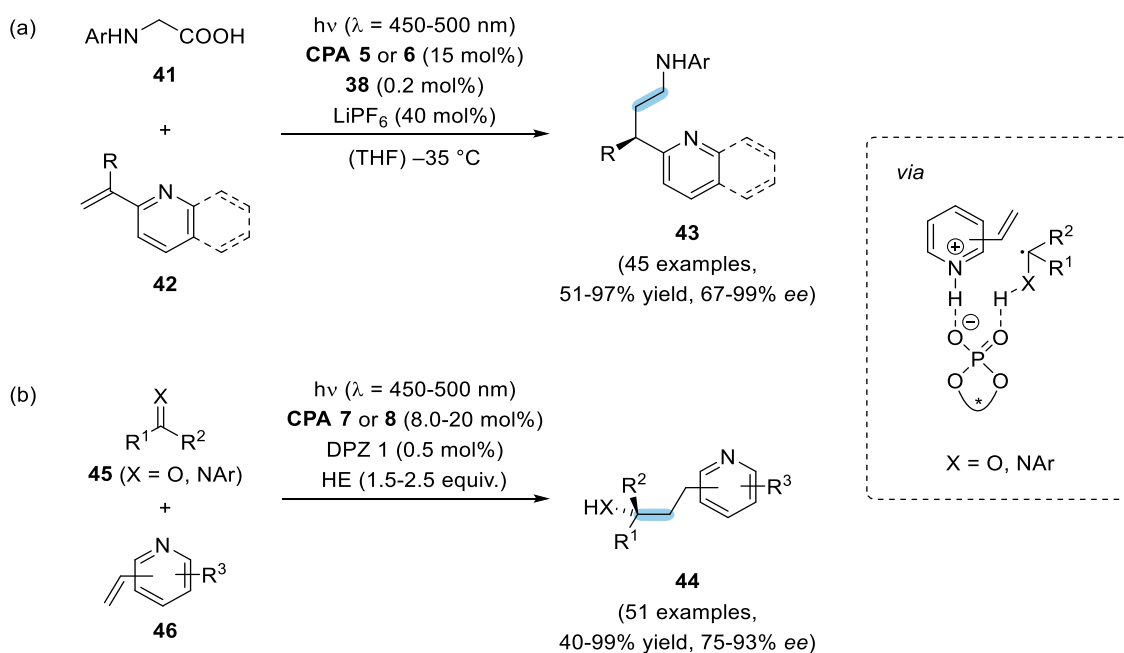
Scheme 6. Conjugate addition/enantioselective protonation of *N*-aryl glycines **41** (a) and ketone/imine derivatives **45** (b) to vinylazaarenes by *Jiang* and coworkers. Newly formed bonds are marked in blue.

3.2.2. Single Catalyst

As outlined in Chapter 2.1, *dual catalysis* that combines chiral phosphoric acid and electron transfer catalysis has found ample use in enantioselective transformations in recent years.[40, 123] However, there has been no precedent for a *single* catalyst that encompasses both a chiral phosphoric acid and a photoactive moiety. After our initial report on a chiral phosphoric acid sensitizer in 2020,[140] *Masson* and coworkers also reported the preparation and photophysical evaluation of BINOL-derived chiral phosphoric acids **47a-47c** that incorporate one or two thioxanthone[49] moieties (Figure 13).[141]
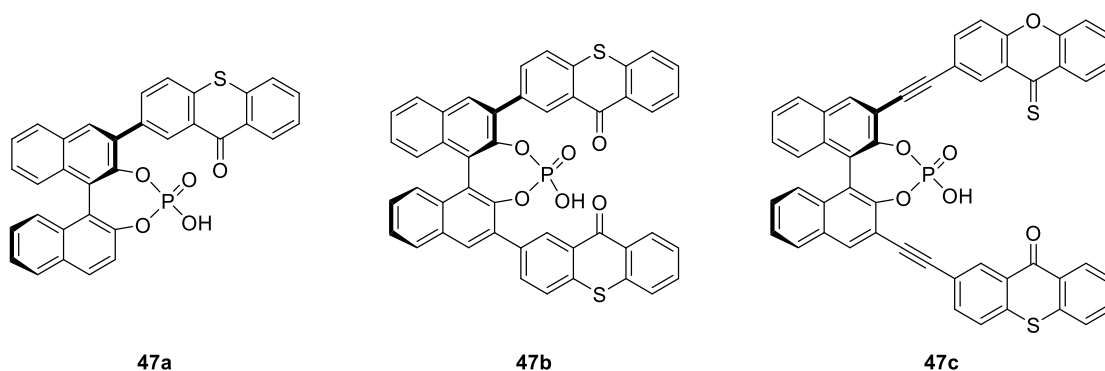
Figure 13: BINOL-derived chiral phosphoric acid catalysts with thioxanthone attached to the chiral backbone.

C_1-symmetric catalyst **47a** was found to effectively catalyze the one-pot electrophilic amination of enecarbamates **48** with diazenes **49** followed by the photoinduced nucleophilic

addition of various azoles (**48**→**50**, Scheme 7). C$_2$-symmetric catalyst **47b** gave similar results, albeit lower yields, and catalyst **47c** was found to be inactive in the transformation giving only trace amounts of racemic product **50**.

Mechanistically, the tandem process gave access to substituted 1,2-diamines **50** via oxidation of thermally generated α-carbamoylsulfide **51** to a sulfur radical cation and subsequent mesolytic cleavage to imine **52**. The latter was then attacked by azole to give products **50** in high yields and enantioselectivities (up to 99% *ee*). The authors were not able to discriminate between an oxidation mechanism based on excited state chiral thioxanthone **47a** and a pathway involving singlet oxygen that could be generated by sensitization of natural triplet oxygen by the triplet excited state of **47a**. Notably, both stereodetermining steps in this reaction are thermal, while the only photochemical step generates the reactive imine intermediate.
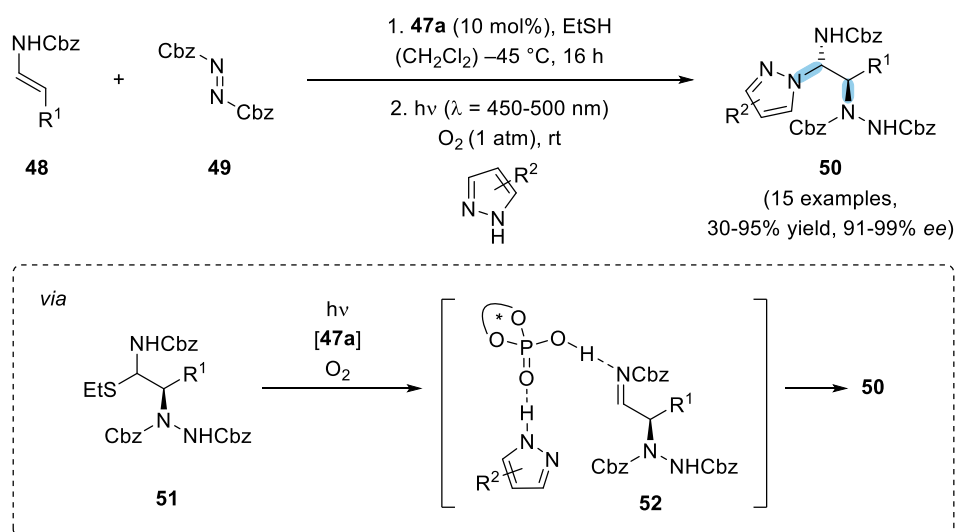
Scheme 7. Enantioselective three component amination/photoinduced addition catalyzed by bifunctional chiral phosphoric acid thioxanthone **47a**. Newly formed bonds are marked in blue. Cbz = benzyloxycarbonyl.

4. PROJECT AIM

Given the impressive versatility and performance of chiral phosphoric acids in ground state transformations[86-91] as well as the success of bifunctional chiral photocatalysts[54, 142-143] such as **7** in photochemical transformations (see Chapter 2.1), we conceptualized a novel BINOL-derived chiral phosphoric acid photocatalyst of the general structure **53** (Scheme 8). We envisioned that photoactive substituents in *C*-3/*C*-3' position could promote energy transfer while simultaneously inducing enantioface differentiation towards a substrate bound by the phosphoric acid moiety. The synthesis of a bifunctional catalyst of type **53** was to be realized starting from commercially available (*R*)-BINOL by lithiation-borylation at the *C*-3/*C*-3' position and subsequent *Suzuki* cross-coupling with the photoactive coupling partner.[144] Finally, deprotection followed by phosphorylation[145] would yield the desired bifunctional catalysts.
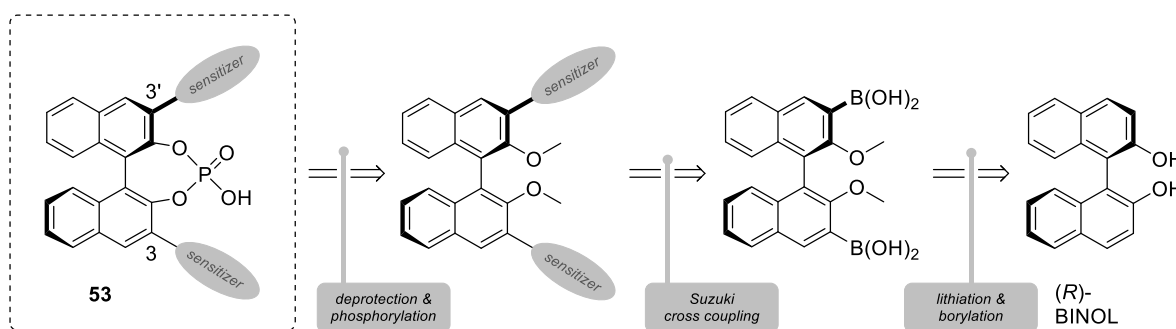
Scheme 8. General structure **53** of a chiral phosphoric acid sensitizer and retrosynthetic analysis thereof.

Due to its C_2 symmetry,[146] we envisaged catalysts of type **53** to conveniently invite the coordination of substrates with a symmetric binding motif. *List* and coworkers had already established that carboxylic acid derivatives can be activated with chiral phosphoric acids in ground state transformations.[147-148] NMR studies showed that a heterodimeric complex of carboxylic acid derivatives with chiral phosphoric acid catalysts is formed, thus activating them by HOMO raising[149] towards the electrophilic attack of aziridines and epoxides. Hence, carboxylic acid derivatives seemed to be suitable substrates for the exploration of the synthetic potential of catalysts **53** in excited state transformations (Scheme 9a). Moreover, previous studies by *Piva* and coworkers demonstrated that enone carboxylic acid **54** underwent an intermolecular [2+2] photocycloaddition reaction with cyclic alkenes such as cyclopentene upon UV irradiation (λ = 366 nm) (**54**→**55**, Scheme 9b).[150] Enone **54** was, therefore, chosen as the model substrate as we anticipated that the application of chiral phosphoric acid photocatalysts would render the transformation enantioselective.
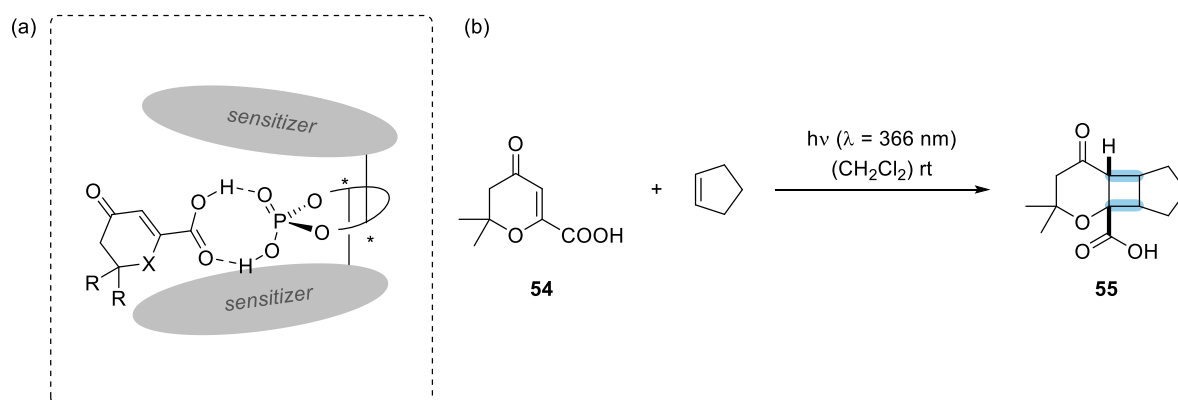
Scheme 9. (a) Proposed two-point binding of carboxylic acid derivatives to a chiral phosphoric acid sensitizer. (b) Intermolecular [2+2] photocycloaddition of enone carboxylic acids with cyclic alkenes by *Piva* and coworkers. Newly formed bonds are marked in blue. * = stereogenic center.

Seeking to further explore the potential of catalysts **53**, we were inspired by previous research on the activation of *O,O*-acetals[151] **56** and *S,S*-acetals[152-153] **57** by protonation towards a bathochromic shift in absorption (Scheme 10a). Protonation of thioacetals **57** with strong acids allowed their intramolecular [2+2] photocycloaddition upon irradiation with visible light (λ_{max} = 405 nm).[152]
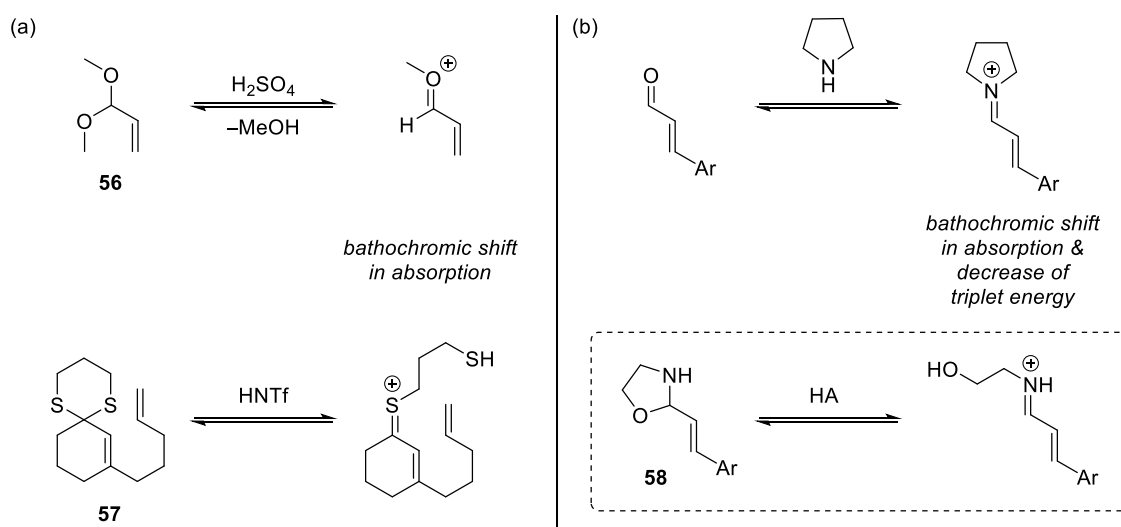
Scheme 10. (a) Formation of onium and thionium ions in presence of *Brønsted* acid. (b) Formation of iminium ions with pyrrolidine and from *N,O*-acetals with *Brønsted* acid (HA).

As already discussed in Chapter 2.1, an alternative way to modulate the reactivity of carbonyl compounds is their transformation into iminium ions as they exhibit a bathochromic shift of the $\pi\pi^*$ absorption and a decrease of the triplet energy compared to the respective aldehyde and imines (Scheme 10b).[154-155] We, therefore, envisioned *N,O*-acetals **58** derived from cinnamaldehyde to be an alternative substrate class for catalyst **53** as they form iminium ions upon protonation that could be activated towards energy transfer.[7] Furthermore, they display

two coordination sites, namely the nitrogen atom and hydroxyl group, for the coordination to a chiral phosphoric acid such as **53** (Figure 14a).

A similar binding motif was reported in 2004 by *Akiyama* and coworkers when they disclosed the first application of BINOL-derived chiral phosphoric acids. They employed *N*-(*ortho*-hydroxyphenyl) substituted imines in the *Mannich* reaction with silyl ketene acetals and proposed a bidentate binding of the imine substrates by the chiral phosphoric acid catalyst (Figure 14b). Along these lines, we hypothesized that chiral phosphoric acid catalyst **52** would protonate *N,O*-acetals and bind the concurrent iminium ions sufficiently strong as to allow for an enantioselective [2+2] photocycloaddition.
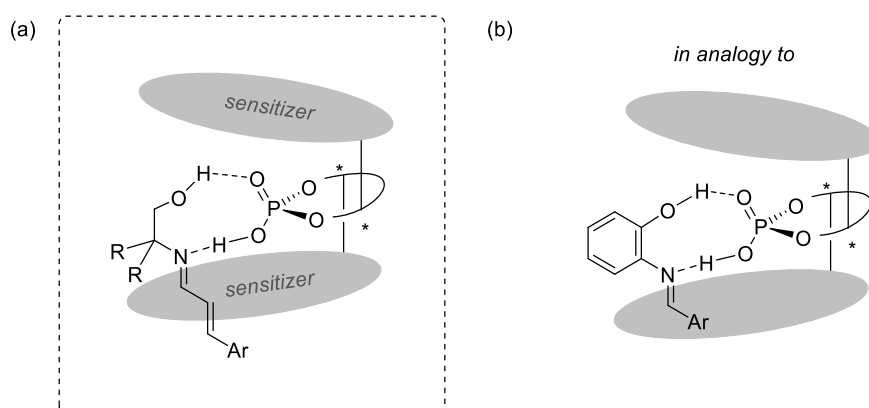
Figure 14. (a) Proposed two-point binding of cinnamoyl *N,O*-acetals to a chiral phosphoric acid sensitizer. (b) Previously established analogous model for the enantioselective addition to *N*-(*ortho*-hydroxyphenyl) substituted imines with a chiral phosphoric acid. * = stereogenic center.

In short, we aimed to synthesize a chiral phosphoric acid sensitizer, analyze its photophysical properties and evaluate its performance in the enantioselective intermolecular [2+2] photocycloaddition of cyclic enone carboxylic acids as well as *N,O*-acetals derived from cinnamaldehyde derivatives.

5. A Thioxanthone Sensitizer with a Chiral Phosphoric Acid Binding Site: Properties and Applications in Visible Light-Mediated Cycloadditions

Content: Chiral bifunctional catalysts bearing a photoactive thioxanthone moiety have proven their worth in multiple enantioselective photochemical transformations. However, chiral phosphoric acid catalysts have so far not been explored as a potential chiral scaffold and binding motif in this context. In the presented work, a novel BINOL-derived chiral phosphoric acid catalyst with two thioxanthone moieties at the *C*-3/*C*-3' position was synthesized and its performance in enantioselective intermolecular [2+2] photocycloaddition reactions of β-carboxyl substituted cyclic enones was examined. A variety of olefins was tested and enantioselectivities of up to 85% *ee* were achieved. Based on the triplet energy determination of the catalyst (E_T = 235 ± 2 kJ mol^{-1}) and enone carboxylic acid (E_T = 288 ± 2 kJ mol^{-1}) we suggest that the triplet energy of the substrate is lowered upon association to the catalyst, thus making energy transfer feasible. Low-temperature NMR studies validated the two-point hydrogen bonding between catalyst and substrate and the potential structure of the 1:1 complex was obtained by DFT calculations.

The conceptual contribution was made by T. Bach. Y.-Q. Zou planned and executed the syntheses of chiral phosphoric acid sensitizers and conducted preliminary irradiation experiments. F. Pecho planned, performed, and analyzed the racemic and catalyzed [2+2] photocycloaddition reactions of enone carboxylic acid derivatives. F. Pecho performed and analyzed photophysical measurements and determined the absolute configuration of the major enantiomer. A. Bauer conducted phosphorescence measurements. T. Mori calculated the circular dichroism (CD) spectrum of the major enantiomer. DFT calculations on the catalyst–substrate complex were carried out by S. M. Huber. J. Gramüller analyzed the catalyst–substrate complex by low-temperature NMR studies. F. Pecho, J. Gramüller and T. Bach wrote the manuscript.

║ Asymmetric Catalysis

A Thioxanthone Sensitizer with a Chiral Phosphoric Acid Binding Site: Properties and Applications in Visible Light-Mediated Cycloadditions

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Abstract: A chiral phosphoric acid with a 2,2′-binaphthol core was prepared that displays two thioxanthone moieties at the 3,3′-position as light-harvesting antennas. Despite its relatively low triplet energy, the phosphoric acid was found to be an efficient catalyst for the enantioselective intermolecular [2+2] photocycloaddition of β-carboxyl-substituted cyclic enones (e.r. up to 93:7). Binding of the carboxylic acid to the sensitizer is suggested by NMR studies and by DFT calculations to occur by means of two hydrogen bonds. The binding event not only enables an enantioface differentiation but also modulates the triplet energy of the substrates.

Recent interest in visible light-mediated reactions has triggered a large number of studies towards the synthesis of new chromophores and chiral catalysts.[1] The long known thioxanthone chromophore[2] has been revisited in the context of triplet sensitization[3] and it has been attached to chiral scaffolds for applications in enantioselective photochemistry.[4] The most frequently used chiral modification is represented by compound **1** (Figure 1)[4a] in which a thioxanthone is attached via an oxazole to position C7 of 1,5,7-trimethyl-3-azabicyclo[3.3.1]-nonan-2-one. The latter device serves as a hydrogen bonding site[5] and allows to process lactams in [2+2] photocycloaddition[4a, 6] and deracemization[7] reactions. By attachment to a chiral bisoxazoline, thioxanthone can be part of a bifunctional chiral metal catalyst and ligand **2** has been successfully employed in the Ni-catalyzed oxygenation of β-ketoesters.[4b] Chiral imidazolinone-based organocatalysts have recently been reported for enamine catalysis in which the thioxanthone acts via single electron transfer.[4d] However, not any binding motif known from thermal reactions will automatically lead to a successful chiral catalyst. Thiourea-linked thioxanthones such as **3**, for example, did not display the expected enantioselectivity in photochemical reactions.[4c]

Nonetheless, given the limited number of substrates that can yet be processed by chiral thioxanthones, it seems desirable to further investigate possible binding motifs to which a thioxanthone entity can be attached. In this communication, we describe the synthesis of a C_2-symmetric chiral phosphoric acid with two thioxanthone units and report on preliminary studies as to its mode of action in photochemical [2+2] cycloaddition reactions.

Since their initial use in organocatalysis,[8] chiral phosphoric acids have emerged as a highly efficient class of compounds for a plethora of applications.[9] Most phosphoric acids display aryl groups in positions C3 and C3′ of the 2,2′-binaphthol core and we envisaged that these positions would serve as suitable points of attachment for a thioxanthone unit. However, the direct linkage of a 9-oxo-9*H*-thioxanthen-3-yl group to posi-

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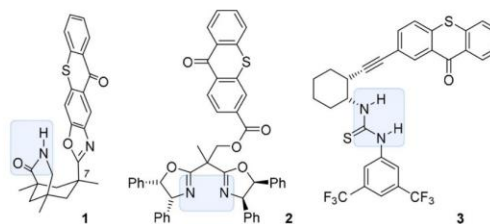
Figure 1. Structure of chiral thioxanthones **1**–**3** with a substrate or metal binding site (in gray).

tions C3 and C3′ led to a phosphoric acid which did not induce any enantioselectivity in photochemical test reactions (see Supporting Information for further details). Upon further screening, a more promising catalyst **4** (Scheme 1) was discovered which was prepared by Suzuki cross-coupling of aryl bromide **7** and known diboronic acid **8**.[10] The former component was obtained by a dehydrogenative condensation[11] of 3-bromobiphenyl (**5**) and thiosalicylic acid (**6**). After demethylation
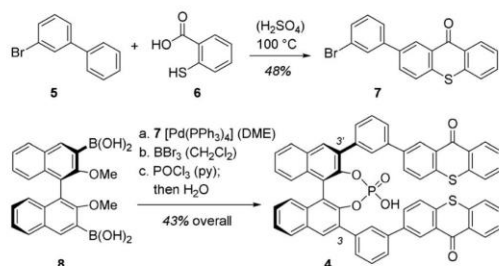
Scheme 1. Synthesis of phosphoric acid **4** from boronic acid **8** and aryl bromide **7**. Conditions and yields for the individual steps a–c: (a) 2.5 equiv **7**, 10 mol% Pd(PPh₃)₄, 10 equiv 2 M Na₂CO₃ (aq), 85 °C, 16 h (DME), 96%; (b) 6.0 equiv BBr₃, 0 °C→rt, 2 h (CH₂Cl₂), 83%; (c) 2.0 equiv POCl₃, 95 °C, 12 h (py), then H₂O, 95 °C, 54%.

and phosphorylation the free acid was liberated by treatment with water. A major asset of phosphoric acid **4** as compared to thioxanthones **1** and **3** is its C_2 symmetry which invites the coordination of substrates with a symmetric binding motif. In this context, carboxylic acids RCOOH seemed particularly interesting to us because studies by List and co-workers had established that they can be activated in thermal reactions by coordination to chiral phosphoric acids.[12]

Preliminary experiments commenced with 3,4-dihydro-2,2-dimethyl-4-oxo-2H-pyran-6-carboxylic acid (**9**, Scheme 2) which had been previously employed in intermolecular [2+2] photocycloaddition reactions upon UV irradiation ($\lambda = 366$ nm).[13] To our delight, we found that the previously reported reaction with cyclopentene to racemic products *rac*-**10** could be con-

ducted with visible light in the presence of parent thioxanthone (thioxanthen-9-one, see Supporting Information for further details). With catalytic quantities of acid **4**, the reaction proceeded at $\lambda = 437$ nm with improved chemoselectivity (vide infra) and the desired product was isolated as a mixture of two diastereoisomers with the *cis-anti-cis* diastereoisomer **10a** prevailing over the *cis-syn-cis* diastereoisomer (d.r. = 69/31).
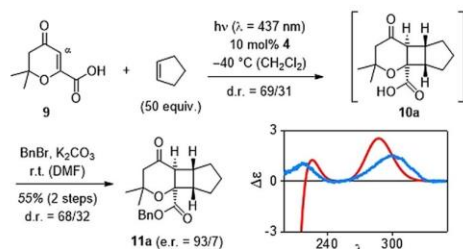
Although isolation of products **10** was possible (61% yield), the enantiomeric ratio (e.r.) could not be determined by chiral HPLC analysis. Derivatization to the UV active benzyl ester was feasible and esters **11** were formed in 55% yield over two steps. Benzyl ester **11a** displayed a remarkable e.r. of 93/7 which suggests a high enantioface differentiation in the [2+2] photocycloaddition to product **10a**. The absolute configuration of the major enantiomer was determined by comparison of the measured and calculated CD spectra of compound **10a**. Formally, the absolute configuration corresponds to a *Si* face approach onto the α-carbon atom in the α,β-unsaturated carbonyl compound **9**.

Cyclohex-2-enone-3-carboxylic acid (**12**) had been previously involved in an enantioselective [2+2] photocycloaddition[14,15] employing a chiral amine as chiral template. Enantioselectivities of up to 24% *ee* (e.r. = 62/38) had been achieved employing five equivalents of the template ($\lambda > 320$ nm). Products had not been isolated and the enantioselectivity had been determined by GLC upon derivatization. In our case, it was possible to perform the reaction with visible light ($\lambda = 437$ nm) employing only 10 mol% of catalyst **4** but the separation of the polar regioisomeric products **13** and **14** was not feasible. The benzylation turned out to be sluggish and yields of products **15** and **16** were low (Scheme 3).

Scheme 3. Catalyzed enantioselective [2+2] photocycloaddition of 2-cyclohexenone-3-carboxylic acid (**12**) and 2-ethylbutene and subsequent benzylation; inset: structure of the decarboxylation product **17** obtained from intermediate **13**.

Like for product **11a** a significant enantioface differentation was recorded with the higher e.r. (89/11) being found for the minor regioisomer **16**. The absolute configuration of chiral product **13** was assessed by decarboxylation[16] to known cyclobutane **17**.[17] The direction of attack at the α-carbon atom of enone **12** is identical to the direction of attack for compound **9** (*Si* face). The assignment of the absolute configuration for all other major enantiomers in the [2+2] photocy-
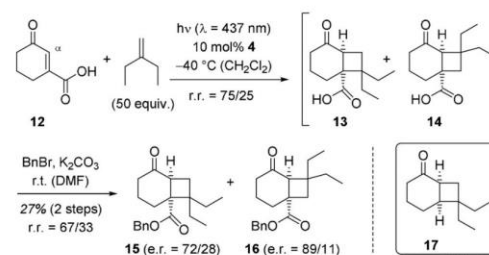

Scheme 2. [2+2] Photocycloaddition of cyclopentene to acid **9** catalyzed by thioxanthone **4** and subsequent benzylation; schematic CD spectrum (calculated in red, vs. measured in blue) of acid **10** (for full details, see Supporting Information).

cloaddition of **9** and **12** was based on analogy. Indeed, it was established that other olefins also react successfully under sensitized conditions in the presence of chiral phosphoric acid **4**. After benzylation, products **18–21** were isolated with high to moderate enantioselectivities (Figure 2). However, the yield for
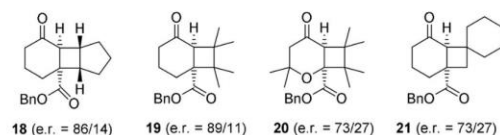

Figure 2. Structure and enantiomeric ratio of [2+2] photocycloaddition products **18–21** obtained from acids **9** and **12** via energy transfer from chiral phosphoric acid **4**.

the two-step protocol remained relatively low, presumably due to the non-optimized benzylation protocol (26–42%, see Supporting Information for further details).

A notable feature of thioxanthone **4** as compared to the parent compound (thioxanthen-9-one) was the fact that undesired decarboxylation reactions were suppressed and that the photocycloaddition reaction was more efficient (see Supporting Information for further details). Luminescence measurements in dichloromethane (Figure 3) revealed that the triplet
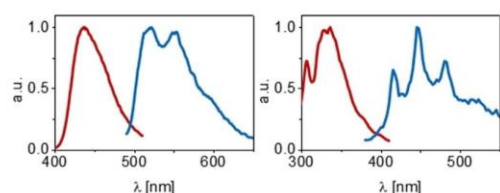

Figure 3. Fluorescence (red) and phosphorescence (blue) spectra recorded at r.t. (fluorescence) and 77 K (phosphorescence) for catalyst **4** (left) in a dichloromethane matrix and for acid **9** (right) in a pentane/isopentane matrix (for futher details, see the Supporting Information).

energy (E_T) of compound **4** is surprisingly low. From the phosphorescence emission (77 K, dichloromethane) at the long wavelength shoulder the energy was calculated as $E_T = 235 \pm 2$ kJ mol^{-1} which is much lower than the reported triplet energy of thioxanthen-9-one ($E_T = 272$ kJ mol^{-1}).[18] Luminescence spectra of the two carboxylic acids showed the typical signature of α,β-unsaturated enones[19] with a readily detectable 0-0 transition. The triplet energy calculated from this transition was $E_T = 288 \pm 2$ kJ mol^{-1} for compound **9** and $E_T = 287 \pm 2$ kJ mol^{-1} for compound **12** (77 K, pentane/isopentane).

Combined with the results obtained from the thioxanthen-9-one irradiation experiments, the data suggest a preferred energy transfer within a complex between the carboxylic acids and compound **4** while thioxanthen-9-one leads to partial oxidation of the acid. Given the high energy difference of the triplet energies in a non-complexed situation it is also likely that

the phosphoric acid lowers the triplet energy of the carboxylic acids upon association. Although it is known that coordination of Lewis acids to carbonyl groups alters the triplet state energy[1, 20] we are not aware of this phenomenon having been observed for phosphoric acid/carboxylic acid combinations.

At the reaction temperature (−40°C) binding of carboxylic acid **9** to phosphoric acid **4** was proven by NMR studies in CD$_2$Cl$_2$. The identification of two NOE contacts between **4** and **9** as well as Diffusion Ordered Spectroscopy (DOSY) experiments validated **4·9** complex formation, the latter showing a significant increase (≈ 1.7 Å) of the hydrodynamic radius of carboxylic acid **9** in the presence of catalyst **4** (see Supporting Information for details and spectra).[12a] Significant line broadening and a slight highfield shifting (≈ 0.1 ppm) of the signals of **9** in the presence of **4** demonstrate a fast exchange on the NMR timescale between complex **4·9** and the separated molecules **4** and **9** at this temperature (see Supporting Information for spectra).

Next, NMR measurements between −40°C and −93°C were applied to gain information about the hydrogen bond situation in this system. Indeed, specific signals of hydrogen bonds could be detected, which is to our knowledge the first time for complexes between chiral phosphoric acids and carboxylic acids. The hydrogen bond region[21] of **4** showed various minor populated signals summarized as H^X (blue region in Figure 4) and two distinct signals H^2 and H^3 (green region). The temperature coefficients of H^2 and H^3 are very small (−0.9 ppb K^{-1}) indicating that these protons are effectively sequestered from solvent interactions. This is typical for molecules featuring strong internal H-bonds or stable complexes with internal H-bonds, for example, dimers (or higher aggregates) of **4**.[22] The minimum temperature coefficient of the signals labelled H^X is significantly higher (−9.6 ppb K^{-1}) than that for H^2 and H^3, but still by far smaller than the one of carboxylic acid **9** (−38.6 ppb K^{-1}). This indicates a partial sequestration of the H^X protons from the solvent, which would be rational for different rotational isomers of monomeric **4**. Indeed, signals H^X of the
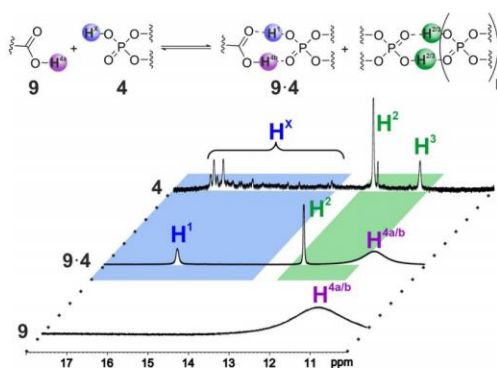

Figure 4. Hydrogen bond region of the ^{1}H-NMR spectra of **4**, **9** and an equimolar solution of **4** and **9** at 600 MHz and −40°C in CD$_2$Cl$_2$, showing the presence of different species of the catalyst.

catalyst collapse to one signal H[1] in the presence of **9**, while signals H[2] and H[3] are unaffected.[23] The respective ^{31}P NMR spectra show a similar behaviour (see the Supporting Information) and thus support the assignment of H[X] and H[1] as monomeric, and H[2] and H[3] as dimeric (or oligomeric) catalyst species. The averaged proton signal H[1] indicates very low rotation barriers of and within the 3,3'-substituent in the **4·9** complex, which is in accordance with the theoretical calculations (vide infra). In contrast, in the absence of **9** the various proton signals H[X] indicate higher rotation barriers in monomeric **4** despite reduced absolute steric hindrance. The combination of a medium temperature coefficient, higher rotation barriers and significant spreading of the chemical shifts of H[X] protons over ≈3 ppm hints at various internal hydrogen bonds of the phosphoric acid to the aromatic moieties of the 3,3'-substituent (see the Supporting Information for further discussion), which stabilize different rotational isomers of the free catalyst. To the best of our knowledge, this feature has not yet been observed for chiral phosphoric acids and is potentially useful as a concept for pre-organization.

Preliminary DFT calculations revealed a relatively shallow energy hypersurface for the 1:1 complex of catalyst **4** with carboxylic acid **12**. There are several local minima detected upon rotation around the indicated bonds (for more details, see the Supporting Information). Due to the free rotation around the thioxanthone-phenyl bond (Figure 5, left) the C_2 symmetry of the catalyst is lost in most rotamers which complicates the analysis. The energetically lowest diastereomeric conformation is according to the calculation 3.5 kJ mol^{-1} more stable than the shown conformation (Figure 5, right). While the former conformation does not account for the correct product configuration, the latter arrangement illustrates the observed preferential approach of the olefin from the *Si* face of the α-carbon atom. The extent of the enantioface differentiation depends on the exact trajectory of the olefin and on the position of initial attack.
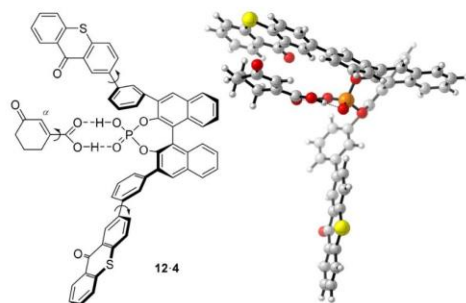

Figure 5. Models for the complex of cyclohex-2-enone-3-carboxylic acid (**12**) with chiral phosphoric acid **4**: Rotatable single bonds influencing the reactive conformation (left), optimized structure of a 1:1 complex in which the *Si* face at the α-carbon atom of acid **12** is accessible (right). DFT calculations were performed using the M06-2X functional[24] with the def2-TZVP[25] basis set for all atoms employing Gaussian09[26] with D3 dispersion[27] and low-frequency entropy[28] corrections by Grimme.

In conclusion, the first member of a new class of bifunctional photocatalysts has been synthesized and screened in [2+2] photocycloaddition reactions. The catalyst appears to lower the triplet energy of the substrates by hydrogen bonding and enables a notable enantioface differentiation. Different catalyst species (monomeric rotational isomers and higher aggregates) were observed by NMR, but only the monomeric catalyst participates in the complexation to the substrate, while higher aggregates are not affected by the substrate. The formation of a catalyst substrate complex was proven by NMR studies and a potential structure of the 1:1 complex was revealed by DFT calculations. A better understanding of the binding mode and of the interaction between the sensitizing unit and the substrate is expected to facilitate the design of modified catalysts.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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

Content: Iminium ions – an attractive binding motif for chiral phosphoric acids in ground state chemistry – can be activated towards energy transfer in [2+2] photocycloaddition reactions. In the presented work, a photoactive chiral phosphoric acid catalyst was employed in the enantioselective [2+2] photocycloaddition of *N,O*-acetals derived from cinnamaldehydes and (1-aminocyclohexyl)methanol. A high degree of variation in the substitution pattern of the aryl moiety and the olefins was allowed and chiral cyclobutane carbaldehydes were synthesized with excellent yields and enantioselectivities (19 examples, 54-96% yield, 84-98% *ee*). Triplet energy determination proved that energy transfer between catalyst ($E_T = 235 \pm 2$ kJ mol^{-1}) and substrate ($E_T \approx 213 \pm 2$ kJ mol^{-1}) is feasible and low-temperature NMR studies validated the bidentate binding of the substrate to the chiral phosphoric acid catalyst in a hydrogen bond-assisted ion pair.

The conceptual contribution was made by Y. Sempere and T. Bach. Y. Sempere conducted screening experiments of the dual catalytic system of commercially available chiral phosphoric acids and photocatalysts. F. Pecho, Y. Sempere and F. Hörmann synthesized and analyzed *N,O*-acetals from the respective cinnamaldehydes. F. Hörmann optimized the reaction conditions. F. Pecho planned, performed, and analyzed the racemic and catalyzed [2+2] photocycloaddition reactions of cinnamoyl *N,O*-acetals. F. Pecho performed and analyzed photophysical measurements and prepared a suitable iminium ion for the triplet energy determination. J. Gramüller analyzed the catalyst–substrate complex by low-temperature NMR studies. F. Pecho, J. Gramüller and T. Bach wrote the manuscript.

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Communication

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

Franziska Pecho,[#] Yeshua Sempere,[#] Johannes Gramüller, Fabian M. Hörmann, Ruth M. Gschwind, and Thorsten Bach*

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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 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] photo-

cycloaddition by protonation with strong acids (3, Tf = trifluoromethylsulfonyl) and by formation of thioniumions, such as 2 (Scheme 1).[10a] Unfortunately, the search for chiral

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)
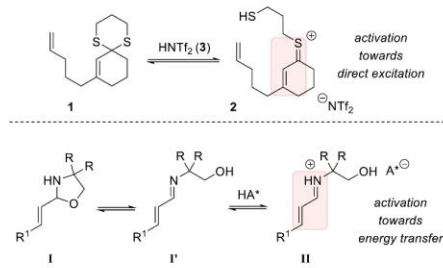
acids that allow for a protonation of dithianes remained unsuccessful which is why other acetals were considered as potential precursors for a [2 + 2] photocycloaddition reaction. Pioneering work by Akiyama and co-workers on the Mannich reaction of aldimines derived from ortho-hydroxyaniline[11] inspired us to study N,O-acetals for this purpose. It was

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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(PF₆)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
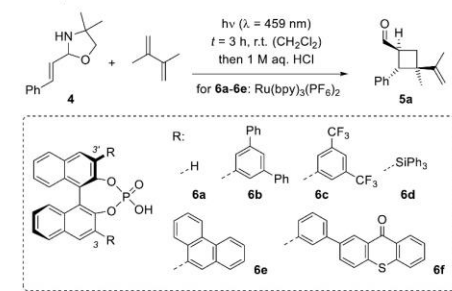
Although a catalytic reaction was observed, the enantioselectivity did not exceed 34% ee (see the Supporting Information for details). A major breakthrough was achieved when phosphoric acid 6f was employed as a single catalyst.

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, CH₂Cl₂).[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%

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

5a (81%)	5b (91%)	5c (93%)	5d (82%)[a]	5e (83%)
dr = 95/5	dr = 95/5	dr = 93/7	dr = 93/7	dr = 95/5
95% ee	89% ee	93% ee	84% ee	87% ee

5f (54%)	5g (56%)[b]	5h (54%)[b,c]	5i (96%)	5j (90%)
dr = 88/12	dr = 97/3	dr = 92/8	dr = 96/4	dr = 87/13
93% ee	83% ee	88% ee	92% ee	94% ee

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

yield and with 95% ee. A single diastereoisomer prevailed, and only traces of a second diastereoisomer were detectable (dr = diastereomeric ratio).

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.

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

8a (89%)	**8b** (95%)	**8c** (85%)	**8d** (69%)	**8e** (74%)
dr = 66/34	dr = 69/31	dr = 95/5	dr = 75/25	dr = 85/15
92% ee/93% ee	98% ee	95% ee	98% ee	98% ee

8f (82%)	**8g** (90%)[a]	**8h** (95%)	**8i** (88%)
dr = 58/42	dr = 89/11	dr = 93/7	dr = 75/25
91% ee/95% ee	93% ee	97% ee	98% ee
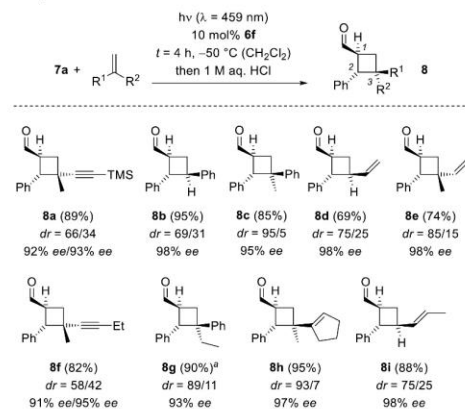
[a]Irradiation time t = 15 h.

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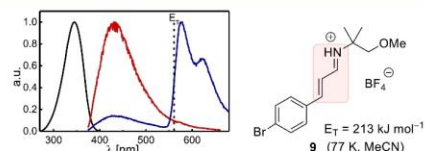
Figure 1. Absorption and luminescence spectra (λ_{exc} = 360 nm) of iminium ion 9 in MeCN. Colors: Absorption, black; fluorescence (rt), red; phosphorescence (77 K), blue. The energy of the (0,0) transition was calculated from the point of inflection at λ = 562 nm.

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.
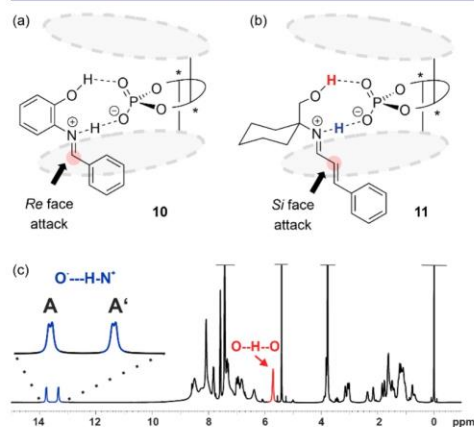
The enantioselectivity of the [2 + 2] photocycloaddition can be tentatively explained in analogy to a model proposed by Akiyama and co-workers for the addition to related prochiral iminium ions. They suggested a 1:1 complex 10 with the chiral phosphoric acid in which the aryl groups of the acid invite 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$_2$Cl$_2$) 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, ^{1}H$_\alpha$ 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

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 cyclobutane-carbaldehydes 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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Notes

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7. SUMMARY

Since pioneering work by Akiyama[31] and Terada[32] chiral phosphoric acids derived from axially chiral biaryls have emerged as efficient catalysts for a variety of synthetic transformations.[3] As of now, chiral phosphoric acid catalysis is well established in ground state chemistry and there have been several applications in photoinduced electron transfer catalysis in recent years.[4] However, chiral phosphoric acids had not been successfully employed in catalytic enantioselective [2+2] photocycloaddition reactions.

To this end, we developed a novel BINOL-derived chiral phosphoric acid sensitizer **59** that displays two thioxanthone chromophores in *C*-3/*C*-3' position which capture long wavelength light (λ_{max} = 394 nm), promote energy transfer (E_T = 235 ± 2 kJ mol^{-1}), and simultaneously induce enantioface differentiation.
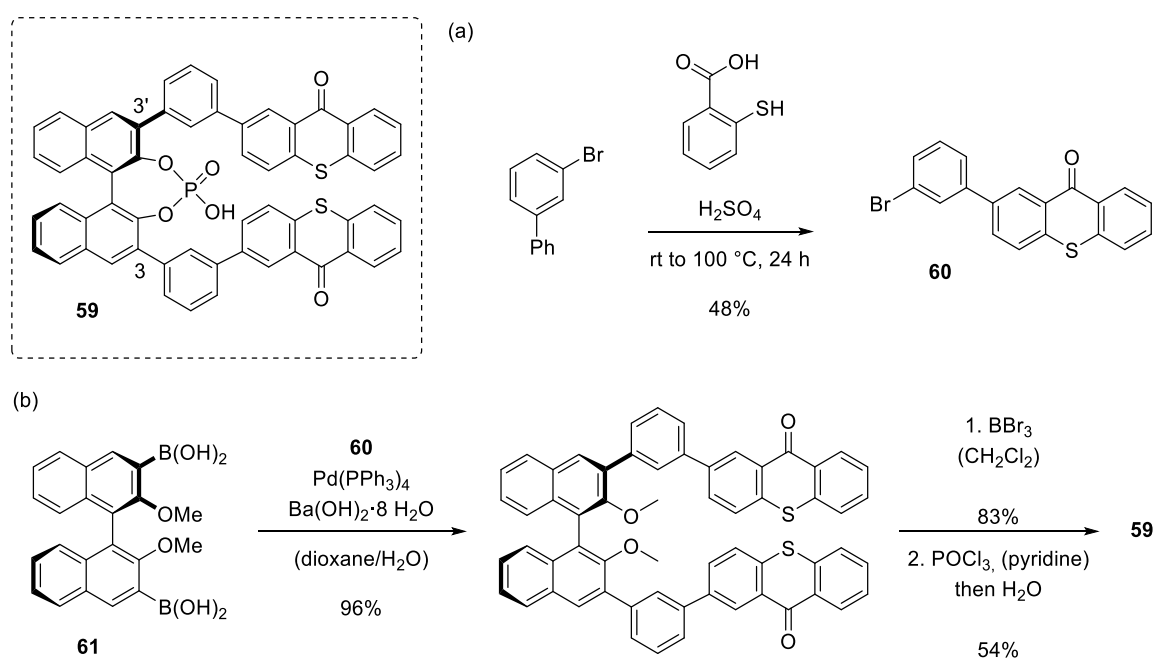
Scheme 11. Synthesis of chiral phosphoric acid sensitizer **59** from bromothioxanthone **60** (a) and (*R*)-BINOL diboronic acid **61** (b).

Catalyst **59** was prepared by dehydrogenative condensation of 3-bromobiphenyl and thiosalicylic acid to bromothioxanthone **60** and subsequent *Suzuki* cross-coupling with BINOL diboronic acid **61**. Demethylation and phosphorylation yielded the desired catalyst in an overall yield of 21% (Scheme 11).

In a proof-of-principle reaction, catalyst **59** was successfully employed in the [2+2] photocycloaddition of cyclic enone-3-carboxylic acids **62** (X = CH$_2$, O) with a variety of alkenes (Scheme 12). Despite low yields due to an undesired decarboxylation side reaction,

cyclobutanes **63** were isolated with up to 85% *ee* highlighting the synthetic potential of bifunctional catalyst **59**.[5] Determination of the triplet energy of the catalyst (E_T = 235 ± 2 kJ/mol) and enone carboxylic acid **54** (E_T = 288 ± 2 kJ/mol), furthermore, suggested that the triplet energy of the substrate is lowered upon association to the catalyst thus making an energy transfer feasible. The published work represents the first report on an enantioselective [2+2] photocycloaddition reaction that was successfully catalyzed by a chiral phosphoric acid catalyst.
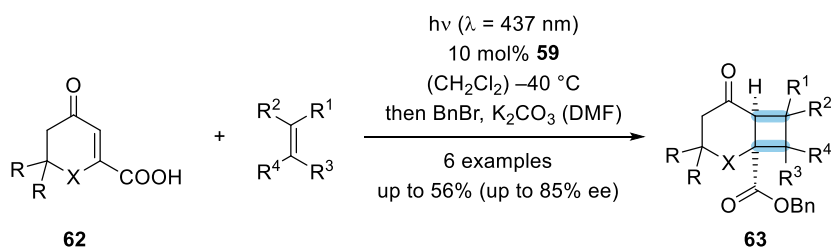
Scheme 12. Enantioselective intermolecular [2+2] photocycloaddition of cyclic enone carboxylic acids **62** with a variety of alkenes mediated by chiral phosphoric acid catalyst **59**. Newly formed bonds are marked in blue.

In our quest to expand the scope of application of catalyst **59**, we sought after other possible substrates. *N,O*-acetals **58** derived from α,β-unsaturated β-aryl substituted aldehydes and (1-aminocyclohexyl)methanol indeed underwent a catalytic enantioselective [2+2] photocycloaddition in excellent yiel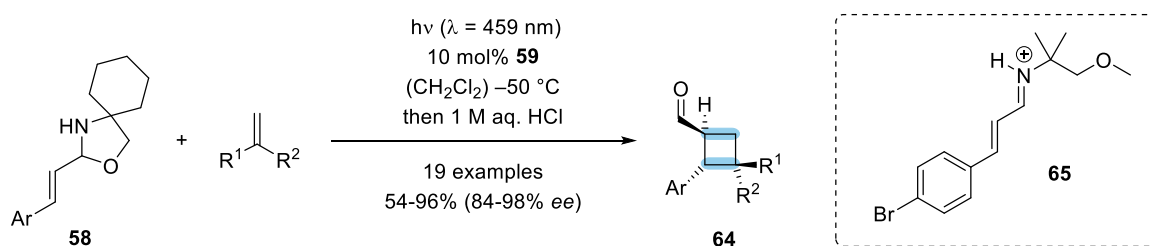ds and enantioselectivities (19 examples, 54-96% yield, 84-98% *ee*) (**58→64**, Scheme 13).[8] The protocol accommodated different substitution patterns and functional groups on the cinnamaldehyde core and a variety of olefines such as styrenes, 1,3-enynes and 1,3-dienes.

Scheme 13. Enantioselective intermolecular [2+2] photocycloaddition of cinnamoyl *N,O*-acetals **58** with a variety of alkenes mediated by chiral phosphoric acid catalyst **59**. Newly formed bonds are marked in blue.

The mode of activation is based on the formation of iminium ions from the *N,O*-acetal derivatives **58** upon protonation and subsequent association to the chiral phosphate anion. Triplet energy transfer from catalyst **59** (E_T = 235 kJ mol^{-1}) to the iminium ion derivatives (E_T (**65**) = 235 kJ mol^{-1}) selectively occurred within its chiral environment and thus facilitated asymmetric induction in the intermolecular [2+2] photocycloaddition. Extensive low-

temperature NMR studies in collaboration with the group of Prof. *Gschwind*, furthermore, validated the proposed bidentate binding motif between the formed iminium ion and the chiral phosphoric acid counter ion in a hydrogen-bond assisted ion pair. There has been no previous report on the application of *N,O*-acetals in combination with chiral phosphoric acid catalysts.

In conclusion, we reported the first synthesis of a bifunctional catalyst combining a photosensitizer with a chiral phosphoric acid moiety and its application in the successful enantioselective [2+2] photocycloaddition of enone carboxylic acids and cinnamoyl *N,O*-acetals.

8. LICENSES

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