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-carboxylic acid-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 chrophores 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[4d,5] and deracemization[5] 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.[6] Chiral imidazolinone-based organocatalysts have recently been reported for enamine catalysis in which the thioxanthone acts via single electron transfer.[7] However, not any binding motif known from thermal reactions will automatically lead to a successful chiral catalyst. Thiourea-linked thioxanthenes such as 3, for example, did not display the expected enantioselectivity in photochemical reactions.[8]

Nonetheless, given the limited number of substrates that can yet be processed by chiral thioxanthenes, 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 C2-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 thioxanthene unit. However, the direct linkage of a 9-oxo-9H-thioxanthen-3-yl group to posi-

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Figure 1. Structure of chiral thioxanthenes 1–3 with a substrate or metal binding site (in gray).
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 racem products rac-10 could be conducted 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.$_R$ 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 $\alpha$-carbon atom in the $\alpha, \beta$-unsaturated carboxylic acid 9.

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(PPh$_3$)$_4$, 10 equiv 2× Na$_2$CO$_3$ (aq), 65 $^\circ$C, 16 h (DME), 96%; (b) 6.0 equiv BBr$_3$, 0 $^\circ$C--rt, 2 h (CH$_2$Cl$_2$), 83%; (c) 2.0 equiv POCl$_3$, 95 $^\circ$C, 12 h (py), then H$_2$O, 95 $^\circ$C, 54%.

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

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

Like for product 11a a significant enantioface differentiation was recorded with the higher e.r.$_R$ (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 $\alpha$-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] photocycloaddition reactions 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.[11] The former component was obtained by a dehydrogenative condensation[11] of 3-bromobiphenyl (5) and thiosalicylic acid (6). After demethylation
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 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 (thioxanthene-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 energy (E\text{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 thioxanthene-9-one ($E_T = 272$ kJ mol$^{-1}$).\cite{18} Luminescence spectra of the two carboxylic acids showed the typical signature of $\alpha,\beta$-unsaturated enones 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 thioxanthene-9-one irradiation experiments, the data suggest a preferred energy transfer within a complex between the carboxylic acids and compound 4 while thioxanthene-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,\cite{19} 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 (\approx 1.7 Å) of the hydrodynamic radius of carboxylic acid 9 in the presence of catalyst 4 (see Supporting Information for details and spectra).\cite{20} Significant line broadening and a slight highfield shifting (\approx 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 of 4 showed various minor populated signals summarized as H\text{a} (blue region in Figure 4) and two distinct signals H\text{b} and H\text{c} (green region). The temperature coefficients of H\text{a} and H\text{b} 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.\cite{21} The minimum temperature coefficient of the signals labelled H\text{b} is significantly higher (–9.6 ppb K$^{-1}$) than that for H\text{a} and H\text{c}, 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\text{b} protons from the solvent, which would be rational for different rotational isomers of monomeric 4. Indeed, signals H\text{a} of the
catalyst collapse to one signal H₁ in the presence of 9, while signals H² and H³ are unaffected.[23] The respective ³¹P NMR spectra show a similar behaviour (see the Supporting Information) and thus support the assignment of H² and H³ as monomeric, and H² and H³ as dimeric (or oligomeric) catalyst species. The averaged proton signal H² 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 H³ 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 H³ 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 thioxanthenone-phenyl bond (Figure 5, left) the C₂ 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.

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.

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Conflict of interest

The authors declare no conflict of interest.

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