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# Syntheses of new chiral chimeric photo-organocatalysts†

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A new family of chiral chimeric photo-organocatalysts derived from phosphoric acid were synthesized and their spectroscopic and electrochemical properties were investigated. Then, the ability of these photo-activable molecules to catalyse an asymmetric tandem electrophilic β-amination of enecarbamates was evaluated.

## Introduction

Enantioselective photocatalysis[1,2] has been recognized as a powerful method for the construction of useful enantiomerically enriched compounds. The past two decades have witnessed tremendous progress using mainly two approaches.[3] The first one relies on the combination of two separated catalytic species, one acting as a photosensitizer, the second one bringing chiral information in a dual or cooperative way.[1,4–6] The second approach employs bifunctional catalysts in which a single molecule contains both a photoactive group and a chiral unit. This strategy has allowed the development of chiral metallic complexes bearing either an ancillary organic binding domain or an ancillary organo photosensitized or purely bifunctional organocatalysts.[7] In the last strategy, an early example documented by Bach *et al.*[8] using chiral bifunctional catalysts **A** (Fig. 1) has paved the way for further developments of chiral chimeric photo-organocatalysts.[1,9,10] For instance, Sibi and Sivaguru *et al.*[11] proposed a chiral catalyst **B** which merges a thiourea unit and a photoactive binaphthyl moiety, for enantioselective (2 + 2) photocycloaddition. Thiourea was also chosen as organocatalytic part and connected to thioxanthone **C** to deliver a modestly effective chiral catalyst for photocyclization.[12] Combining thioxanthone with chiral secondary amine furnished an effective bifunctional photocatalyst **D** for enantioselective alkylation of aldehydes.[13] Given the diverse classes of organocatalysts, whether chiral or photosensitive, many novel merged structures can be expected. 1,1′-Bi-2-naphthol (BINOL)-derived chiral phosphoric acids occupy a central place in organocatalysis[14] and have found application in dual catalysis in combination with redox photosensitizers.[1,15] As such, building phosphoric acid centered photosensitizer could provide an avenue to diverse enantioselective photo promoted reactions.

Indeed, two independent reports have recently presented new chiral organophotocatalysts in which a BINOL-derived phosphoric acid was attached to thioxanthone dyes. Bach et *al.* showed that C2-symmetric catalyst **E** containing a phenyl linker between BINOL and thioxanthone unit was competent

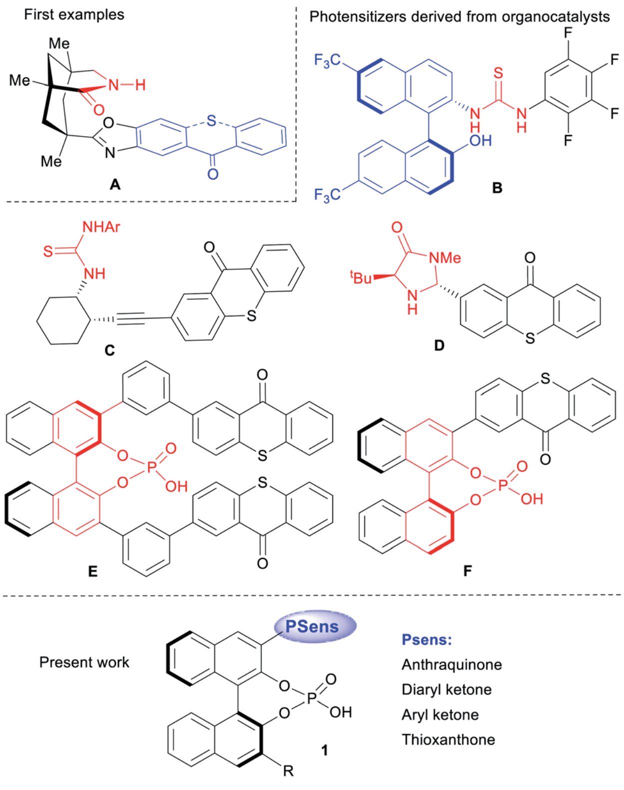

Fig. 1 Chiral chimeric photo-organocatalysts.

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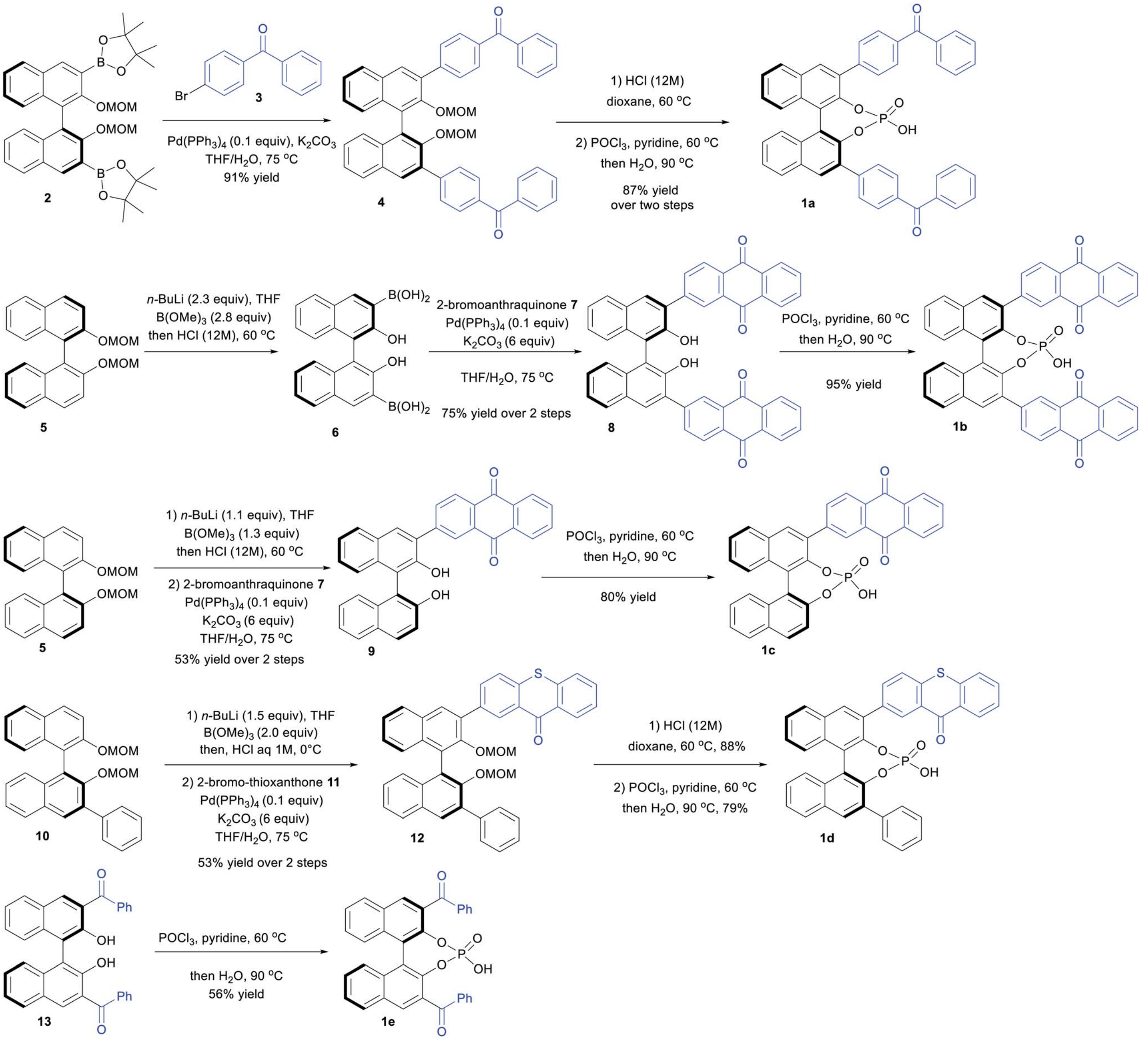
catalyst for enantioselective [2 + 2] cycloadditions.[16] Nearly at the same time, our group found that chiral BINOL phosphoric acid **F** with one thioxanthone unit in the 3-position (Fig. 1) could promote a tandem three-component electrophilic amination of enecarbamates with dibenzyl azodicarboxylate and pyrazoles with high enantioselectivity.[17]

During this work we also considered other chimeric chiral photocatalysts, derived from a phosphoric acid scaffold and known active photosensitizers.[18] Among them, ketones have a long history in photochemistry and, not only in pure organic synthesis, but also in environmental chemistry.[19] In particular, aryl ketones, such as benzophenone,[20] thioxanthone[18a] and anthraquinone[21] have long been appreciated for their long-lived triplet states and ability to act as effective photosensitizers in a wide number of photochemical transformations. Herein, we report the synthesis, the photophysical properties as well as some photocatalytic capabilities of these new chiral BINOL phosphoric acid photocatalysts bearing different photoactivable aromatic ketones at the 3 or 3,3′ positions.

## Results & discussion

The synthesis of targeted bifunctional molecules incorporating diphenyl ketone, anthraquinone, aryl ketone as well as thioxanthone was undertaken. The C2-symmetric (4-phenyl)(-phenyl) methanone photocatalyst **1a** was easily prepared in high yield through a three-step procedure. Performed under classical conditions, the Suzuki–Miyaura coupling of known 3,3′-substituted BINOL bis pinacol boronate ester **2** with 4-bromobenzophenone **3**, furnished compound **4** in high yield (91%).[22] HCl promoted MOM-hydrolysis, gave a crude bis-phenol



Scheme 1 Syntheses of chiral phosphoric acid photocatalysts.

derivative that was directly converted to phosphoric acid in an overall 70% yield for two steps. A related but modified sequence in which phenol deprotection would be performed prior to the arylation was adopted for the synthesis of C2-symmetric anthraquinone photocatalyst **1b**. Double *ortho*-lithiation of protected BINOL **5** followed by trapping with cheap B(OMe)$_3$ and subsequent hydrolysis led to phenol-free bis boronic acid **6**.[23] Interestingly, while purification was difficult, engaging the crude extract in the subsequent cross coupling with 2-bromoanthraquinone **7** proved to be highly effective. Final phosphorylation delivered compound **1b** in 71% over the entire sequence.[24] In our preliminary report, we reported that the C1-symmetric thioxanthone catalyst **1a** was superior to the corresponding C2-symmetric in terms of reactivity.[17] Based on this observation, we became interested in the synthesis of C1-symmetric derivatives. Mono-substituted anthraquinone **1c** was therefore synthesized following a similar route to its C2-symmetric counterpart. By reducing the amount of BuLi used in the initial *ortho*-lithiation step from 2.8 to 1.5 equivalent, a relatively selective monoborylation could be obtained. Subsequent hydrolysis, cross coupling and phosphorylation went uneventfully to deliver compound **1c**. A newly designed C1-symmetric thioxanthone having a phenyl substituent at the 3-position **1d** was also considered. Synthesis began from easily accessible 3-mono-phenyl-substituted BINOL derivative **10**,[25] which could be borylated. Controlled hydrolysis (HCl at 0 °C) at the end of this first step allowed to isolate MOM-protected bis boronic acid that then participated in the Suzuki–Miyaura coupling with 2-bromo-thioxanthone **11** to afford the C1-symmetric product **12** in 53% yield over two steps. Then, MOM deprotection and phosphorylation gave the desired product **1d** in good yield. Since phenylmethanone bearing BINOL derived **13** was available following the procedure reported by Wang et *al.*,[26] we also prepared phosphoric acid **1e** by simple phosphorylation for comparative purpose (Scheme 1).

With these diverse chiral chimeric organophotocatalysts **1** in hand, we next turned our attention to their photophysical properties by recording UV-vis and emission spectra in DCM as shown in Table 1 (for absorbance and fluorescence spectra, see in the ESI†). Photosensitizers expected to be activated by visible light were evaluated first.

Table 1 Spectroscopic data in DCM for chiral photocatalyst **1a**, **1c–e** and in DMSO for **1b** (molar absorption coefficient ε, absorption maxima $\lambda_{abs}$, fluorescence emission quantum yield $\phi_f$ determined using quinine sulphate as a reference and emission maxima $\lambda_{em}$)

| Entry | PCat | $\lambda_{abs}$/nm ($\varepsilon$/L mol$^{-1}$ cm$^{-1}$) | $\lambda_{em}$/nm | $\phi_f$ |
|---|---|---|---|---|
| 1 | **1a** | 296 ($4.3 \times 10^4$) | | <0.01 |
| 2 | **1b** | 267 ($7.8 \times 10^4$)<br>335 (sc) | | <0.01 |
| 3 | **1c** | 259 ($5.1 \times 10^4$)<br>325 ($1.4 \times 10^4$) | 580 | 0.01 |
| 4 | **1d** | 256 ($5.8 \times 10^4$)<br>397 ($3.2 \times 10^4$) | 448 | 0.054 |
| 5 | **1e** | 262 ($4.7 \times 10^4$) | | <0.01 |

Chiral phosphoric acid-thioxanthone photocatalyst **1d** exhibits absorption maxima $\lambda_{max}$ at 256 nm and 397 nm in DCM. The bis-substituted anthraquinone catalyst **1b** and mono-anthraquinone photocatalyst **1c** showed an absorption $\lambda_{max}$ at 267 and 259 nm, respectively. However, the monosubstituted photocatalyst **1c** has an additional burst at 329 nm. It should be mentioned that absorption was still significant for thioxanthone **1d** and both anthraquinones **1b**, **1c** up to 448 nm meaning that they could work in the visible light region. The absorbance $\lambda_{max}$ values of catalysts bearing acyclic ketones **1a** and **1e** were at 262 and 296 nm, respectively. While **1a** absorbed only below 380 nm, **1e** could exhibited residual absorption up to 430 nm.

The fluorescence emission spectrum of **1d** displayed a peak centered at 448 nm with a moderate fluorescence quantum yield. There are nearly no fluorescence of acyclic ketones **1a** and **1e** as well as for substituted bis-anthraquinone **1b**. On the contrary, a slight emission intensity was observed for the mono-substituted anthraquinone catalyst **1c** indicating much less quenching occurred in this structure.

The electrochemical activity of the chiral photocatalysts was determined by cyclic voltammetry analyses in DCM using ferrocene as internal reference (Table 2). The C1 symmetric thioxanthone catalyst **1d** exhibits a reversible one-electron reduction around −1.70 V. The cyclic voltammogram of C2- and C1-symmetric anthraquinone-based catalyst **1b** and **1c** showed two reduction peaks which correspond to two single-electron reductions of each ketone on the anthraquinone dye. On the other hand, one reduction peak at −1.96 V was observed for the C2-symmetric benzophenone-based catalyst **1a**. Differently, the C2-symmetric photocatalyst bearing ketone **1e** exhibits two successive one-electron reduction processes with the redox peaks at −1.72 V and −2.04 V, respectively, and only one oxidation process was observed. This result indicates that **1e** can be partially reversibly reduced. Finally, the estimation of the $E_{0,0}$ from absorption spectra of **1** allowed us to evaluate the excited state oxidation potential of **1***. The values decreased in the order **1c** > **1b** > **1d** > **1e** > **1a**.

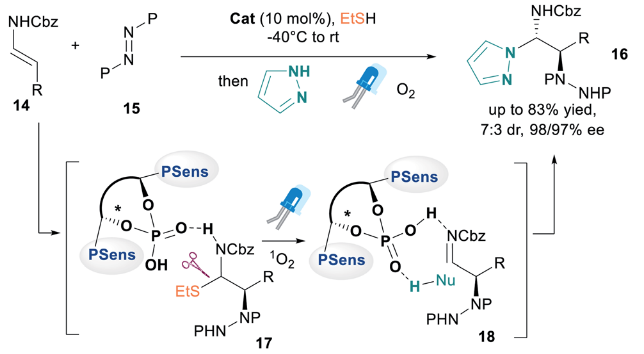
In order to evaluate the ability of the novel objects to act as chiral chimeric photocatalysts, the asymmetric electrophilic amination of α-unsubstituted enecarbamates was chosen as a benchmark reaction.[27] The process involves the β-addition of an enecarbamate **14** to azodicarboxylate **15** in presence of EtSH[28] followed by the photoinduced coupling of an azole with the *in situ* generated α-carbamoylsulfide **17**.[29] Partial racemization of the imine intermediate **18** was observed when the reaction with pyrazole was performed with two distinct catalysts (a chiral phosphoric acid and a distinct photocatalyst).

However, as demonstrated in our recent publication,[17] a bifunctional chiral chimeric photocatalyst, such as **F** is able to (1) promote the generation of imine from **17** by photooxidation of sulfur atom involving the participation of singlet oxygen but also to (2) bring nucleophile and electrophile in close proximity *via* a pseudo intramolecular hydrogen-bonding transition state **18**, and thereby favors a rapid addition of pyrazole to imine (Scheme 2). This approach overcomes the partial racemization and leads to product **16** with high enantioselectivity. As such

Table 2 Electrochemical data for chiral photocatalysts **1c–g** in DCM. Cyclic voltammetry of photocatalysts (V *vs.* Ag$^+$/Ag), in dichloromethane (with 0.1 M $Bu_4NPF_6$ as electrolyte) on glassy carbon electrode. Concentrations are about 2 × $10^{-3}$ mmol mL$^{-1}$

| PCat | $E_{1/2}$ (**1**/**1**$^{\bullet-}$, V *vs.* Ag$^+$/Ag) | $E_{1/2}$ (**1**$^{\bullet-}$/**1**$^{2-}$, V *vs.* Ag$^+$/Ag) | $E_{1/2}{}^a$ (**1***/**1**$^{\bullet-}$*, V *vs.* Ag$^+$/Ag) | $E_{1/2}{}^a$ (**1**$^{\bullet-}$*/**1**$^{2-}$, V *vs.* Ag$^+$/Ag) |
|---|---|---|---|---|
| **1a** | −1.96 | | +1.10 | |
| **1b** | −1.10 | −1.48 | +1.70 | +1.32 |
| **1c** | −1.09 | −1.53 | +1.71 | +1.27 |
| **1d** | −1.70 | | +1.17 | |
| **1e** | −1.72$^b$ | −2.04 | | +1.22 |

[a] Calculated using the relationship $E°(\text{Pcat } \mathbf{1}^*/\mathbf{1}^{\bullet-}) = E_{1/2}\ (\text{Pcat } \mathbf{1}/\mathbf{1}^{\bullet-}) + E_{0,0}\ (\text{Pcat } \mathbf{1}^*/\mathbf{1})$ and $E_{0,0}$ values were estimated spectroscopically from the position of the long wavelength tail of the absorption spectrum (Table S1 in the ESI). [b] No oxidation peak.



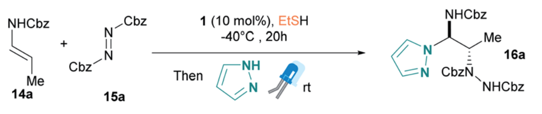
Scheme 2 Enantioselective tandem three-component electrophilic amination of enecarbamates for bifunctional catalyst evaluation.

this reaction constitute a perfect benchmark reaction to evaluate chiral chimeric photocatalysts.

Therefore, we examined the reaction of (*E*)-benzylprop-1-enylcarbamate (**14a**) with dibenzyl azodicarboxylate (**15a**), one equivalent of EtSH in the presence of 10 mol% of the newly synthesized catalysts (Table 3). With **1d** under a 405 nm irradiation, we were delighted to find that desired 1,2-diamide **16a** was produced in good yield in a 1 : 1.5 diastereomeric ratio and with high enantioselectivity. Compared to our previous work performed with catalyst **F**,[17] only marginal differences were noted, demonstrating that substitution at the 3′ position in such structure is not determinant, but interestingly, is possible. To our surprise, only trace of α-carbamoylsulfide **17a** was observed when the bis-substituted anthraquinone catalyst **1b** was used. The lack of reactivity might be due to the presence of multiple H-bond hydrogen-acceptor sites in the structure of **1b**, thereby disturbing the dual activation of both reaction partners with such structure. Interestingly, when the mono-substituted anthraquinone **1c** was evaluated, a little reactivity was recovered, allowing the formation of **16a** in moderate yield and enantioselectivity. Acyclic ketone photocatalysts **1a** and **1e** were also investigated under near UV (365 nm) or visible light (405 nm) irradiation and afforded a contrasting result, since the first catalyst **1a** gave a good enantioselectivity, whereas the second one **1e** led to racemic product.

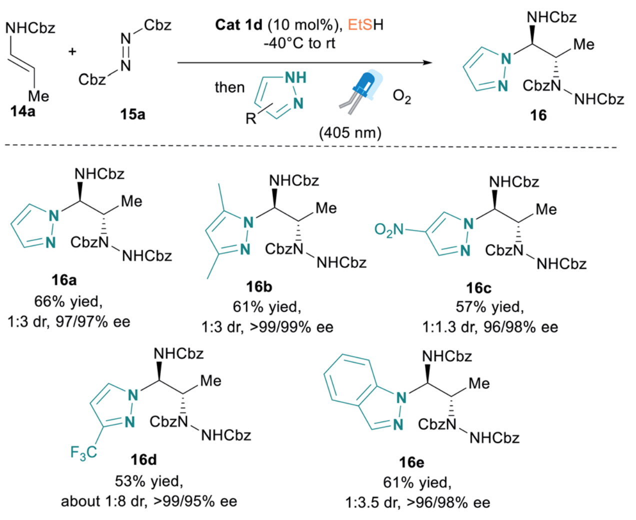
In order to verify the generality of the result obtained with catalyst **1d**, several 1-(hetero)aryl-1,2-diamines **16** were subsequently synthetized by changing the pyrazole partners (Scheme

Table 3 Evaluation of organophoto-catalytic activity$^a$



| Entry | Pcat **1** | $\lambda^b$ (nm) | Yield$^c$ (%) | dr$^d$ | ee (%)$^{e,f}$ |
|---|---|---|---|---|---|
| $1^{a,c}$ | **1a** | 365 | 60 | 1 : 2 | (−) 92/93$^e$ |
| $2^a$ | **1b** | 405 | — | — | — |
| $3^{a,c}$ | **1c** | 405 | 31 | 1 : 2.5 | (−) 37/43 |
| $4^a$ | **1d** | 405 | 72 | 1 : 1.5 | (−) 97/97$^e$ |
| $5^d$ | **1e** | 405 | 63 | 1 : 1.3 | 0/0 |

[a] Reaction conditions: **14a** (0.1 mmol), **15a** (0.15 mmol) and EtSH (0.25 mmol) and **1** (0.01 mmol) in 1 mL of $CH_2Cl_2$ at −40 °C for 20 hours; then 1*H*-pyrazole (0.3 mmol), LED, rt under $O_2$ atmosphere for 16 h. [b] Wavelength of irradiation. [c] Isolated yield after column chromatography. [d] dr was determined by $^1$H-NMR analysis and *anti*-diastereoselectivity assumed by analogy with our previous work. [e] Enantiomeric excess was determined by HPLC analysis on chiral stationary phase. [f] (+) refers to absolute *S* configuration, (−) refers to *R* configuration, assigned based on our previous work (ref. 17).



Scheme 3 Enantioselective tandem three-component electrophilic amination of enecarbamate **14a** and dibenzyl azodicarboxylate **15a** with various azoles.

3). As such, compound **16a–e** were all obtained with good yields and excellent enantioselectivities. Diastereoselectivity was modest for compound **16c** (1 : 1.3), significant for compounds **16a**, **16b** and **16e** (close to 1 : 3) and quite important for compound **16d** (1 : 8). Except for the later one, diastereoselectivity follows the same trend as the one obtained in our previous work with catalyst **F**,[17] but with slight improvement. Overall, this implies that tuning the nature of the substituent at the 3′ position of C1-symmetric thioxanthone catalyst (**1d** *vs.* **F**), also not decisive, offers opportunities for further design.

## Conclusions

In summary, we have developed an efficient reaction sequence providing a short and efficient syntheses of new chimeric photo-organocatalysts with C1 and C2 symmetry. Photophysical properties were recorded for each new object. Contrasting photocatalytic activities have been established in asymmetric electrophilic amination of α-unsubstituted enecarbamates providing hints for further studies.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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