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Preparation of Chiral Photosensitive Organocatalysts and their Application for the Enantioselective Synthesis of 1,2-diamines

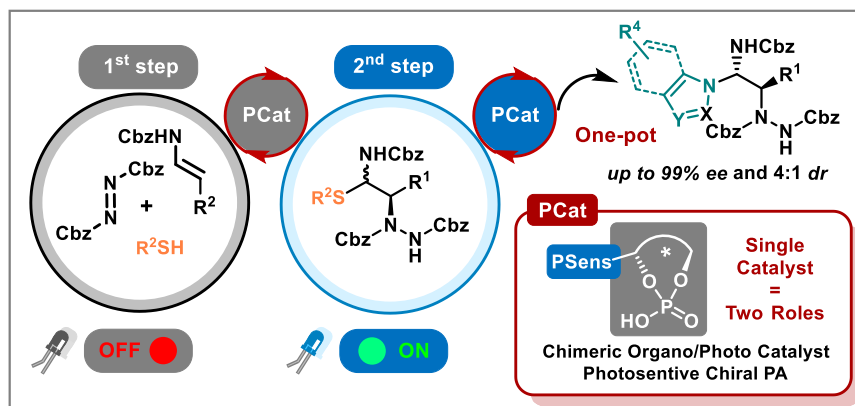
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ABSTRACT



Chiral phosphoric acid based organocatalysis and visible-light photocatalysis have both emerged as promising technologies for the sustainable production of fine chemicals. In this context, we have envisioned the design and the synthesis of a new class of chimeric catalytic entities that would feature both catalytic capabilities. Given their multitask nature, such catalysts would reveal

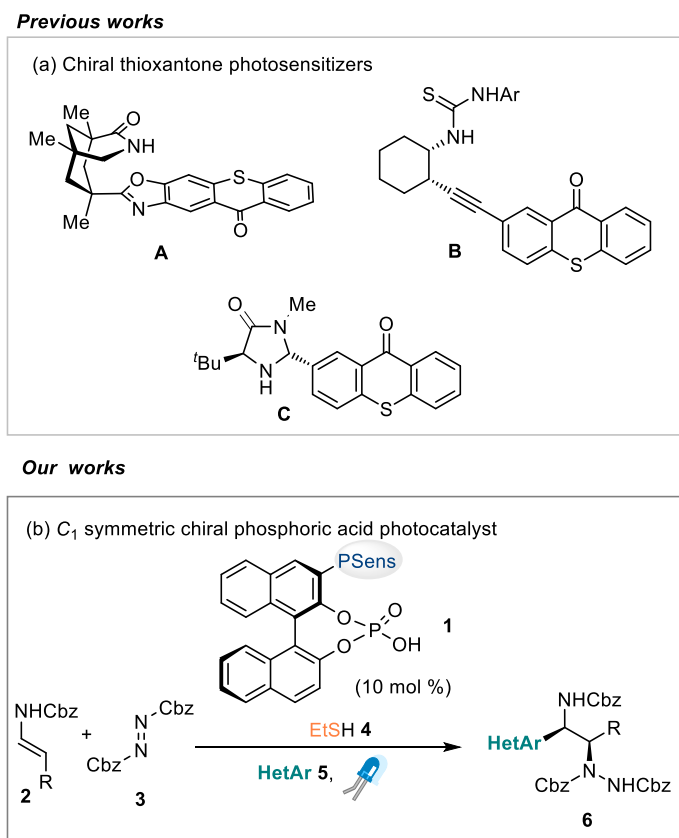
particularly attractive for the development of new catalytic transformations, tandem processes in particular. To this aim, several BINOL-based chiral phosphoric acids backbone presenting one or two visible-light sensitive thioxanthone moieties have been prepared and studied. The utility of these new photoactive chiral organocatalysts is then demonstrated in the enantioselective tandem three-component electrophilic amination of enecarbamates. Of note, the C_1 -symmetric organo/photo catalyst has given a better catalytic activity than those presenting a C_2 symmetry.

INTRODUCTION

Over the past 50 years, catalysis has become one of the best answers to the sustainability challenge raised by the ever-increasing need for raw and fine chemicals. In this context, different catalytic strategies have been explored, among which organocatalysis has emerged as an especially viable option for the asymmetric production of enantiopure compounds. For instance, thanks to the seminal work of Akiyama and Terada, chiral BINOL-derived phosphoric have been instrumental in the development of highly efficient bifunctional H-bonding catalysis.¹ Meanwhile, visible-light photoredox catalysis² has arose as an appealing “green” strategy, inasmuch as it allows to harness what certainly is the most inexpensive, abundant, and environmentally benign source of energy: solar energy. By relying on metal-based^{2a} or purely organic photosensitive entities,^{2b,d,e,h} a wide array of chemical transformations has been achieved under mild reaction conditions, either exploiting the capacity of such catalysts to induce redox processes or to promote energy transfers. Consequently, intertwining visible light-activated chemistry with asymmetric organocatalysis has been the object of high interest as it represents a wonderful opportunity of implementing both enantioselectivity

and photocatalyzed processes.^{2c,f,3} To this aim, a great deal of work has concerned the development of dual catalytic systems wherein both an organocatalyst and a photoredox catalyst are employed.^{2c,f,3} Whereas this approach has found a huge success ever since the seminal report of MacMillan *et al.* was published in 2008,⁴ the prospect of using chimeric catalysts which, within the same catalytic entity, encompass an organocatalytic activating group and a photoactive moiety has comparatively been overlooked.⁵⁻⁷ Considering visible-light based processes, Bach *et al.* reported the first chiral organophotocatalyst in which a thioxanthone chromophore and an amide hydrogen bond donor/acceptor were incorporated to a rigid backbone structure (**A**, Scheme 1(a)).^{6a-c} It has demonstrated its efficiency in enantioselective [2+2] cycloadditions as well as the deracemization of allenes. Then, the same group also described a thiourea-thioxanthone hybrid photocatalyst which was used to photocyclize a substituted cyclohexanone with a low *ee* (**B**, Scheme 1(a)).^{6d} More recently, Alemán *et al.* designed a bifunctional photoaminocatalyst based on the introduction of a thioxanthone moiety on an imidazolidinone core for the enantioselective α -alkylation of aldehydes (**C**, Scheme 1(a)).^{6e} In this particular context, given our interest in enantioselective organocatalysis⁸ and photoredox catalysis,⁹ we became interested in designing a new class of photoactive organocatalyst which, based on the BINOL-phosphoric acid backbone, would possess one or two photoactive groups in the 3,3' position. Such chimeric chemical entities would offer the opportunity, depending on the presence or the absence of an adequate source of light, to either induced a defined asymmetric organocatalytic transformation or, following the concept of assisted tandem catalysis,¹⁰ a photocatalyzed process. Inspired by Bach's and Alemán's works, the heterocyclic thioxanthone unit was selected as the visible light photosactive moiety for the synthesis of our targeted bifunctional organo/photo catalysts.^{3,6,7c,11} Herein, we describe our initial efforts

toward the development of this new class of catalysts and their evaluation in the enantioselective multicomponent syntheses of 1,2-diamines (Scheme 1(b)). Worthy of note, during the course of this study, Bach and co-workers reported other C_2 -symmetric chiral photensitizers derived from chiral phosphoric acids which he applied to enantioselective [2+2] photo-cycloadditions.¹²

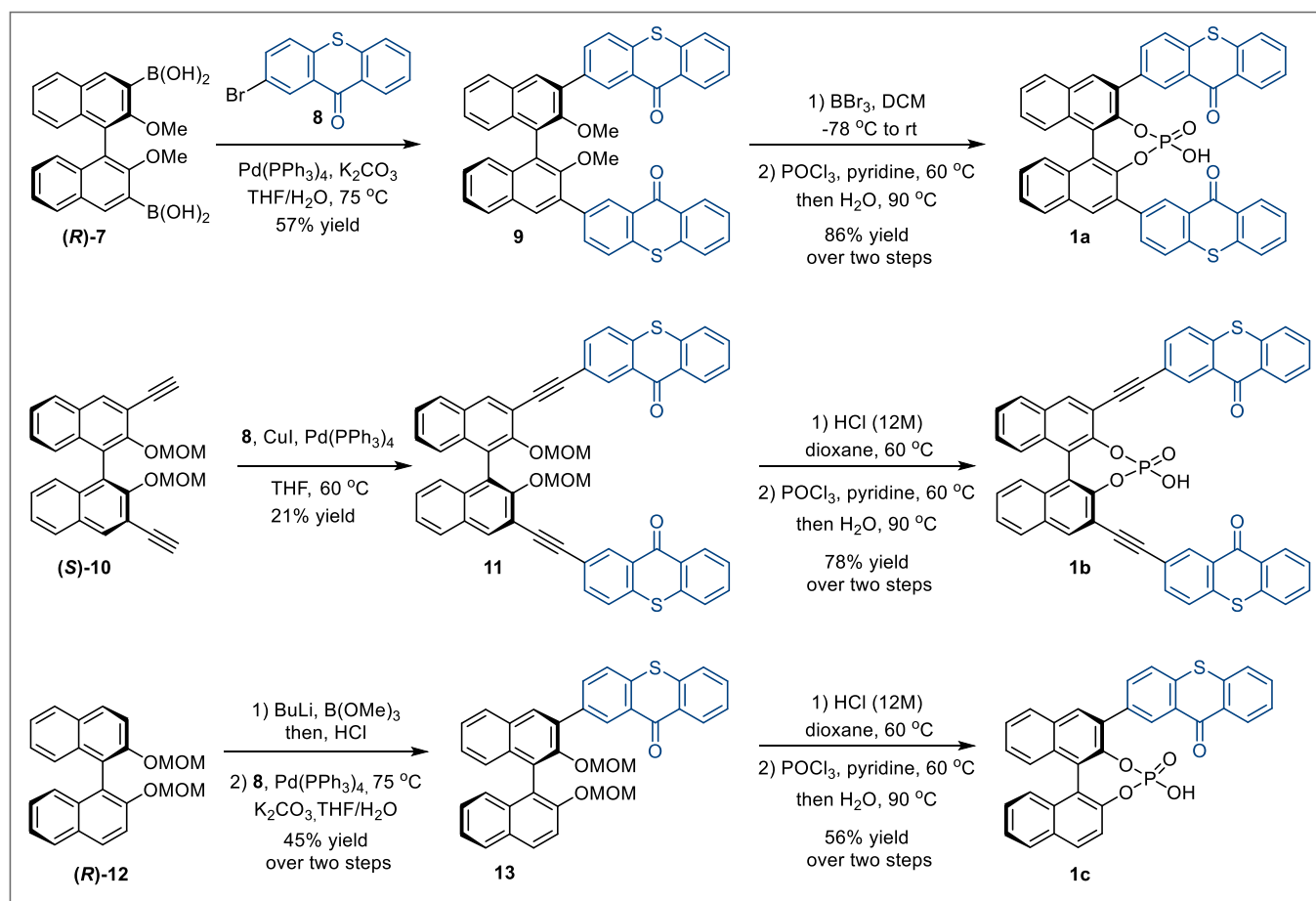


Scheme 1. Enantioselective catalytic photochemical reactions.

RESULTS AND DISCUSSION

The new phosphoric acids **1a-c** bearing a visible-light sensitive thioxantone moiety were easily accessible in few steps starting from optically pure BINOL derivatives, according to the route outlined in Scheme 2. The first C_2 -symmetric compound **9** was prepared in a convergent manner by Suzuki–Miyaura cross-coupling of the adequate (*R*)-BINOL dimethyl ether 3,3-bisboronic acid **7**¹³

with the 2-bromo-thioxanthone **8**. The second type of C_2 -symmetric MOM-protected BINOL **11** with an alkyne spacer between the BINOL and thioxanthone core was obtained *via* the Sonogashira coupling of diacetylene (*S*)-**10** with **8**.¹⁴ Additionally, we were interested in synthesizing the C_1 -symmetric catalyst **1c** having a simple thioxanthone unit linked to the (*R*)-BINOL backbone. To this end, starting from **12**, the *in situ* generated mono-substituted BINOL boronic acid¹⁵ was subjected to Suzuki–Miyaura coupling in the presence of **8** to give the desired product **13** in 45% yield over two-steps. Finally, the resulting BINOL derivatives **9**, **11** and **13** were converted into the desired photocatalysts **1a-1c** *via* deprotection and subsequent phosphorylation.



Scheme 2. Syntheses of chiral phosphoric acid photocatalysts.

With these chimeric organo/photo catalysts **1a-c** in hand, we next turned our attention to their photophysical properties by initially recording their UV–visible absorption profiles in DCE. Chiral phosphoric acid-thioxanthone photocatalysts **1a**, **1b** and **1c** showed similar absorption properties with λ_{max} at 390, 400 and 390 nm, respectively (Table 1). It confirmed their ability to absorb light in the visible region, until approximately 440 nm. (See the absorption spectra, Figure S1 in the Supporting Information). The fluorescence emission spectrums of **1a-1c** displayed a wide peak centered at 437, 453 and 425 nm, respectively, with moderate fluorescence quantum yields (See the fluorescence spectra, Figure S2 in the Supporting Information). It is interesting to note that **1a** is three times less fluorescent than **1c** suggesting an intramolecular bleaching between the two thioxanthone residues. We then determined the electrochemical properties of chiral photocatalysts **1** by conducting cyclic voltammetry (CV) experiments in DCE¹⁶ as reported in Table 1 (See the cyclic voltammograms, Figure S3-S5 in the Supporting Information). These derivatives exhibit similar electrochemical behaviors with reversible reduction waves. The reduction peaks of **1a**, **1b** and **1c** were found at -1.55, -1.46 and -1.53 V *vs* SCE, respectively. Then, the redox potential of the excited states **1a^{*}-1c^{*}** (range from +1.19 to +1.24 *vs* SCE) were estimated according to Rehm-Weller approximation.¹⁷

Table 1. Photophysical and electrochemical data of **1** in DCE.

entry	Pcat 1	λ_{abs} nm	λ_{em} nm	ϕ_{f}	$E_{1/2}$ (Pcat 1 / 1^{•-}) V <i>vs</i> SCE)	$E_{1/2}$ (Pcat 1[*] / 1) V <i>vs</i> SCE) ^a
1	1a	390	437	0.014	-1.55 V	+1.19 V
2	1b	400	453	0.014	-1.46 V	+1.20 V
3	1c	390	425	0.049	-1.53 V	+1.24 V

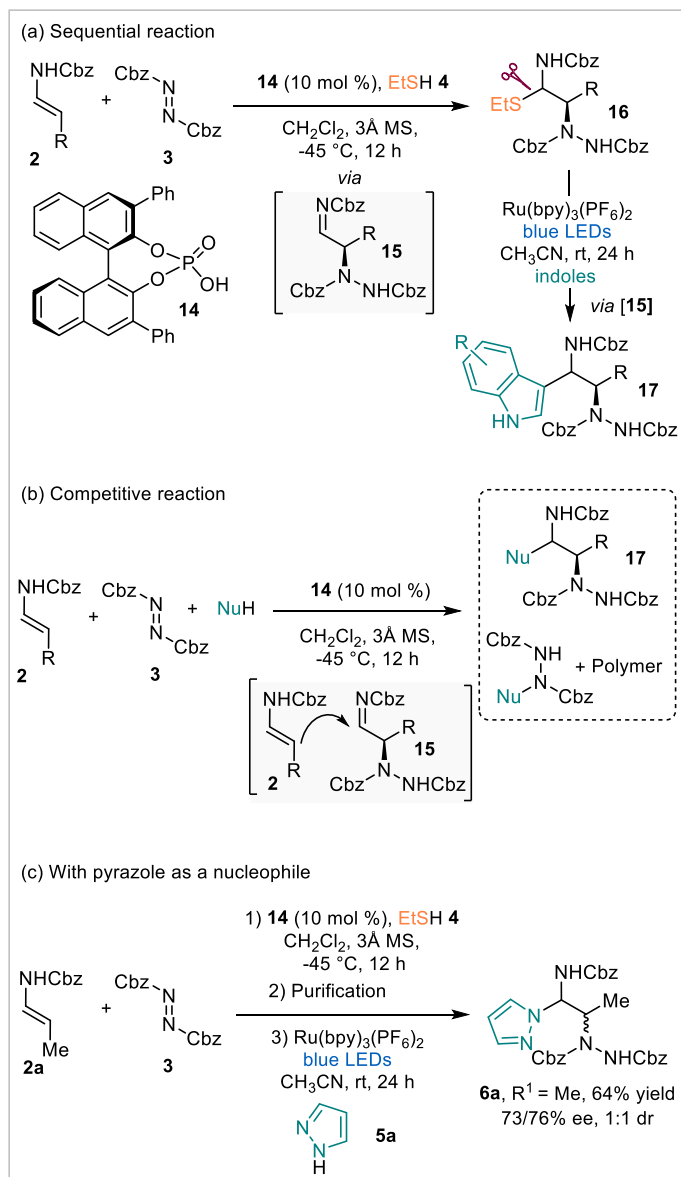
λ_{abs} absorption wavelength. ϵ molar absorption coefficient. E^0 measured in 1,2-dichloroethane (DCE) with a 2 mM concentration of **1**, 0.1M TBABF₄. ^a Calculated using the relationship $E^0(\text{Pcat } \mathbf{1}^*/\mathbf{1}^{\bullet-}) = E_{1/2}(\text{Pcat } \mathbf{1}/\mathbf{1}^{\bullet-}) + E_{0,0}(\text{Pcat } \mathbf{1}^*/\mathbf{1})$ and $E_{0,0}$ values were estimated spectroscopically from the position of the long wavelength tail of the absorption spectrum (Table S1 in the Supporting Information).

We then started to explore the catalytic activities of this new catalysts. Last year, we have reported a sequential asymmetric vicinal difunctionalization of α -unsubstituted enecarbamates^{8c,d} by the combination of phosphoric acid and photoredox catalysis.¹⁸ The sequence, which consists in a three-component electrophilic amination of enecarbamates followed by an indole-based Friedel–Crafts reaction, delivers potentially bioactive β -amino α -substituted tryptamine derivatives in excellent enantioselectivity (Scheme 3(a)). The main challenges observed in this “one pot” three-component transformation (Scheme 3(b)) was due to competitive processes such as the direct addition of the indole partner to the azodicarboxylate and the polymerization by successive addition of the enecarbamate to the imine intermediate **15** (generated during electrophilic amination). To prevent these competitive reactions, we have developed a strategy based on the use of a thiol as a temporary nucleophile to trap the unstable imine **15**. By means of a subsequent ruthenium-based photocatalytic process, the resulting α -carbamoylsulfides **16** allowed the regeneration of the enantioenriched imine intermediates **15**, able so to undergo a very neat Friedel–Crafts reaction with indoles. However, the “one-pot sequential” process was regrettably not feasible because the solvents required for achieving good yields in each step were mismatched (the Ru-catalyzed Friedel–Crafts step was not effective in CH₂Cl₂,^{18,19} whereas moderate enantioselectivity/yield were observed in the electrophilic amination carried out in CH₃CN). Additionally, it was found that the purification step of **16** was required to provide the β -amino α -substituted tryptamines **17**. On the other hand, when a less nucleophilic pyrazole was used to form the *N*-alkylated product (R=Me) **6a**, moderate enantioselectivity was observed, possibly due to partial racemization of the imine intermediate **15** (Scheme 3(c)). To solve this issue, we hypothesized that our newly developed chiral photocatalyst

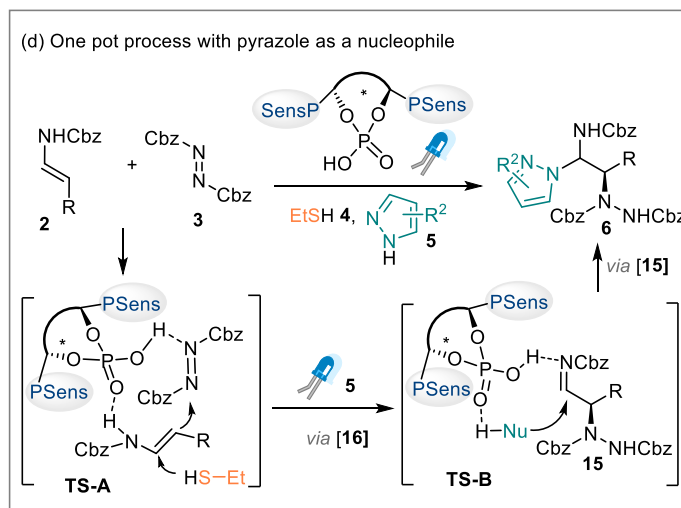
could be good candidates to promote both steps of this sequence (Scheme 3(d)): it would (1) induce high enantioselectivity in the electrophilic amination *via* the well-organized transition state **TS-A**;^{1,8c,d} (2) promote the photocatalyzed imine regeneration reaction *via* the C–S bonds cleavage of **16**^{9b-e,18} and (3) allow, while avoiding undesired racemization, the *N*-alkylation step. Indeed, during the second step of the process, the simultaneous dual activation of the two reacting partners **15** and NuH by the phosphoric acid catalyst was anticipated to accelerate the rate of addition of pyrazoles *via* **TS-B**, over racemization (most probably occurring through imine–enamine tautomerism). To validate these assumptions, we carried out the one pot three-component direct amination of α -unsubstituted enecarbamate **2a** with dibenzyl azodicarboxylate **3** and ethanethiol **4** in the presence of these new chiral photosensitive phosphoric acid catalysts **1a-c**. Based on our previous work, the reaction was initially performed with 10 mol% of *C*₂-symmetric **1a** at -45°C in CH₂Cl₂, away from the light (Table 2). After 16 h, the pyrazole was added and the resulting reaction mixture was irradiated under blue LED light strips (7.2 W, 420–510 nm, See the emission spectrum, Figure S9 in the Supporting Information) at room temperature under oxygen atmosphere. To our delight, the desired product **6a** was isolated in a decent yield (64%) and with an excellent enantioselectivity (98% *ee*) for each diastereomer couple (entry 1). Strikingly, catalyst **1b** possessing an alkyne linker was found inefficient and only trace amounts of **6a** could be isolated, in nearly racemic form (entry 2). This suggests that both efficiency and selectivity of **1** seem to depend on the exact position of the two active functions (phosphoric acid/thioxanthone). To our delight, the *C*₁-symmetric photocatalyst **1c** gave better yield (73% yield) and, contrary to what is generally observed with these types of chiral monophosphoric acid catalysts, without compromising enantioselectivity (entry 3 vs 1).²⁰ The higher activity of **1c** is very much consistent with the results of quantum yield

determinations. The use of 3.0 equiv of pyrazole (**5a**) under standard conditions did increase the yield (entry 4). Interestingly, the reaction promoted by the combined use of two distinct catalysts, the chiral phosphoric acid **14** and thioxanthone, provided the 1,2-diamide derivatives **6a** with a much lower 21% yield and a significant loss of enantiomeric purity, thus validating the superiority of our bifunctional catalytic strategy (entry 5). Worthy of note, when a similar reaction was performed in absence of thioxanthone, **6a** was only detected in trace amounts (entry 6) and, under continuously dark reaction conditions, only the intermediate **16** was formed (entry 7).²¹ Moreover, a parallel control experiments showed that dioxygen (entry 8) was also compulsory for the full sequence to occur (entry 8). Finally, a 1-mmol-scale reaction using **1c** was performed, affording the 1,2-diamine product **6a** in equal yield and enantioselectivity (entry 9).

Our previous work

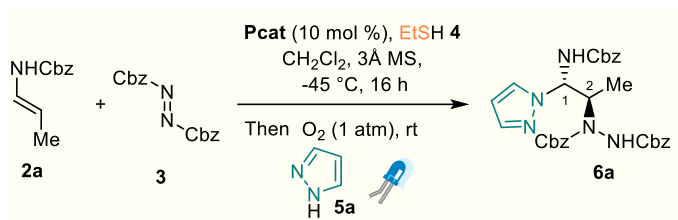


Our proposal



Scheme 3. Asymmetric α -amination and photocatalyzed pyrazole addition.

Table 2. Optimization of the tandem processes.



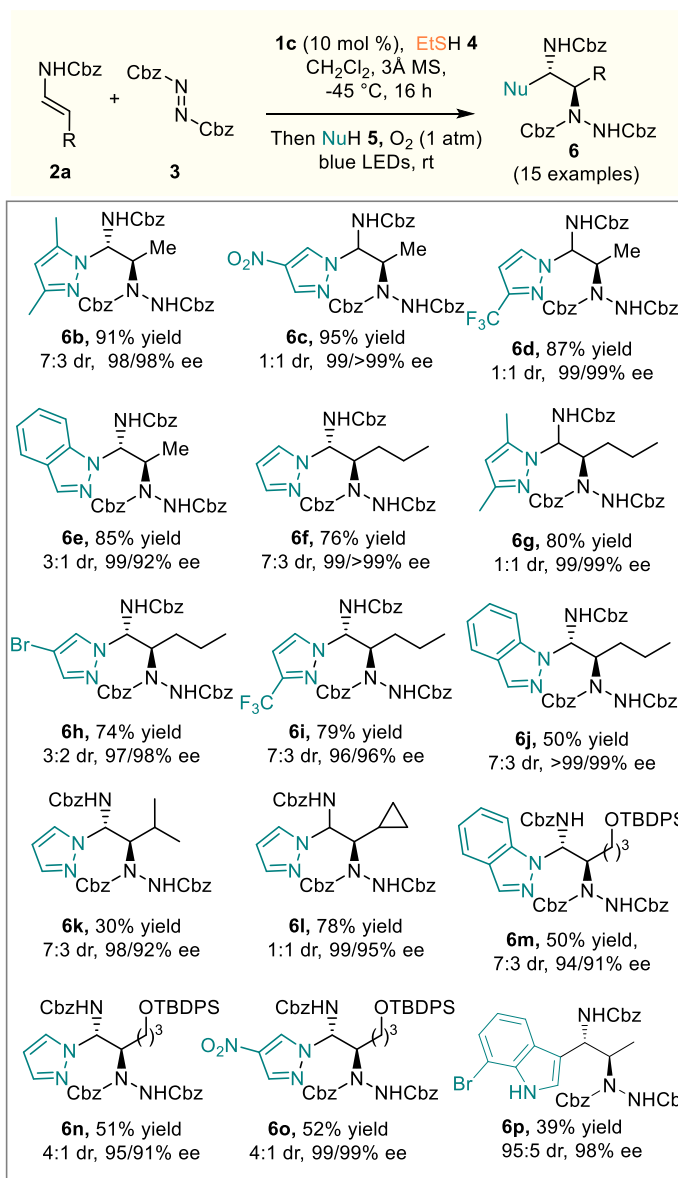
entry	Pcat	yield (%) ^{a,b}	<i>dr</i> ^c	<i>ee</i> (%) ^d
1	1a	64	6:4	98/98 ^e
2	1b	28	2:1	<5
3	1c	72	7:3	98/98 ^e
4	1c^f	83	7:3	98/97 ^e
5	14^{f,g}	21	7:3	90 ^e
6	14^f	trace	nd	nd
7	1c^{f,h}	trace	nd	nd
8	1c^{f,i}	10 ^j	7:3	nd
9	1c^{f,k}	88	7:3	98/97 ^e

^a General condition: enecarbamate **1a** (0.10 mmol), dibenzylazodicarboxylate (0.15 mmol), ethanethiol (0.10 mmol), 3Å molecular sieve (20 mg), and (*S*)-**1** (0.010 mmol), in CH₂Cl₂ (1.0 mL) at -45 °C for 16 h followed by addition of pyrazole **5a** (0.15 mmol) and irradiation with a blue LED light strips at rt under O₂ atmosphere for 16 h. ^b Yields refer to chromatographically pure products. ^c *dr* was determined by ¹H-NMR analysis and *anti*-diastereoselectivity assumed by analogy with our previous work, see the supporting information. ^d Enantiomeric excess was determined by HPLC analysis on chiral stationary phase. ^e Refers to (*2R*)-absolute configuration assumed by analogy with our previous work, see ref. 8c and 8d. ^f With 0.30 mmol of pyrazole **5a**. ^g With thioxanthone (0.020 mmol). ^h Reaction fully performed in the dark. ⁱ Reaction conducted under argon atmosphere. ^j Determined by ¹H-NMR using bromoform as internal standard. ^k Reaction performed on a 1.0 mmol scale of **2a** and 490 mg of **6a** was obtained.

Having established the optimal reaction conditions, we then probed the generality of this catalytic asymmetric β-amination/nucleophilic addition sequence with a variety of azoles and enecarbamates. As shown in Table 3, a range of pyrazoles bearing electron-donating or electron-withdrawing group at various positions on the heteroaromatic ring proved compatible and smoothly afforded the desired 1,2-diamide derivatives **6b-6d** in good yields and excellent enantioselectivities, although with somewhat moderate diastereoselectivities. The reaction of benzopyrazole afforded

the corresponding adduct **6e** in a high enantioselectivity and 3:1 dr. In addition, enecarbamates β -substituted with linear alkyl chains reacted efficiently to produce the desired products **6f-6j** with high enantioselectivities. The presence of a *tert*-butyldiphenylsilyl ether was well tolerated, which allowed to obtain the corresponding enantioenriched products (**6m-o**). The introduction of *iso*-propyl group at the β -position of the ene moiety gave **6k** in reduced yield. However, when the β -substituted cyclopropyl enecarbamate was used, the expected 1,2-diamine **6l** was isolated in higher yield. We also tested the enantioselective tandem three-component electrophilic amination of enecarbamates with other nucleophiles than azoles. While the reaction with trimethoxybenzene gave only trace of product, 7-bromoindole reacted to form the desired product **6p** with an excellent enantioselectivity and as a single diastereomer.

Table 3. Substrate scope of the enantioselective synthesis of 1,2-diamines.^{a-d}

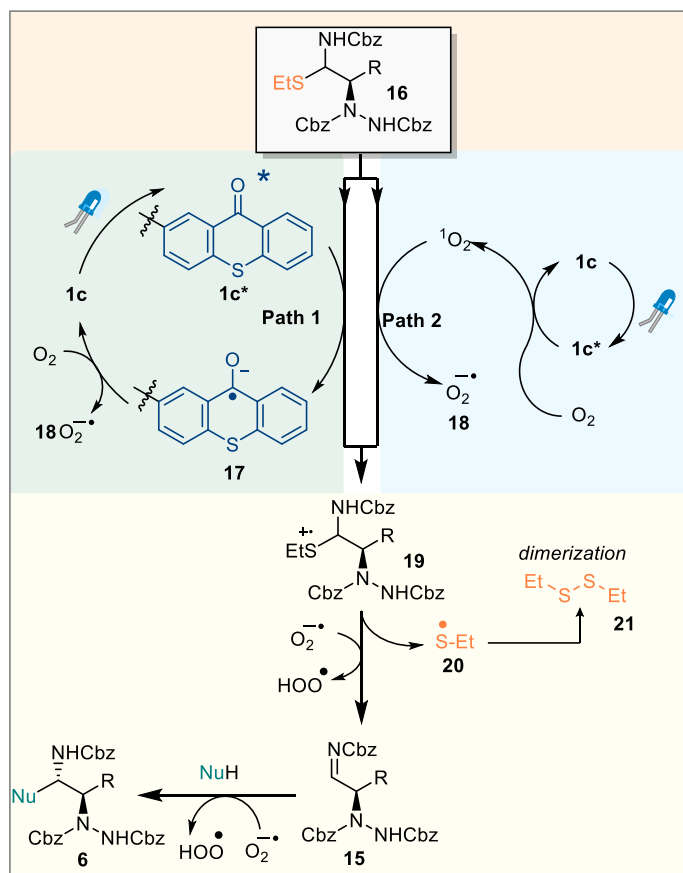


^a General condition: enecarbamate **1** (0.10 mmol), dibenzylazodicarboxylate (0.15 mmol), ethanethiol (0.10 mmol), 3Å molecular sieve (20 mg), and (*S*)-**1c** (0.010 mmol) in CH₂Cl₂ (1.0 mL) at -45 °C for 16 h followed by addition of **5** (0.30 mmol) with a blue LED light strips at rt under O₂ atmosphere for 16 h. ^b Yields refer to chromatographically pure products. ^c dr determined by ¹H-NMR analysis. ^d Enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

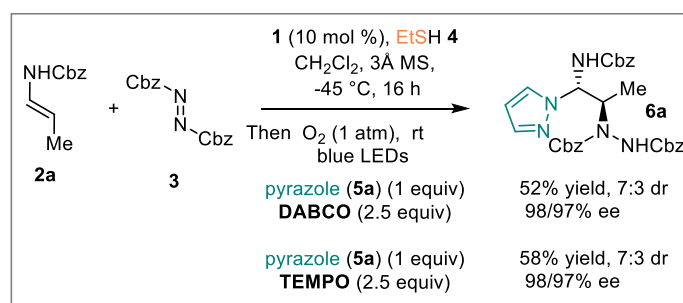
Based on other reports^{2,6,7c,11,22} and our previous studies,^{9b-e,18} we proposed a plausible reaction pathway for the photochemical C-S bonds cleavage as depicted in Scheme 4. After the electrophilic three-component thio-amination step, the resulting chiral α-carbamoylsulfide **16** would be oxidized by the excited chiral thioxanthone **1c***,^{2e,2h,6,7c,11,23} thereby generating the ketyl radical anion **17** and the sulfur radical cation **19**. A single electron transfer from the ketyl radical anion **17** to O₂ would

regenerate the thioxanthone photocatalyst **1c** and simultaneously produce the superoxide radical anion ($O_2^{\cdot-}$) **18**. In the meantime, generation of a positive charge on **S** in the radical cation **19** would weaken the C-S bond resulting in a mesolytic cleavage to produce the imine **15** and the thiyl radical **20** (the later would dimerize to form the disulfide **21**). Finally, the addition of the azole partner **5** onto the imine **15** and the subsequent hydrogen atom abstraction from $O_2^{\cdot-}$, would afford the enantioenriched diamine product **6**.²⁴ Interestingly, the conservation of enantioselectivity which is typically observed supports a dual activation mechanism in which the phosphoric acid **1c** would ensure a rapid attack of the azole **5** onto the imine **15** via the dual activation of both reaction partners according to the presumed hydrogen bonding TS-B (Scheme 3). The observations provided by the control experiments reported above (Table 2, entries 6 to 8) established that visible light, thioxanthone and oxygen were all essential which is in good agreement with the proposed mechanism. The fact that the reaction proceeded in merely 10% conversion in the absence of O_2 (entry 8) also suggests that no turnover was achievable without it. Hence, O_2 might be involved in the oxidative regeneration of the catalyst, the fast dimerization of the thiyl radical **20** disfavoring a classical radical propagation process. The on/off visible light irradiation experiment supports a non-radical-chain propagation process (see Table S2 and Figure S10, in the Supporting information).²⁵ However, another pathway involving the oxidation of the carbamoylsulfide **16** by singlet oxygen (generated by triplet-triplet annihilation between natural triplet oxygen and the triplet excited state of **1c**)^{7c} could also explain the formation of the sulfur radical cation **19** (Path 2). To distinguish between these two mechanisms, the C-S bond cleavage of **16** was carried out in the presence of the singlet oxygen quencher, DABCO, and the superoxide radical anion quencher, TEMPO (Scheme 5). In both cases, the desired product was isolated in substantial amount (Scheme 5, 52 and 58%,

respectively) but in lower yield when compared to standard condition (entry 4, Table 2). Thus, these results do not allow us to clearly discriminate between these two possible oxidation mechanisms.²⁶ Moreover, when we conducted fluorescence quenching experiments of **1c***, a nonlinear Stern–Volmer relationship between I_0/I and the concentrations of **16a** was observed (Figure S7 and S8 in the Supporting Information). If the quenching mechanism is mainly due to a dynamic process or a static process, a linear Stern–Volmer relationship is expected. In our case, we observed a higher fluorescence intensity with increased concentrations of **16a**, suggesting the formation of a supramolecular complex between the photocatalyst **1c** and compound **16a** that would enhance the fluorescence of **1c**. Accordingly, this prevents us from quantifying the efficiency of the photoinduced electron transfer in this system through Stern–Volmer analysis and thus we cannot conclude about the mechanism involved. Finally, the electrochemical oxidation potential of the α -carbamoylsulfide **16a** ($E_{P/2} = +1.56$ V vs SCE, Figure S6 in the Supporting Information) and that of the photoexcited state of the chiral thioxanthone **1c*** ($E_{1/2} = +1.24$ V vs. SCE)²⁷ suggest that a direct electron transfer is not thermodynamically favorable. Hence, it advocates that such a process most probably proceeds via the second pathway (Scheme 4, path 2).²⁸



Scheme 4. Considered reaction mechanisms



Scheme 5. Control experiments

CONCLUSION

In summary, we have developed a new family of chimeric chiral photocatalysts in which a BINOL-derived phosphoric acid embeds one or two thioxanthone dyes. We have demonstrated the efficiency of these new photocatalysts in a one pot three-component electrophilic amination

reaction followed by a photoinduced nucleophilic addition of various azoles. This assisted tandem process gives access to fully substituted 1,2-diamines in excellent enantioselectivities. Notably, the monosubstituted *C*₁-symmetric organo/photo catalyst exhibits a superior catalytic efficiency than the *C*₂-symmetric counterparts. Further studies and applications of these novel chiral catalysts are currently underway.

EXPERIMENTAL SECTION

Materials and General methods. All reactions requiring anhydrous conditions and inert atmosphere were carried out under argon atmosphere in dried glassware. Immersion coolers IMC-40 and TC100E fitted with a temperature probe and a flexible cooling tube were used to perform reactions at low temperature. The heat source employed for the synthesis of catalyst and substrates was an oil bath. Solvents were distilled by standard methods using the appropriate drying agent and stored over molecular sieves under argon. All other reagents were obtained from commercial suppliers and directly used unless otherwise noted. Flash column chromatography was carried out using 40-63 μm particle sized silica gel with air pressure. Analytical thin layer chromatography (TLC) plates (silica gel 60 F254) were visualized either with a UV lamp (254 nm), or by submersion in potassium permanganate, ninhydrine or iodine. Melting points were recorded using a melting point apparatus (Büchi B-540) and are uncorrected. Specific rotations for chiral compounds were recorded on a Perkin Elmer 141 using sodium D ray (589 nm) at room temperature in a 700- μL cell with a path length of 1 dm in CH_2Cl_2 . Infrared spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and the characteristic IR absorption frequencies are reported in cm^{-1} . Proton NMR (^1H) spectra were recorded on a Bruker Avance 500 MHz or 300 MHz and proton-decoupled carbon 13 NMR ($^{13}\text{C}\{^1\text{H}\}$) spectra were recorded at 75 MHz. NMR experiments were carried out in deuteriochloroform (CDCl_3) or in

trideuteroacetonitrile (CD₃CN). Proton-decoupled fluorine ¹⁹F NMR (¹⁹F{¹H}) spectra were recorded at 282 MHz. Proton-decoupled phosphorus ³¹P NMR (³¹P{¹H}) spectra were recorded at 202 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent as an internal reference (¹H: 7.26, ¹³C: 77.16 ppm for CHCl₃/CDCl₃ and ¹H: 1.94, ¹³C: 1.32 ppm for CHD₂CN/CD₃CN). The following abbreviations are used for the multiplicities: s: singlet; d: doublet; t: triplet; q: quadruplet; quint: quintuplet; m: multiplet or overlap of non-equivalent resonances; br s: broad singlet; app: apparent; rot: rotamer. Coupling constants (*J*) are reported in Hertz (Hz). High resolution mass spectra were determined on an AEI MS-9 using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer. Enantiomeric excesses were determined by high performance liquid chromatography (HPLC) equipped with diode array UV detectors, using Chiralpak® AD-H, OD-H, AS-H, OJ-H, IA and IB columns. Reactions were irradiated using a ruban of Flexled INSPIRE LED lamp (45 LEDs, 7.2 W, λ_{max} = 458 nm; commercial supplier: Linda Zhu Yichun Yaozhou Electronic Technology Co; purchased from Leroy Merlin) without any filters, and a cooling fan was placed over the reaction vessels to keep temperature at 25°C. The spectral distribution and intensity of the lamp is shown in Figure S9 (in the Supporting Information). The distance from the light source to the irradiation vessel is 5 cm. The round bottom flask was made of borosilicate glass. Enecarbamate starting materials **2a-2e** were prepared according to literature procedure.²⁹

Preparation of Photocatalyst (1a):

(R)-2,2'-(2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)bis(9H-thioxanthen-9-one) (9). In an 100 mL round bottom flask equipped with a stir bar and a reflux condenser were placed **7¹³** (1 equiv, 2.0 mmol, 0.8 g), 2-bromo-thioxanthone **8¹⁴** (2.3 equiv, 4.6 mmol, 1.33 g), K₂CO₃ (6 equiv, 12 mmol, 1.7 g) and Pd(PPh₃)₄ (0.1 equiv, 0.01 mmol, 0.23 g) under argon. Then, a degassed 10:1 mixture of THF/H₂O was added through the condenser (56 mL). The resulting mixture was vigorously stirred and refluxed for 12 h under an argon atmosphere. The mixture was cooled to room temperature, diluted with

brine and CH₂Cl₂ (50 mL) and transferred into a separatory funnel. The layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using Petroleum Ether (PE)/EtOAc as eluent (gradient from 10:1 to 5:1) to afford **9** as a yellow solid (859 mg, 1.1 mmol, 57%). [α]_D²⁵ -75.0 (*c* 1.0, CH₂Cl₂); IR (neat) ν (cm⁻¹): 1736, 1636, 1591, 1493, 1475, 1457, 1437, 1405, 1388, 1353, 1321, 1283, 1264, 1246, 1213, 1163, 1148, 1122, 1069, 1040, 1017, 998, 960, 928, 892; mp: 102-109 °C; ¹H{¹³C} NMR (300 MHz, CDCl₃) δ 9.03 (d, *J* = 0.9 Hz, 2H), 8.68 (d, *J* = 8.0 Hz, 2H), 8.19 – 8.08 (m, 4H), 7.97 (d, *J* = 8.1 Hz, 2H), 7.71 – 7.57 (m, 6H), 7.54 – 7.41 (m, 4H), 7.37 – 7.23 (m, 3H), 3.23 (s, 6H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 180.0, 153.9, 137.4, 137.2, 136.4, 134.0, 133.8, 133.5, 132.3, 131.0, 130.9, 130.0, 129.9, 129.5, 129.3, 128.3, 126.8, 126.4, 126.1, 125.9, 125.8, 125.3, 60.8; HRMS (ESI/Q-TOF) *m/z*: [M+H]⁺ Calcd for C₄₈H₃₁O₄S₂ [M+H]⁺ 735.1683, Found 735.1694.

(R)-2,2'-((4R)-4-hydroxy-4-oxidodiphthalto[2,1-d:1',2'-f][1,3,2]dioxaphosphine-2,6-diyl)bis(9H-thioxanthen-9-one) (1a). **9** (1 equiv, 1.24 mmol, 0.91 g) was dissolved in dry CH₂Cl₂ (24 mL) in a 50 mL dry round bottom flask covered by aluminum foil and cooled at -78 °C. BBr₃ (3 equiv, 1M in CH₂Cl₂, 3.7 mmol, 3.7 mL) was added slowly. After complete addition, the mixture was stirred for 30 min at -78 °C and for 4 h at room temperature. Upon completion (monitored by TLC), the mixture was cooled to 0 °C and carefully quenched with water (20 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic phases were concentrated under reduced pressure. The residue (0.88 g) was weighed in a 2.5 mL dry round bottom flask. Pyridine (0.2 mL) and freshly distilled POCl₃ (2.0 equiv, 2.48 mmol, 0.23 mL) were added at room temperature under argon. The mixture was stirred for 12 h at 60 °C. Upon completion (monitored by TLC), the mixture was cooled to room temperature, water (0.25 mL) was added and the reaction mixture was stirred under reflux for 3 h. Then aq. HCl (6M, 1 mL) was added. The aqueous phase was extracted with CH₂Cl₂ (3x20 mL). The combined organic phases were concentrated under reduced pressure, and the residue was purified by

flash column chromatography on silica gel using CH₂Cl₂/MeOH as eluent (10:1). The obtained solid was then taken up in a mixture of aq. HCl (6M)/dioxane (1:1, 30 mL) and stirred at 60 °C until complete solubilization. The mixture was then extracted with CH₂Cl₂ (3 x 20 mL). The combined organic extracts were concentrated under vacuum to afford **(R)-1a** as a yellow solid (0.82 g, 1.1 mmol, 86%). [α]_D²⁵ +176.0 (*c* 1.0, CH₂Cl₂); IR (neat) ν (cm⁻¹): 1633, 1589, 1496, 1477, 1460, 1438, 1420, 1391, 1318, 1263, 1186, 1078, 1018, 947, 883, 864, 825; mp: 326-338 °C; ¹H{¹³C} NMR (300 MHz, DMSO-*d*₆) δ 8.79 (s, 2H), 8.68 – 8.61 (m, 2H), 8.52 (d, *J* = 7.9 Hz, 2H), 8.27 (s, 2H), 8.16 (d, *J* = 8.2 Hz, 2H), 7.93 (dd, *J* = 16.9, 8.2 Hz, 4H), 7.81 (t, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H). ¹³C{¹H} NMR (75 MHz, DMSO-*d*₆) δ 178.9, 151.3, 137.4, 136.5, 135.2, 134.4, 133.9, 133.0, 130.2, 129.8, 129.1, 128.7, 128.4, 128.3, 128.2, 126.8, 126.6, 126.5, 126.2, 124.0, 123.1, 115.0. ³¹P{¹H} NMR (202 MHz, DMSO-*d*₆) δ 3.43; HRMS (ESI/Q-TOF) *m/z*: [M - H]⁻ Calcd for C₄₆H₂₄O₆PS₂ 767.0752; Found 767.0758.

Preparation of Photocatalyst (1b):

(S)-2,2'-((2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(ethyne-2,1-diyl))bis(9H-thioxanthen-9-one) (11). A 250 mL round bottom flask was charged with **(S)-10** (1 equiv, 2 mmol, 0.84 g), 2-bromo-thioxanthone **8**¹⁴ (2.5 equiv, 5.21 mmol, 1.45 g), Pd(PPh₃)₄ (0.1 equiv, 0.2 mmol, 0.23 g), CuI (0.2 equiv, 0.4 mmol, 0.076 g) and purged with argon. A mixture of freshly distilled and degassed Et₃N/THF (1:1, 100 mL) was added and the reaction was stirred for 8 h at 60 °C. After cooling down to room temperature, diethyl ether (50 mL) was added. The heterogeneous mixture was filtered through a pad of Celite, washing with diethyl ether (50 mL). The filtrate was concentrated in vacuum, and the resulting residue was purified by flash column chromatography on silica gel using PE/EtOAc as eluent (gradient from 10:1 to 5:1) to give **(S)-11** as a yellow solid (859 mg, 1.10 mmol, 21%). [α]_D²⁵ -44 (*c* 1.0, CH₂Cl₂); IR (neat) ν (cm⁻¹): 1638, 1589, 1470, 1437, 1396, 1317, 1283, 1264, 1226, 1202, 1155, 1119, 1096, 1076, 1056, 1033, 984, 968, 911, 892; mp: 137-164 °C; ¹H{¹³C} NMR (300 MHz,

CDCl₃) δ 8.80 (d, *J* = 1.5 Hz, 2H), 8.62 (d, *J* = 7.9 Hz, 2H), 8.29 (s, 2H), 7.90 (d, *J* = 8.1 Hz, 2H), 7.75 (dd, *J* = 8.4, 1.7 Hz, 2H), 7.67 – 7.41 (m, 10H), 7.33 (dd, *J* = 13.9, 7.4 Hz, 4H), 5.24 (d, *J* = 6.1 Hz, 2H), 5.01 (d, *J* = 6.1 Hz, 2H), 2.58 (s, 6H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 179.2, 153.1, 137.3, 136.8, 134.52, 134.48, 134.0, 132.9, 132.5, 130.4, 130.0, 129.2, 129.1, 127.7, 127.5, 126.6 (2 peaks overlapping), 126.2, 126.1, 125.9, 125.7, 121.5, 116.9, 99.0, 92.6, 87.9, 56.2; HRMS (ESI/Q-TOF) *m/z*: [M + Na]⁺ Calcd for C₅₄H₃₄O₆S₂Na 865.1695; Found 865.1702.

(S)-2,2'-((2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(ethyne-2,1-diyl))bis(9H-thioxanthen-9-one) (22). Hydrochloric acid (24 equiv, 12M in methanol, 1.5 mmol, 0.12 mL) was added to a solution of **(S)-11** (1 equiv, 0.06 mmol, 51 mg) in dioxane (2 mL) and heated at 60 °C for 12 h. After cooling down to room temperature, water (5 mL) and CH₂Cl₂ (5 mL) were added. The phases were separated and the organic phase was extracted with CH₂Cl₂ (2 x 5 mL). The combined organic phases were washed with aq. NaHCO₃ (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using PE/EtOAc as eluent (gradient 5:1 to 1:1) to afford **(S)-22** as a yellow solid (0.041 g, 0.057 mmol, 95%) which was used in the next step without further purification. [*α*]_D²⁵ –60 (*c* 1.0, CH₂Cl₂); IR (neat) *ν* (cm⁻¹): 1639, 1588, 1575, 1470, 1436, 1396, 1319, 1286, 1265, 1190, 1146, 1120, 1074, 1019, 967, 937, 915, 887, 873; mp: 188-227 °C; ¹H{¹³C} NMR (300 MHz, DMSO-*d*₆) δ 9.14 (s, 2H), 8.69 (s, 2H), 8.47 (d, *J* = 10.4 Hz, 2H), 8.35 (s, 2H), 8.00 – 7.92 (m, 5H), 7.89 – 7.87 (m, 2H), 7.83 – 7.82 (m, 2H), 7.65 – 7.52 (m, 3H), 7.42 – 7.21 (m, 4H), 6.95 (d, *J* = 8.0 Hz, 2H); ¹³C{¹H} NMR (75 MHz, DMSO-*d*₆) δ 178.2, 136.8, 136.2, 134.8, 134.1, 133.5, 133.2, 131.8, 129.2, 128.5, 128.2, 128.0, 127.9, 127.3, 127.2, 127.1, 126.7, 124.2, 123.4, 121.2, 115.7, 113.0, 92.4, 88.3; HRMS (ESI/Q-TOF) *m/z*: [M + H]⁺ Calcd for C₅₀H₂₇O₄S₂ 755.1351; Found 755.1358.

(S)-2,2'-((4-hydroxy-4-oxidodiphthalto[2,1-d':1',2'-f][1,3,2]dioxaphosphine-2,6-diyl)bis(ethyne-2,1-diyl))bis(9H-thioxanthen-9-one) (1b). To a stirred suspension of **(S)-22** (1 equiv, 0.04 mmol, 0.03

g) in distilled pyridine (0.27 mL) was added dropwise distilled POCl₃ (2.0 equiv, 0.08 mmol, 7.5 μL) at room temperature. The solution mixture was heated at 60 °C for several hours, monitoring the evolution by TLC. After cooling down to room temperature, water (0.35 mL) was added and the reaction mixture was stirred under reflux for 3 h. Then aq. HCl (6M, 1.5 mL) was added and the mixture was further heated at reflux with vigorous stirring for 1 h. The dark reaction mixture was then extracted with CH₂Cl₂ (3×20 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using CH₂Cl₂/MeOH as eluent (gradient from 20:1 to 10:1). The obtained compound was taken up in CH₂Cl₂ (10 mL) and vigorously washed with aq. HCl (4M, 3 x 10 mL). The organic layer was concentrated under reduced pressure to afford a crude residue, which was co-evaporated several times with toluene, and finally dried under high vacuum at 50 °C for several hours to afford (S)-1b as a yellow solid (0.025 g, 0.03 mmol, 78%). [α]_D²⁵ +168 (c 1.0, CH₂Cl₂); IR (neat) ν (cm⁻¹): 1636, 1590, 1472, 1438, 1422, 1399, 1264, 1207, 1162, 1096, 1034, 962, 918, 892, 837; mp: 235-245 °C; ¹H{¹³C} NMR (300 MHz, DMSO-*d*₆) δ 8.62 (s, 2H), 8.55 (s, 2H), 8.48 (d, *J* = 7.9 Hz, 2H), 8.12 (d, *J* = 8.0 Hz, 2H), 8.02 – 7.73 (m, 8H), 7.58 (dt, *J* = 15.0, 7.4 Hz, 4H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 179.0, 146.3, 146.2, 137.0, 135.0, 134.6, 132.6, 132.2, 132.0, 131.7, 131.0, 129.8, 128.6, 128.3, 128.2, 127.3, 127.0, 126.12, 126.0, 125.8, 121.8, 121.2, 116.2, 93.8, 85.7; ³¹P{¹H} NMR (202 MHz, CDCl₃) δ 3.68; HRMS (ESI/Q-TOF) *m/z*: [M + H]⁺ Calcd for C₅₀H₂₆O₆S₂P 817.0908; Found 817.0900.

Preparation of Photocatalyst (1c):

(R)-2-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalen]-3-yl)-9H-thioxanthen-9-one (13). To a stirred solution of **(R)-12** (1 equiv, 3.0 mmol, 1.12 g) in THF (15 mL) was added *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 3.3 mmol, 1.32 mL) at 0 °C. After stirring for 30 min, freshly distilled B(OMe)₃ (1.3 equiv, 4 mmol, 440 μL) was added and the reaction mixture was stirred for 30 min at 0 °C. Aq. HCl (4M, 5 mL) was added and the reaction mixture was stirred for 30 min at room temperature. Water (10 mL) was

added and the reaction mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated on a rotary evaporator. The residue was placed in a 250 mL round bottom flask and dried under high vacuum for 2 h. Then a magnetic stir bar, 2-bromo-thioxanthone **8**¹⁴ (1.5 equiv, 4.5 mmol, 1.3 g), K₂CO₃ (6 equiv, 18 mmol, 2.5 g) and Pd(PPh₃)₄ (0.1 equiv, 0.3 mmol, 0.35 g) were added. The flask was purged with argon. A mixture of THF/H₂O (9:1, 84 mL, freshly degassed by bubbling argon for 15 min in a ultrasonic bath) was added. The reaction mixture was heated for 12 h at 75 °C. After cooling down to room temperature, the reaction mixture was extracted by CH₂Cl₂ (3x50 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using PE/EtOAc as eluent (gradient from 15:1 to 5:1) to afford **(R)-13** as a yellow solid (0.79 g, 1.35 mmol, 45% over 2 steps). [α]_D²⁵ +88 (c 1.0, CH₂Cl₂); IR (neat) ν (cm⁻¹): 1635, 1591, 1508, 1471, 1317, 1261, 1241, 1148, 1069, 1032, 1009, 970, 922, 795; mp: 120-140 °C; ¹H{¹³C} NMR (300 MHz, CDCl₃): δ 8.90 (d, *J* = 1.9 Hz, 1H), 8.58 (d, *J* = 7.8 Hz, 1H), 8.07 – 7.97 (m, 2H), 7.93 – 7.75 (m, 3H), 7.55 (ddd, *J* = 7.7, 7.3, 2.6 Hz, 3H), 7.46 – 7.25 (m, 3H), 7.25 – 7.16 (m, 4H), 7.15 – 7.00 (m, 1H), 5.07 (dd, *J* = 23.9, 6.9 Hz, 2H), 4.26 (dd, *J* = 14.4, 5.6 Hz, 2H), 3.18 (s, 3H), 2.26 (s, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 179.9, 153.0, 150.8, 137.6, 137.2, 136.2, 134.1, 132.3, 131.3, 131.1, 130.6, 130.3, 130.0, 129.8, 129.7, 129.3, 128.4, 128.2, 127.9, 127.4, 126.7, 126.6, 126.4, 126.1, 125.9, 125.7, 125.4, 124.3, 124.2, 124.0, 120.8, 117.8, 116.6, 98.8, 95.0, 56.2, 56.0; HRMS (ESI/Q-TOF) *m/z*: [M + H]⁺ Calcd for C₃₇H₂₉O₅S 585.1736; Found 585.1731.

(R)-2-(2,2'-dihydroxy-[1,1'-binaphthalen]-3-yl)-9H-thioxanthen-9-one (23). To a stirred solution of **(R)-13** (1 equiv, 1.35 mmol, 0.8 g) in dioxane (45 mL) was slowly added HCl (12 M in MeOH, 24 equiv, 2.7 mL). After complete addition, the resulting suspension was stirred at 60 °C overnight. Upon completion (monitored by TLC), water (25 mL) was added at room temperature. The aqueous phase was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic phases were washed with aq. NaHCO₃ (50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to afford **(R)-23** (0.64

g, 1.3 mmol, 95%) which was used in the next step without further purification. $[\alpha]_{\text{D}}^{25} +123$ (c 1.0, CH_2Cl_2); IR (neat) ν (cm^{-1}): 1619, 1588, 1501, 1436, 1381, 1326, 1263, 1175, 1122, 1078, 1014, 965, 894; mp: 173-180 °C; $^1\text{H}\{^{13}\text{C}\}$ NMR (500 MHz, CD_3CN): δ 9.09 (d, $J = 1.9$ Hz, 1H), 8.79 (d, $J = 8.0$ Hz, 1H), 8.36 (s, 1H), 8.32 (dd, $J = 8.4, 2.1$ Hz, 1H), 8.28 – 8.14 (m, 3H), 8.07 – 7.92 (m, 3H), 7.85 – 7.75 (m, 1H), 7.66 – 7.49 (m, 6H), 7.39 (d, $J = 8.3$ Hz, 1H), 7.29 – 7.15 (m, 2H), 6.80 (s, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 179.9, 152.9, 150.2, 137.2, 136.5, 136.1, 133.8, 133.4, 133.1, 132.3, 131.8, 131.6, 131.4, 130.5, 130.0, 129.5, 129.2, 129.1, 128.6, 128.4, 127.7, 127.6, 126.4, 126.1, 125.8, 124.6, 124.14 (2 peaks overlapping), 124.11 (2 peaks overlapping), 117.9, 112.0, 110.8; HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{33}\text{H}_{21}\text{O}_3\text{S}$ 497.1211; Found 497.1214.

2-((4R)-4-hydroxy-4-oxidodinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphopin-2-yl)-9H-thioxanthen-9-one (1c). To a stirred suspension of (**R**)-**23** (1 equiv, 0.68 mmol, 0.34 g) in distilled pyridine (4.5 mL), was added dropwise distilled POCl_3 (2.0 equiv, 1.36 mmol, 0.12 mL). The resulting mixture was heated at 60 °C for several hours, monitoring the evolution by TLC. After 12 h, the mixture was cooled down to room temperature, H_2O (6 mL) was added and the reaction mixture was stirred under reflux for 3 h. Then, aq. HCl (6M, 22 mL) was added and the reaction mixture was heated under reflux with vigorous stirring for 1 h. The dark reaction mixture was then extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using $\text{CH}_2\text{Cl}_2/\text{MeOH}$ as eluent (gradient from 20:1 to 10:1). The obtained compound was then taken up in CH_2Cl_2 (20 mL) and vigorously washed with aq. HCl (4M, 3 x 20 mL). The organic layer was concentrated under reduced pressure to afford a crude residue, which was co-evaporated several times with toluene, and finally dried under high vacuum at 50 °C for several hours to afford (**R**)-**1c** as a yellow solid (0.3 g, 0.58 mmol, 85%). $[\alpha]_{\text{D}}^{25} -62$ (c 1.0, CH_2Cl_2); IR (neat) ν (cm^{-1}): 1634, 1590, 1509, 1460, 1420, 1392, 1320, 1284, 1262, 1216, 1191, 1068, 1010, 977, 947, 892; mp: 272-284 °C; $^1\text{H}\{^{13}\text{C}\}$ NMR (300 MHz, $\text{DMSO}-d_6$): δ 8.79 (t, $J = 7.8$ Hz, 1H), 8.53 (d, $J = 7.8$ Hz, 1H), 8.41 – 8.30 (m, 2H), 8.20 (dd, $J = 8.3,$

5.3 Hz, 2H), 8.11 (d, $J = 8.2$ Hz, 1H), 8.00 (d, $J = 8.5$ Hz, 1H), 7.92 (d, $J = 7.9$ Hz, 1H), 7.82 (t, $J = 7.6$ Hz, 1H), 7.68 – 7.59 (m, 1H), 7.54 (dd, $J = 8.7, 5.0$ Hz, 2H), 7.40 (t, $J = 7.7$ Hz, 2H), 7.34 – 7.11 (m, 3H). ^{13}C $\{^1\text{H}\}$ NMR (75 MHz, DMSO- d_6): δ 179.3, 148.5, 148.4, 145.9, 145.8, 137.0, 136.4, 135.0, 133.6, 133.0, 132.3, 132.1, 131.5, 131.4 (2 peaks overlapping), 131.3, 130.4, 129.7, 129.3, 129.1, 128.9, 128.7, 127.5, 127.4, 127.3, 127.2, 126.9, 126.6, 126.5, 126.3, 125.8, 122.8, 121.9; $^{31}\text{P}\{^1\text{H}\}$ NMR (202 MHz, CDCl_3): δ 3.71; HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{33}\text{H}_{20}\text{O}_5\text{PS}$ 559.0769; Found 559.0778.

General procedure for the enantioselective synthesis of azoles substituted vicinal diamines:

Under argon, the (*E*)-enecarbamate **2** (0.1 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.4 mL) in a flame-dried flask containing activated powdered 3Å molecular sieves (20 mg). The solution was stirred at room temperature for 10 min before being cooled to -45 °C and stirred for additional 10 min. Dibenzyl azodicarboxylate (44.7 mg, 0.15 mmol, 1.5 equiv) dissolved in CH_2Cl_2 (0.3 mL) was added and the reaction mixture was stirred for 10 min. Then EtSH (7 μL , 0.1 mmol, 1 equiv) and finally the chiral catalyst **1** (0.01 mmol, 0.1 equiv) were added as a solution in CH_2Cl_2 (0.3 mL) and the reaction mixture was stirred for 16 h at -45 °C. Then, the suitable azole nucleophile was added (0.3 mmol, 3 equiv) and the reaction was stirred at room temperature under an O_2 atmosphere and blue light irradiation for 16 h. Completion of the reaction was checked by TLC. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (PE/EtOAc 8:3).

Note: The presence of the Cbz groups create rotamers for the compounds **6**. The NMR conduct at room temperature give spectra with broad signals. Running the NMR in deuterated acetonitrile (CD_3CN) instead of CDCl_3 furnish acceptable spectra.

Dibenzyl 1-((1*S*,2*R*)-1-(((benzyloxy)carbonyl)amino)-1-(1*H*-pyrazol-1-yl)propan-2-yl)hydrazine-1,2-dicarboxylate (6a). Following the general procedure, **6a** was obtained from the corresponding (*E*)-

enecarbamate **2a**^{8d} (19.1 mg, 0.1 mmol) and pyrazole (20 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6a** as a colourless oil (47 mg, 7:3 *dr*, 98/97% *ee*) in 83% yield. *dr* was determined by ¹H NMR via integration of the singlets at 6.21 and 6.24 ppm; [α]_D²⁵ –6.5 (*c* 1.0, CH₂Cl₂); IR (neat) ν (cm⁻¹): 1699, 1498, 1402, 1299, 1215, 1041, 1016, 733, 695; ¹H{¹³C} NMR (500 MHz, CD₃CN) mixture of diastereomers and rotamers: δ 7.91 – 6.73 (m, 19H), 6.24 (s, 0.18H, major diastereoisomer), 6.21 (s, 0.45H, minor diastereoisomer), 5.82 (s, 1H), 5.30 – 4.60 (m, 7H), 1.30 – 1.12 (m, 2H), 0.90 – 0.55 (m, 1H); ¹³C{¹H} NMR (126 MHz, CDCl₃) mixture of diastereoisomers and rotamers: δ 157.2, 156.7, 155.3, 149.7, 140.0, 139.1, 136.4, 136.1, 135.9, 128.2, 128.2, 128.1, 127.9, 127.8, 127.7, 127.5, 127.2, 117.0, 105.2, 140.9, 69.5, 69.4, 69.2, 67.6, 67.2, 67.0, 66.8, 66.7, 66.4, 66.2, 56.9, 55.8, 55.6, 13.7, 13.2, 12.6; HRMS (ESI/Q-TOF) *m/z*: [M + Na]⁺ Calcd for C₃₀H₃₁N₅O₆Na 580.2167; Found 580.2168; enantiomeric excesses were determined by HPLC (Chiralpak IA, Heptane/*i*-PrOH = 85:15, flow rate = 1.0 mL.min⁻¹, 214 nm): major diastereoisomer: *t*₁ = 31.8 min (major enantiomer), *t*₄ = 86.9 min (minor enantiomer); minor diastereoisomer: *t*₂ = 39.2 min (major enantiomer), *t*₃ = 76.4 min (minor enantiomer).

Dibenzyl 1-((1*S*,2*R*)-1-(((benzyloxy)carbonyl)amino)-1-(3,5-dimethyl-1*H*-pyrazol-1-yl)propan-2-yl)hydrazine-1,2-dicarboxylate (6b). Following the general procedure, **6b** was obtained from the corresponding (*E*)-enecarbamate **2a** (19.1 mg, 0.1 mmol) and 3,5-dimethylpyrazole (28.8 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6b** as a colorless oil (53 mg, 7:3 *dr*, 98/98% *ee*) in 91% yield. *dr* was determined by ¹H NMR via integration of the singlets at 5.76 and 5.69 ppm; [α]_D²⁵ –9 (*c* 1.0, CH₂Cl₂); IR (neat) ν (cm⁻¹): 1719, 1498, 1455, 1407, 1306, 1027, 738, 696; ¹H{¹³C} NMR (500 MHz, CD₃CN) mixture of diastereoisomers and rotamers: δ 7.81 (s, 1H), 7.34 – 7.23 (m, 17H), 5.76 (s, 0.7H, major diastereoisomer), 5.69 (s, 0.3H, minor diastereoisomer), 5.12 – 5.01 (m, 7H), 2.31 – 1.94 (m, 6H), 2.31 – 2.11 (m, 6H), 1.28 – 0.88 (m, 3H); ¹³C{¹H} NMR (126 MHz, CDCl₃) mixture of diastereoisomers and

rotamers: δ 156.6, 156.1, 155.6, 149.7, 149.3, 136.0, 135.6, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 105.6, 68.8, 68.6, 68.2, 67.9, 68.0, 67.5, 67.3, 65.3, 65.0, 13.7, 13.5, 10.9; HRMS (ESI/Q-TOF) m/z : $[M + H]^+$ Calcd for $C_{32}H_{36}N_5O_6$ 586.2666; Found 586.2682; enantiomeric excesses were determined by HPLC (Chiralpak IA, Heptane/*i*-PrOH = 95:5, flow rate = 1.0 mL.min⁻¹, 214 nm): major diastereoisomer: $t_1 = 44.0$ min (minor enantiomer), $t_2 = 47.0$ min (major enantiomer); minor diastereoisomer: $t_3 = 52.6$ min (major enantiomer), $t_4 = 70.5$ min (minor enantiomer).

Dibenzyl 1-((2*R*)-1-(((benzyloxy)carbonyl)amino)-1-(4-nitro-1*H*-pyrazol-1-yl)propan-2-yl)hydrazine-1,2-dicarboxylate (6c). Following the general procedure, **6c** was obtained from the corresponding (*E*)-enecarbamate **2a** (19.1 mg, 0.1 mmol) and 4-nitro-1*H*-pyrazole (34.0 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6c** as a colorless oil (57 mg, 1:1 *dr*, 99/99% *ee*) in 95% yield; *dr* was determined by ¹H NMR via integration of the multiplets at 1.3 and 1.0 ppm; $[\alpha]_D^{25} -5$ (*c* 1.0, CH₂Cl₂); IR (neat) ν (cm⁻¹): 1704, 1510, 1455, 1406, 1304, 1258, 1226, 1024, 872, 817, 797, 752; ¹H{¹³C} NMR (500 MHz, CD₃CN) mixture of diastereoisomers and rotamers: δ 8.58 (m, 1H), 8.27-8.13 (m, 1H), 8.01-7.79 (m, 1H), 7.48 – 7.05 (m, 16H), 6.05 – 5.75 (m, 7H), 5.23 – 4.60 (m, 7H), 1.32 – 1.31 (m, 1.5H diastereoisomer 1), 1.03 – 0.91 (m, 1.5H, diastereoisomer 2); ¹³C{¹H} NMR (75 MHz, CDCl₃) mixture of diastereoisomers and rotamers: δ 156.9, 156.6, 156.0, 136.8, 135.8, 135.2, 131.9, 129.2, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 71.3, 68.7, 68.4, 68.2, 68.0, 67.7, 56.2, 14.3; HRMS (ESI/Q-TOF) m/z : $[M + Na]^+$ Calcd for $C_{30}H_{30}N_6O_8Na$ 625.1997; Found 625.1986; enantiomeric excesses were determined by HPLC (Chiralpak IA, Heptane/*i*-PrOH = 85:15, flow rate = 1.0 mL.min⁻¹, 214 nm): diastereoisomer 1: $t_1 = 39.0$ min (major enantiomer), $t_2 = 45.4$ min (minor enantiomer); minor diastereoisomer 2: $t_3 = 55.0$ min (major enantiomer), $t_4 = 70.8$ min (minor enantiomer).

Dibenzyl 1-((2*R*)-1-(((benzyloxy)carbonyl)amino)-1-(3-(trifluoromethyl)-1*H*-pyrazol-1-yl)propan-2-yl)hydrazine-1,2-dicarboxylate (6d). Following the general procedure, **6d** was obtained from the

corresponding (*E*)-enecarbamate **2a** (19.1 mg, 0.1 mmol) and 3-(trifluoromethyl)pyrazole (40.8 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6d** as a colorless oil (54 mg, 1:1 *dr*, 99/99% *ee*) in 87% yield; *dr* was determined by ^{19}F NMR via integration of the singlets at -61.8 and -62.0 ppm; $[\alpha]_{\text{D}}^{25}$ -27 (*c* 1.0, CH_2Cl_2); IR (neat) ν (cm^{-1}): 1702, 1525, 1455, 1409, 1298, 1258, 1218, 1131, 1026, 967, 794, 739; $^1\text{H}\{^{13}\text{C}\}$ NMR (500 MHz, CDCl_3) mixture of diastereoisomers and rotamers: δ 7.64–7.49 (m, 1H), 7.33–7.26 (m, 14H), 7.13 (s, 1H), 7.00–6.53 (m, 1H), 6.84–6.40 (m, 1H), 6.00–5.60 (m, 1H), 5.29–4.80 (m, 7H), 1.32–1.37 (m, 1.4H), 1.27–1.02 (m, 1.6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) mixture of diastereoisomers and rotamers: δ 156.4, 155.9, 155.5, 135.6, 135.4, 134.8, 131.7, 128.8, 128.7, 128.6, 128.4, 128.3, 127.7, 122.2, 104.5, 70.8, 70.4, 69.7, 68.6, 68.3, 68.0, 67.8, 67.1, 56.6, 14.2, 13.7; $^{19}\text{F}\{^1\text{H}\}$ NMR (282 MHz, CDCl_3) δ -61.8 (s, 1.5F, diastereoisomer 1), -62.0 (s, 1.5F, diastereoisomer 2); HRMS (ESI/Q-TOF) *m/z*: $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{31}\text{H}_{31}\text{F}_3\text{N}_5\text{O}_6$ 626.2189; Found 626.2221; enantiomeric excesses were determined by HPLC (Chiralpak IA, Heptane/*i*-PrOH = 85:15, flow rate = 1.0 mL.min $^{-1}$, 214 nm): minor diastereoisomer: t_1 = 13.01 min (major enantiomer), t_3 = 20.13 min (minor enantiomer); major diastereoisomer: t_2 = 14.7 min (minor enantiomer), t_4 = 34.7 min (major enantiomer).

Dibenzyl 1-((1*S*,2*R*)-1-(((benzyloxy)carbonyl)amino)-1-(1*H*-indazol-1-yl)propan-2-yl)hydrazine-1,2-dicarboxylate (6e). Following the general procedure, **6e** was obtained from the corresponding *E*-enecarbamate **2a** (19.1 mg, 0.1 mmol) and indazole (35.4 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6e** as a colorless oil (52 mg, 3:1 *dr*, 99/92% *ee*) in 85% yield; *dr* was determined by ^1H NMR via integration of the singlets at 8.02 and 7.99 ppm; $[\alpha]_{\text{D}}^{25}$ -15 (*c* 1.0, CH_2Cl_2); IR (neat) ν (cm^{-1}): 1701, 1618, 1498, 1455, 1406, 1294, 1216, 1155, 1118, 1026; $^1\text{H}\{^{13}\text{C}\}$ NMR (500 MHz, CD_3CN) mixture of diastereoisomers and

rotamers: δ 8.02 (s, 0.7H, major diastereoisomer), 7.99 (s, 0.3H, minor diastereoisomer), 7.79 – 7.52 (m, 2H), 7.36 – 7.28 (m, 16H), 7.18 – 7.14 (m, 1H), 7.09 (m, 1H), 6.93 (m, 1H), 6.30 – 6.12 (m, 1H), 5.30 – 4.75 (m, 7H), 1.37 – 1.27 (m, 2H), 0.91 – 0.86 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) mixture of diastereoisomers and rotamers: δ 156.6, 156.3, 155.8, 135.4, 135.0, 128.5, 128.4, 128.2, 128.1, 127.8, 127.6, 127.4, 126.9, 126.8, 123.8, 122.3, 121.4, 121.2, 121.0, 120.6, 117.7, 109.9, 109.1, 68.6, 67.9, 67.3, 67.0, 56.4, 14.1; HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{34}\text{H}_{34}\text{N}_5\text{O}_6$ 608.2509; Found 608.2543; enantiomeric excesses were determined by HPLC (Chiralpak IA, Heptane/*i*-PrOH = 80:20, flow rate = 1.0 mL.min⁻¹, 214 nm): major diastereoisomer: t_1 = 37.6 min (minor enantiomer), t_3 = 80.9 min (major enantiomer); minor diastereoisomer: t_2 = 61.0 min (major enantiomer), t_4 = 98.7 min (minor enantiomer).

Dibenzyl 1-((1*S*,2*R*)-1-(((benzyloxy)carbonyl)amino)-1-(1*H*-pyrazol-1-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6f). Following the general procedure, **6f** was obtained from the corresponding (*E*)-enecarbamate **2b** (21.9 mg, 0.1 mmol) and pyrazole (20 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6f** as a colorless oil (44 mg, 7:3 *dr*, 99/99 % *ee*) in 76% yield; *dr* was determined by ^1H NMR via integration of the singlets at 6.22 and 6.10 ppm; $[\alpha]_{\text{D}}^{25}$ -5 (*c* 1.0, CH_2Cl_2); IR (neat) ν (cm⁻¹): 1704, 1498, 1455, 1400, 1258, 1218, 1145, 1040, 1027, 917, 801; $^1\text{H}\{^{13}\text{C}\}$ NMR (300 MHz, CDCl_3) mixture of diastereoisomers and rotamers: δ 7.76 – 6.93 (m, 18H), 6.78 – 6.37 (m, 1H), 6.22 (s, 0.4H, minor diastereoisomer), 6.10 (s, 0.6H, major diastereoisomer), 6.02 – 5.71 (m, 1H), 5.35 – 4.48 (m, 7H), 1.81 – 1.03 (m, 4H), 0.97 – 0.64 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) mixture of diastereoisomers and rotamers: δ 156.7, 156.1, 155.5, 140.9, 140.2, 139.7, 135.8, 135.7, 135.6, 135.5, 130.2, 130.1, 128.5, 128.4, 128.3, 128.2, 127.7, 105.8, 105.6, 69.6, 69.1, 68.6, 68.2, 67.9, 67.6, 61.0, 30.4, 29.6, 24.4, 19.6, 19.4, 19.2, 14.0, 13.7; HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{32}\text{H}_{36}\text{N}_5\text{O}_6$ 586.2666; Found 586.2669; enantiomeric

excess were determined by HPLC (Chiralpak IB, Heptane/*i*-PrOH = 98:2, flow rate = 1.0 mL.min⁻¹, 214 nm): minor diastereoisomer: $t_1 = 31.1$ min (minor enantiomer), $t_4 = 59.1$ min (major enantiomer); major diastereoisomer: $t_2 = 34.7$ min (minor enantiomer), $t_3 = 44.0$ min (major enantiomer).

Dibenzyl 1-((2*R*)-1-(((benzyloxy)carbonyl)amino)-1-(3,5-dimethyl-1*H*-pyrazol-1-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6g). Following the general procedure, **6g** was obtained from the corresponding (*E*)-enecarbamate **2b** (21.9 mg, 0.1 mmol) and 3,5-dimethylpyrazole (28.8 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6g** as a colorless oil (49 mg, 1:1 *dr*, 99/99% *ee*) in 80% yield; *dr* was determined by ¹H NMR via integration of the multiplets at 0.89 and 0.79 ppm; $[\alpha]_{D^{25}} -25$ (*c* 1.0, CH₂Cl₂); IR (neat) ν (cm⁻¹): 1705, 1498, 1455, 1404, 1289, 1214, 1162, 1040, 1027, 911, 801; ¹H{¹³C} NMR (500 MHz, CD₃CN) mixture of diastereoisomers and rotamers: δ 7.51 – 7.07 (m, 16H), 6.76 – 6.49 (m, 0.5H), 5.82 – 5.58 (m, 1.5H), 5.26 – 5.04 (m, 6H), 4.75 – 4.50 (m, 1H), 2.42 – 2.10 (m, 7H), 1.54 – 1.10 (m, 4H), 0.90 – 0.87 (m, 1.5H, diastereoisomer 1), 0.87 – 0.76 (m, 1.5H, diastereoisomer 2); ¹³C{¹H} NMR (126 MHz, CDCl₃) mixture of diastereoisomers and rotamers: δ 156.6, 156.2, 155.5, 149.4, 135.9, 128.6, 128.5, 128.4, 128.2, 128.1, 127.7, 127.08, 106.0, 105.9, 105.5, 69.7, 69.3, 68.7, 67.9, 67.4, 65.4, 64.9, 64.5, 61.6, 60.5, 30.8, 30.4, 29.5, 19.7, 19.5, 19.3, 19.2, 14.0, 13.9, 13.7, 13.5, 10.9;; HRMS (ESI/Q-TOF) *m/z*: [M + H]⁺ Calcd for C₃₄H₄₀N₅O₆ 614.2979; Found 614.2981; enantiomeric excesses were determined by HPLC (Chiralpak IA, Heptane/*i*-PrOH = 95:5, flow rate = 1.0 mL.min⁻¹, 214 nm): major diastereoisomer: $t_1 = 18.7$ min (major enantiomer), $t_4 = 48.5$ min (minor enantiomer); minor diastereoisomer: $t_2 = 26.7$ min (major enantiomer), $t_3 = 35.1$ min (minor enantiomer).

Dibenzyl 1-((1*S*,2*R*)-1-(((benzyloxy)carbonyl)amino)-1-(4-bromo-1*H*-pyrazol-1-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6h). Following the general procedure, **6h** was obtained from the

corresponding (*E*)-enecarbamate **2b** (21.9 mg, 0.1 mmol) and 4-bromopyrazole (44.1 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6h** as a colorless oil (49 mg, 3:2 *dr*, 97/98% *ee*) in 74% yield; *dr* was determined by ¹H NMR via integration of the multiplets at 0.86 and 0.76 ppm; [α]_D²⁵ -4 (*c* 1.0, CH₂Cl₂); IR 1697, 1498, 1455, 1407, 1258, 1215, 1027, 952, 910, 798; ¹H{¹³C} NMR (500 MHz, CD₃CN) mixture of diastereoisomers and rotamers: δ 7.82 – 6.62 (m, 19H), 6.00 – 5.20 (m, 1H), 5.29 – 4.86 (m, 6H), 4.65 – 4.47 (m, 1H), 1.60 – 1.05 (m, 4H), 0.88 – 0.84 (m, 1.2H, minor diastereoisomer), 0.84 – 0.74 (m, 1.8H, major diastereoisomer); ¹³C{¹H} NMR (126 MHz, CDCl₃) mixture of diastereoisomers and rotamers: δ 156.6, 156.3, 156.0, 141.5, 140.8, 140.6, 135.7, 135.7, 135.5, 130.3, 129.8, 128.8, 128.73, 128.66, 128.58, 128.51, 128.4, 128.0, 127.8, 110.1, 93.6, 69.4, 69.0, 68.5, 68.2, 67.8, 67.5, 60.7, 30.3, 29.8, 19.6, 19.4, 13.7; HRMS (ESI/Q-TOF) *m/z*: [M + Na]⁺ Calcd for C₃₂H₃₄BrN₅O₆Na 686.1590; Found 686.1606; enantiomeric excesses were determined by HPLC (Chiralpak IC, Heptane/*i*-PrOH = 95:5, flow rate = 1.0 mL.min⁻¹, 214 nm): minor diastereoisomer: t₁ = 12.2 min (minor enantiomer), t₂ = 14.7 min (major enantiomer); major diastereoisomer: t₃ = 18.8 min (major enantiomer), t₄ = 28.6 min (minor enantiomer).

Dibenzyl 1-((1*S*,2*R*)-1-(((benzyloxy)carbonyl)amino)-1-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate (**6i**). Following the general procedure, **6i** was obtained from the corresponding (*E*)-enecarbamate **2b** (21.9 mg, 0.1 mmol) and 3-(trifluoromethyl)pyrazole (40.8 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6i** a colorless oil (51 mg, 7:3 *dr*, 96/96% *ee*) in 79% yield; *dr* was determined by ¹⁹F NMR via integration of the singlets at -61.8 and -61.9 ppm; [α]_D²⁵ -5 (*c* 1.0, CH₂Cl₂); IR (neat) ν (cm⁻¹): 1714, 1498, 1455, 1407, 1294, 1255, 1169, 1135, 1028, 966, 741, 696; ¹H{¹³C} NMR (500 MHz,

CDCl₃) mixture of diastereoisomers and rotamers: δ 7.75 – 7.51 (m, 1H), 7.48 – 7.05 (m, 15H), 6.80 – 6.59 (m, 1H), 6.56 – 6.38 (m, 1H), 5.90 – 5.75 (m, 1H), 5.34 – 4.71 (m, 6H), 4.70 – 4.51 (m, 1H), 1.61 – 1.20 (m, 4H), 0.90 – 0.50 (m, 3H); ¹³C{¹H} NMR (126 MHz, CDCl₃) mixture of diastereoisomers and rotamers δ : 156.4, 156.1, 155.5, 136.3, 135.6, 135.5, 132.4, 131.7, 128.7, 128.5, 128.4, 128.4, 128.3, 128.2, 128.0, 104.5, 104.2, 69.2, 69.0, 68.6, 68.4, 67.9, 67.1, 30.2, 29.8, 19.6, 19.3, 13.9, 13.7. ¹⁹F{¹H} NMR (282 MHz, CDCl₃) δ -61.8 (s, 2H, major diastereoisomer), -61.9 (s, 1H, minor diastereoisomer); HRMS (ESI/Q-TOF) m/z: [M + Na]⁺ Calcd for C₃₃H₃₄F₃N₅O₆Na 676.2325; Found 676.2353; enantiomeric excesses were determined by HPLC (Chiralpak IA, Heptane/*i*-PrOH = 90:10, flow rate = 1.0 mL.min⁻¹, 214 nm): minor diastereoisomer: t₁ = 16.2 min (minor enantiomer), t₂ = 18.3 min (major enantiomer); major diastereoisomer: t₃ = 31.9 min (major enantiomer), t₄ = 35.8 min (minor enantiomer).

Dibenzyl 1-((1*S*,2*R*)-1-(((benzyloxy)carbonyl)amino)-1-(1*H*-indazol-1-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6j). Following the general procedure, **6j** was obtained from the corresponding (*E*)-enecarbamate **2d** (21.9 mg, 0.1 mmol) and indazole (35.4 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6j** as a colorless oil (32 mg, 7:3 *dr*, 99/99% *ee*) in 50% yield; *dr* was determined by ¹H NMR via integration of the multiplets at 0.86 and 0.69 ppm; [α]_D²⁵ -6 (*c* 1.0, CH₂Cl₂); IR (neat) ν (cm⁻¹): 1703, 1629, 1515, 1498, 1455, 1404, 1213, 1115, 1027, 1042, 909, 848, 734; ¹H{¹³C} NMR (500 MHz, CD₃CN) mixture of diastereoisomers and rotamers: δ 8.63 – 6.80 (m, 22H), 6.50 – 6.00 (m, 1H), 5.44 – 4.16 (m, 7H), 1.64 – 1.00 (m, 4H),), 0.90 – 0.84 (m, H, major diastereoisomer), 0.84 – 0.66 (m, 1H, minor diastereoisomer); ¹³C{¹H} NMR (75 MHz, CD₃CN) mixture of diastereoisomers and rotamers: δ 156.7, 156.6, 149.9, 137.1, 135.1, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.6, 128.2, 127.6,

127.3, 124.8, 122.7, 122.0, 121.7, 121.5, 118.3, 110.9, 71.5, 69.9, 68.6, 68.3, 68.1, 67.8, 67.5, 62.6, 61.5, 31.0, 20.1, 19.9, 14.1, 13.7, 13.3; HRMS (ESI/Q-TOF) m/z : $[M + Na]^+$ Calcd for $C_{36}H_{37}N_5O_6Na$ 658.2621; Found 658.2636; enantiomeric excesses were determined by HPLC (Chiralpak IC, Heptane/*i*-PrOH = 95:5, flow rate = 1.0 mL.min⁻¹, 300 nm): minor diastereoisomer: t_1 = 39.1 min (major enantiomer), t_2 = 65.1 min (minor enantiomer); major diastereoisomer: t_3 = 75.8 min (major enantiomer), t_4 = 90.5 min (minor enantiomer).

Dibenzyl 1-((1*S*,2*R*)-1-(((benzyloxy)carbonyl)amino)-3-methyl-1-(1*H*-pyrazol-1-yl)butan-2-yl)hydrazine-1,2-dicarboxylate (6k). Following the general procedure, **6k** was obtained from the corresponding (*E*)-enecarbamate **2c** (21.9 mg, 0.1 mmol) and pyrazole (20 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6k** as a colorless oil (20 mg, 7:3 *dr*, 98/92% *ee*) in 30% yield; *dr* was determined by ¹H NMR via integration of the multiplets at 4.57 and 4.34 ppm; $[\alpha]_D^{25}$ -19 (*c* 1.0, CH₂Cl₂); IR (neat) ν (cm⁻¹): 1715, 1498, 1455, 1400, 1299, 1260, 1216, 1045, 738; ¹H{¹³C} NMR (500 MHz, CDCl₃) mixture of diastereoisomers and rotamers: δ 7.64 – 7.03 (m, 16H), 6.80 – 6.50 (m, 1H), 6.23-6.18 (m, 1 H) 6.13 – 6.07 (m, 1H), 5.32 – 4.77 (m, 8H), 4.71 – 4.50 (m, 0.65H, major diastereoisomer), 4.50 – 4.10 (m, 0.35H, minor diastereoisomer), 2.14 – 1.80 (m, 1H), 1.21 – 0.88 (m, 6H). ¹³C{¹H} NMR (126 MHz, CDCl₃) mixture of diastereoisomers and rotamers: δ 157.0, 156.5, 156.0, 140.6, 139.7, 135.9, 135.7, 135.4, 130.1, 129.8, 128.74, 128.68, 128.59, 128.4, 128.3, 128.2, 127.8, 105.6, 69.7, 68.7, 68.4, 68.2, 68.1, 67.6, 67.1, 28.8, 28.2, 19.8, 19.2 HRMS (ESI/Q-TOF) m/z : $[M + Na]^+$ Calcd for $C_{32}H_{35}N_5O_6Na$ 608.2485; Found 608.2485; Enantiomeric excess were determined by HPLC (Chiralpak IA, Heptane/*i*-PrOH = 80:20, flow rate = 1.0 mL.min⁻¹, 214 nm): major diastereoisomer: t_1 = 15.4 min

(major enantiomer), $t_4 = 74.5$ min (minor enantiomer); minor diastereoisomer: $t_2 = 23.9$ min (minor enantiomer), $t_3 = 26.7$ min (major enantiomer).

Dibenzyl 1-((1*R*)-2-(((benzyloxy)carbonyl)amino)-1-cyclopropyl-2-(1*H*-pyrazol-1-yl)ethyl)hydrazine-1,2-dicarboxylate (6l). Following the general procedure, **6l** was obtained from the corresponding (*E*)-enecarbamate **2d** (21.7 mg, 0.1 mmol) and pyrazole (20 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6l** as a colorless oil (45 mg, 1:1 *dr*, 99/95% *ee*) in 78% yield; *dr* was determined by $^1\text{H NMR}$ via integration of the singlets at 6.22 and 6.20 ppm; $[\alpha]_{\text{D}}^{25} -8$ (*c* 1.0, CH_2Cl_2); IR (neat) ν (cm^{-1}): 1714, 1498, 1455, 1400, 1296, 1260, 1118, 1084, 1051, 1028, 974, 917, 753, 696; $^1\text{H}\{^{13}\text{C}\}$ NMR (500 MHz, CD_3CN) mixture of diastereoisomers and rotamers: δ 7.75 – 6.75 (m, 19H), 6.22 (s, 1H, diastereoisomer 1), 6.20 (s, 1H, diastereoisomer 2), 5.12 – 4.75 (m, 6H), 4.00 – 3.50 (m, 1H), 0.92 – 0.88 (m, 1H), 0.58 – 0.08 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) mixture of diastereoisomers and rotamers: δ 156.0, 155.7, 155.5, 140.5, 140.0, 135.9, 135.6, 130.0, 128.6, 128.5, 128.4, 128.3, 128.3, 127.7, 105.5, 68.6, 68.3, 67.9, 67.6, 67.4, 10.6, 5.5, 4.0. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{32}\text{H}_{33}\text{N}_5\text{O}_6\text{Na}$ 606.2310; Found 606.2323; enantiomeric excesses were determined by HPLC (Chiralpak IA, Heptane/*i*-PrOH = 90:10, flow rate = 0.9 mL/min, 214 nm): major diastereoisomer: $t_1 = 41.5$ min (minor enantiomer), $t_2 = 56.5$ min (major enantiomer); minor diastereoisomer: $t_3 = 68.22$ min (major enantiomer), $t_4 = 99.4$ min (minor enantiomer).

dibenzyl 1-((5*S*,6*S*)-5-(1*H*-indazol-1-yl)-10,10-dimethyl-3-oxo-1,9,9-triphenyl-2,8-dioxo-4-aza-9-silaundecan-6-yl)hydrazine-1,2-dicarboxylate (6m). Following the general procedure, **6m** was obtained from the corresponding (*E*)-enecarbamate **2e** (47.3 mg, 0.1 mmol) and indazole (35.4 mg,

0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6m** as a colorless oil (44 mg, 7:3 *dr*, 94/91% *ee*) in 50% yield; *dr* was determined by ^1H NMR via integration of the singlets at 8.02 and 7.98 ppm; $[\alpha]_{\text{D}}^{25} -20$ (*c* 1.0, CH_2Cl_2); IR (neat) ν (cm^{-1}): 1704, 1629, 1587, 1498, 1455, 1406, 1328, 1292, 1214, 1109, 1043, 1027, 976, 909, 823, 736; ^1H $\{^{13}\text{C}\}$ NMR (500 MHz, CD_3CN) mixture of diastereoisomers and rotamers: δ 8.02 (s, 0.7H, major diastereoisomer), 7.98 (s, 0.3H, minor diastereoisomer), 7.80 – 6.73 (m, 30H), 6.66 – 5.93 (m, 1H), 5.30 – 4.56 (m, 8H), 3.90 – 3.15 (m, 2H), 1.87 – 1.09 (m, 4H), 1.00 (s, 9H); ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CD_3CN) mixture of diastereoisomers and rotamers: δ 157.4, 157.1, 156.6, 136.4, 136.3, 135.9, 135.3, 130.7, 130.6, 129.5, 129.4, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 127.9, 127.7, 127.3, 127.2, 125.3, 125.0, 122.8, 122.7, 122.1, 122.0, 121.8, 121.6, 121.5, 77.9, 77.3, 68.8, 68.2, 68.4, 68.2, 67.9, 67.7, 67.2, 67.9, 64.8, 64.6, 64.5, 64.3, 64.1, 63.8, 30.1, 29.9, 27.4, 27.3, 27.2, 27.1, 19.8; HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{52}\text{H}_{55}\text{N}_5\text{O}_7\text{SiNa}$ 912.3746; Found 912.3762; enantiomeric excesses were determined by HPLC (Chiralpak AD-H, Heptane/*i*-PrOH = 90:10, flow rate = 1 $\text{mL}\cdot\text{min}^{-1}$, 214 nm): minor diastereoisomer: $t_1 = 13.85$ min (minor enantiomer), $t_4 = 48.69$ min (major enantiomer); major diastereoisomer: $t_2 = 19.99$ min (major enantiomer), $t_3 = 30.28$ min (minor enantiomer).

Dibenzyl 1-((5*S*,6*S*)-10,10-dimethyl-3-oxo-1,9,9-triphenyl-5-(1*H*-pyrazol-1-yl)-2,8-dioxo-4-aza-9-silaundecan-6-yl)hydrazine-1,2-dicarboxylate (**6n**). Following the general procedure, **6n** was obtained from the corresponding (*E*)-enecarbamate **2e** (47.3 mg, 0.1 mmol) and pyrazole (20 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **6n** as a colorless oil (43 mg, 4:1 *dr*, 95/91% *ee*) in 51% yield; *dr* was determined by ^1H NMR via integration of the multiplets at 5.92 and 5.81 ppm; $[\alpha]_{\text{D}}^{25} -17$ (*c* 1.0, CH_2Cl_2); IR (neat) ν (cm^{-1}

1): 1694, 1498, 1455, 1427, 1398, 1297, 1258, 1213, 1088, 1026, 971, 911, 794; $^1\text{H}\{^{13}\text{C}\}$ NMR (500 MHz, CDCl_3) mixture of diastereoisomers and rotamers: δ 7.65 – 7.61 (m, 4H), 7.41 – 7.26 (m, 21H), 7.14 (s, 2H), 6.35 – 6.06 (m, 1H), 5.95 – 5.90 (m, 0.8H, major diastereoisomer), 5.90 – 5.75 (m, 0.2H, minor diastereoisomer), 5.39 – 4.85 (m, 7.25H), 4.60 – 4.40 (m, 0.75H), 3.89 – 3.47 (m, 2H), 1.90 – 1.52 (m, 4H), 1.03 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) mixture of diastereoisomers and rotamers: δ 156.6, 156.2, 155.5, 141.1, 140.2, 139.8, 135.7, 134.0, 129.7, 128.6, 128.4, 128.3, 128.1, 127.8, 127.7, 106.1, 69.3, 68.7, 68.3, 68.0, 67.7, 63.5, 29.2, 28.9, 27.0, 25.0, 19.3; HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{48}\text{H}_{53}\text{N}_5\text{O}_7\text{SiNa}$ 862.3592; Found 862.3606; enantiomeric excesses were determined by HPLC (Chiralpak OD-H, Heptane/*i*-PrOH = 95:5, flow rate = 0.6 mL.min⁻¹, 214 nm): major diastereoisomer: t_1 = 22.9 min (minor enantiomer), t_3 = 30.0 min (major enantiomer); minor diastereoisomer: t_2 = 26.4 min (minor enantiomer), t_4 = 64.0 min (major enantiomer).

Dibenzyl 1-((5*S*,6*S*)-10,10-dimethyl-5-(4-nitro-1*H*-pyrazol-1-yl)-3-oxo-1,9,9-triphenyl-2,8-dioxo-4-aza-9-silaundecan-6-yl)hydrazine-1,2-dicarboxylate (60). Following the general procedure, **60** was obtained from the corresponding (*E*)-enecarbamate **2e** (47.3 mg, 0.1 mmol) and 4-nitro-1*H*-pyrazole (34.0 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (PE/EtOAc 8:3) to afford **60** as a colorless oil (46 mg, 4:1 *dr*, 99/99% *ee*) in 52% yield; *dr* was determined via integration of the singlets at 8.10 and 7.99 ppm $[\alpha]_{\text{D}}^{25} -20$ (*c* 1.0, CH_2Cl_2); IR (neat) ν (cm⁻¹): 1704, 1515, 1409, 1305, 1257, 1020, 734, 698; $^1\text{H}\{^{13}\text{C}\}$ NMR (500 MHz, CD_3CN) mixture of diastereoisomers and rotamers: δ 8.63 – 8.48 (m, 1H), 8.10 (s, 0.2H, minor diastereoisomer), 7.99 (s, 0.8H, major diastereoisomer), 7.76 – 7.64 (m, 4H), 7.56 – 7.21 (m, 22H), 6.08 – 5.66 (m, 1H), 5.28 – 4.91 (m, 6H), 4.68 – 4.50 (m, 1H), 3.70 – 3.63 (m, 2H), 1.94 – 1.72 (m, 2H), 1.69 – 1.51 (m, 2H), 1.02 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) mixture of diastereoisomers and rotamers: δ 156.6, 155.8, 155.18, 136.68, 136.4, 136.2, 135.9, 135.7, 135.5, 135.5, 135.5, 135.3, 135.0, 133.8, 133.6, 129.8,

129.8, 129.7, 128.6, 128.6, 128.5, 128.4, 128.2, 127.8, 127.8, 127.7, 69.1, 68.4, 68.2, 68.0, 67.7, 67.0, 63.1, 62.8, 31.5, 29.1, 28.6, 26.9, 26.8, 19.1; HRMS (ESI/Q-TOF) m/z : $[M + Na]^+$ Calcd for $C_{48}H_{52}N_6O_9SiNa$ 907.3416; Found 907.3447; enantiomeric excesses are determined by HPLC (Chiralpak IA, Heptane/*i*-PrOH = 95:5, flow rate = 1.0 mL.min⁻¹, 214 nm): major diastereoisomer: t_1 = 15.6 min (minor enantiomer), t_3 = 48.2 min (major enantiomer); minor diastereoisomer: t_2 = 20.7 min (minor enantiomer), t_4 = 60.2 min (major enantiomer).

Dibenzyl 1-((1*S*,2*R*)-1-(((benzyloxy)carbonyl)amino)-1-(7-bromo-1H-indol-3-yl)propan-2-yl)hydrazine-1,2-dicarboxylate (6p). Under argon, the (*E*)-enecarbamate **2a** (19.1 mg, 0.1 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (0.4 mL) in a flame-dried flask containing activated powdered 3Å molecular sieves (20 mg). The solution was stirred at room temperature for 10 min before being cooled to -45 °C and stirred for additional 10 min. Dibenzyl azodicarboxylate **3** (44.7 mg, 0.15 mmol, 1.5 equiv) dissolved in CH₂Cl₂ (0.3 mL) was added and the reaction mixture was stirred for 10 min. Then EtSH (7 μL, 0.1 mmol, 1.0 equiv) and finally the (*S*)-phosphoric acid **1c** (6 mg, 0.01 mmol, 0.1 equiv) as a solution in CH₂Cl₂ (0.3 mL) were added and the reaction mixture was stirred for 16 h at -45 °C. Then, 7-bromoindole (58 mg, 0.3 mmol, 3 equiv) was added and the reaction was stirred at room temperature overnight under O₂ atmosphere and blue light irradiation for 16 h. Completion of the reaction was checked by TLC. Solvents were removed in vacuo and the residue was purified by flash column chromatography (CHCl₃/EtOAc 95/5 to 90/10) to give **6p** as a colorless oil (27 mg, > 95:5 *dr*, 98% *ee*) in 39% yield.

¹H NMR (300 MHz, CD₃CN) δ (ppm): (mixture of rotamers) 9.5 (s, rot. 1, 0.1H), 9.13 (s, 0.9H), 7.99 (brs, 1H), 7.67 (brs, 1H), 7.49 – 7.23 (m, 16H), 7.19 (brs, 1H), 6.85 (brs, 1H), 6.09 (s, 1H), 5.35 – 4.50 (m, 8H), 1.27 (d, *J* = 6.8 Hz, rot. 1, 0.3H), 1.23 (d, *J* = 6.5 Hz, 3H). According to literature data.¹⁸

Procedure for the large-scale synthesis of dibenzyl 1-((1S,2R)-1-(((benzyloxy)carbonyl)amino)-1-(1H-pyrazol-1-yl)propan-2-yl)hydrazine-1,2-dicarboxylate (6a**).**

Under argon, the benzyl (*E*)-prop-1-en-1-ylcarbamate **2a** (1 mmol, 1.0 equiv, 0.191 g) was dissolved in CH₂Cl₂ (4 mL) in a 25 mL flame-dried round-bottom flask containing activated powdered 3Å molecular sieves (0.2 g). The solution was stirred at room temperature for 10 min before being cooled to –45 °C and stirred for additional 10 min. Dibenzyl azodicarboxylate (1.5 mmol, 1.5 equiv, 0.45 g) dissolved in CH₂Cl₂ (3 mL) was added and the reaction mixture was stirred for 10 min. Then EtSH (1 mmol, 1 equiv, 77 µL) and finally the chiral photocatalyst **1c** (0.1 mmol, 0.1 equiv, 60 mg) were added as a solution in CH₂Cl₂ (3 mL) and the reaction mixture was stirred for 16 h at –45 °C. Then, the pyrazole was added (3 mmol, 3 equiv, 0.204 g) and the reaction was stirred at room temperature under an O₂ atmosphere in PhotoRedOx Box (EvoluChem) with a 30 W blue LED (EvoluChem, model: HCK1012-01-008, wavelength 405 nm, LED: CREE XPE) for 24 h. Completion of the reaction was checked by TLC. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (PE/EtOAc 8:3) to afford **6a** as a colourless oil (0.49 g, 7:3 *dr*, 98/97% *ee*) in 88% yield.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/> and contains electrochemical data, UV–vis data, and ¹H, ¹³C NMR and HPLC spectra for all new compounds.

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NOTE

The authors declare no competing financial interest.

AUTHOR CONTRIBUTIONS

All authors have given approval to the final version of the manuscript.

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