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Graphical Abstract

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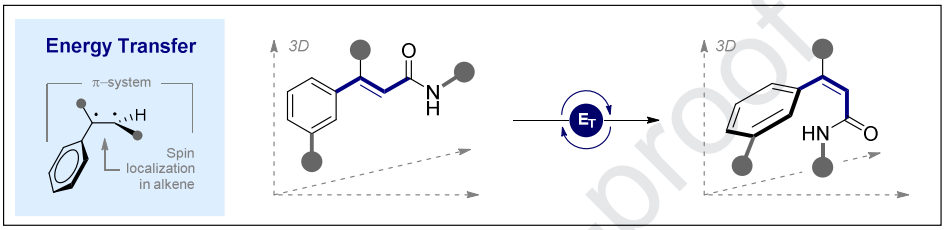

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ABSTRACT

A bio-inspired, photocatalytic *E* → *Z* isomerization of cinnamides is reported using inexpensive (-)-riboflavin (vitamin B_2) under irradiation at λ = 402 nm. This operationally simple transformation is compatible with a range of amide derivatives including -NR_2, -$NHSO_2R$ and $N(Boc)_2$ (up to 99:1 *Z:E*). Selective energy transfer from the excited state photocatalyst to the starting *E*-isomer ensures that directionality is achieved: The analogous process with the *Z*-isomer is inefficient due to developing allylic strain causing chromophore deconjugation. This is supported by X-ray analysis and Stern-Volmer photo-quenching studies. Preliminary validation of the method in manipulating the conformation of a simple model Leu-enkephalin *penta*-peptide is disclosed via the incorporation of a cinnamamide-based amino acid.

1. Introduction

Selective energy transfer from photo-excited small molecule catalysts to pre-existing π-systems constitutes an expansive platform to convert synthetically accessible *E*-alkenes to their *contra*-thermodynamic *Z*-isomers.[1] Through the involvement of a photosensitizer, the excited state of substrate alkene can be explored thereby mitigating the need for direct irradiation.[2] This activation mode significantly reduces the risk of potential side-reactions, and can be harnessed to activate alkenes with closely similar photo-physical behaviour.[3] Geometric alkene isomers embedded in styrenyl motifs lend themselves to selective energy transfer (E_T) from photo-excited catalysts due to the subtle differences in conformation.[4] Whilst planar *E*-isomers are conjugated, 1,3-allylic strain in the *Z*-isomer reduces conjugation and provides an expansive structural basis from which to discriminate these π-systems.[5] Since vulnerabilities associated with ground state geometric isomerization (e.g. microscopic reversibility) are circumvented, this general design concept has a venerable history.[6] The importance of isomerization in regulating biomolecule function,[1,7] and the ability of simple flavins to facilitate biocompatible selective energy transfer,[1b-d] led us to explore the photocatalytic *E* → *Z* isomerization of cinnamides[8] upon incorporation into small, model peptides (Figure 1).

(–)-Riboflavin (vitamin B_2) is well-suited to the photo-isomerization of (poly)enes,[9] on account of its well-defined photo-physical profile, and ability to mediate both energy transfer[10] and photo-induced SET processes.[4c,11] In this study, the competence of (–)-riboflavin in catalyzing the *E* → *Z* isomerization of cinnamides via selective energy transfer is demonstrated. Preliminary validation in manipulating the conformation of a simple *penta*-peptide is also disclosed through the development of a novel amino acid containing an activated alkene motif.

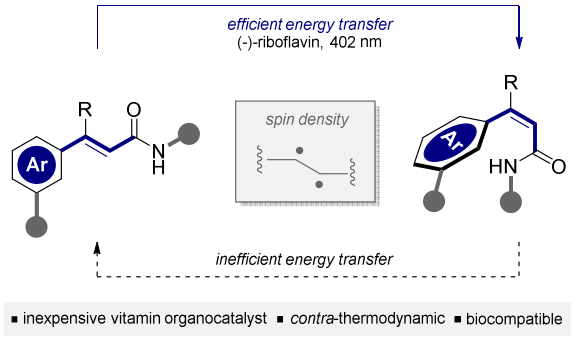

Fig. 1. *Contra*-thermodynamic isomerization of cinnamides.

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2. Results & Discussion

A short process of reaction optimization identified conditions that enabled the smooth conversion of ***E*-1** to ***Z*-1** (Figure 2). This operationally simple isomerization was achieved by charging a flask with the substrate (*E*)-alkene, and (–)-riboflavin (5 mol%) in acetonitrile and irradiated (λ = 402 nm) until the photostationary composition was reached.

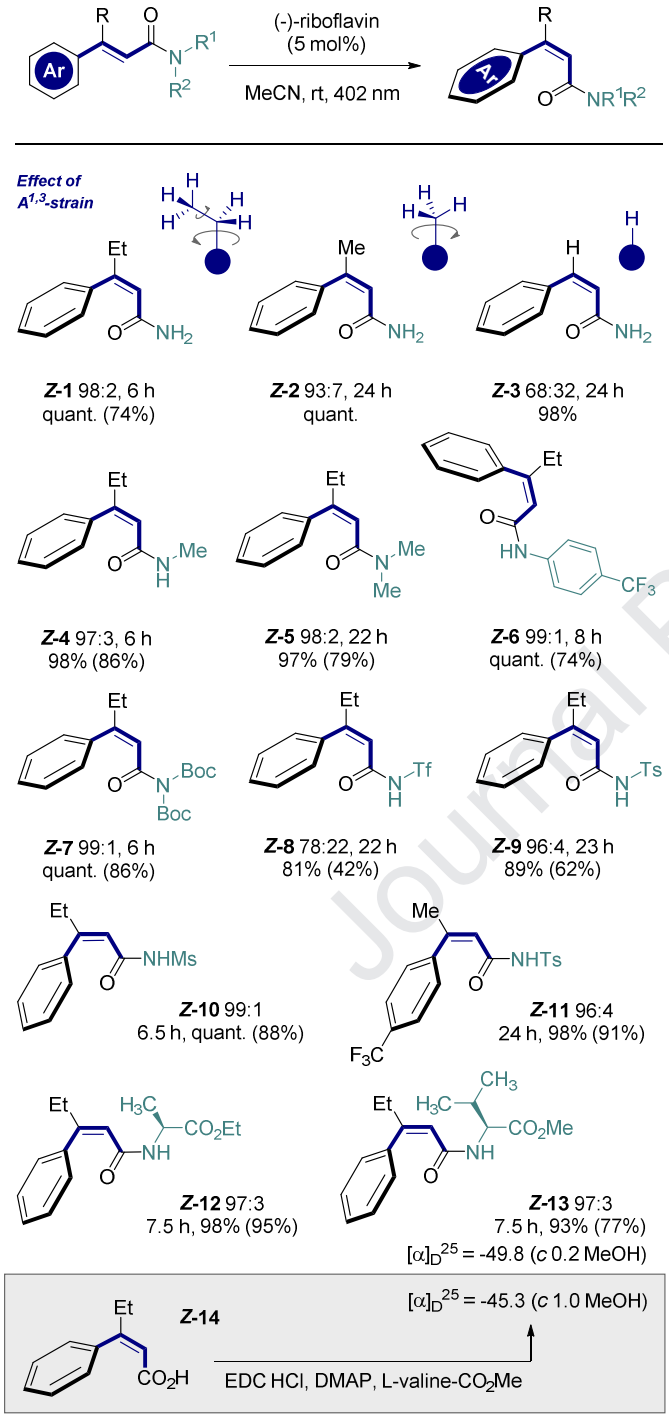

Fig. 2. Exploring the scope of the geometric isomerisation of cinnamamides using (-)-riboflavin. Reactions were performed on 0.1 mmol scale (*E*/*Z* substrate >20:1) with 5 mol% (–)-riboflavin in 1.5 mL MeCN at ambient temperature (λ = 402 nm); combined yields are given (isolated yields of the *Z*-isomer in parentheses). Bottom: Ensuring that optical purity is not compromised under the photoisomerization conditions.

Under these conditions it was possible to generate ***Z*-1** (98:2 *Z:E*) after 6 h. The reaction proved to be sensitive to changes in the β-substituent (R) with substitution of Et to Me resulting in a slight decrease in selectivity (***Z*-2**, 93:7). As a control substrate, the unsubstituted system ***Z*-3** was subjected to the reaction conditions. It was possible to generate the Z-isomer, albeit with a reduction in selectivity (68:32 *Z:E*), thus highlighting the importance of allylic-strain in driving selectivity. Changes to the amino group were then systematically explored. The methyl amino and dimethylamino derivatives were compatible with the reaction conditions and thereby allowing ***Z*-4** and ***Z*-5** to be isolated with synthetically useful levels of selectivity (97:3 and 98:2, respectively). It was also possible to generate the dimethyl amide ***Z*-5**, although an extended reaction time of 22 h was required to reach completion.

Scope extension to include aromatic amines was possible as exemplified by the *p*-CF_3 aniline derivative ***Z*-6** (*Z*/*E* 99:1). An examination of common *N*-protecting groups revealed a general compatibility with this simple protocol allowing the di-Boc protected amide ***Z*-7** to be isolated with a *Z*/*E* ratio of 99:1 in 86% isolated yield. The triflate group (***Z*-8**) proved more challenging leading to a *Z:E* ratio of 78:22 and a diminished yield (42%). Toslyate and mesylate derivatives ***Z*-9**, **10**, and **11** were unproblematic and encouraging levels of stereoselectivity were observed (up to 99:1 *Z:E*). With a view to utilizing this approach to modulate peptide conformation,[12] two simple dipeptides were prepared and studied under the isomerization conditions. Both the L-alanine and L-valine derivatives ***Z*-12** and ***Z*-13**, respectively, were isolated in ≥95% yield and with a *Z:E* ratio of 97:3. Cognizant that certain light sources, and in particular UV-light, is known to cause the racemization of amino acids,[13] ***Z*-13** was prepared by an independent method to allow comparison of the specific optical rotation (Figure 2, bottom). This was achieved by coupling the *Z*-configured carboxylic acid ***Z*-14** with the methyl ester of L-valine using carbodiimide. Closely similar specific rotation values of $[\alpha]_D^{25}$ – 49.8 and – 45.3 were obtained.

To support the proposal that a selective energy transfer manifold was operational, a Stern-Volmer photo-quenching study was performed under an argon atmosphere in a 1:1 mixture of water and acetonitrile (Figure 4). Unfortunately, it was not possible to perform the study in neat acetonitrile due to the sparing solubility of (–)-riboflavin in this medium. To mitigate the risk of catalyst quenching by oxygen, solvents were degassed prior to use. A series of control experiments established the importance of the light source and the photosensitizer (Figure 4, centre left). Moreover, X-ray crystallographic analysis of ***Z*-1** revealed an out of plane tilt of the phenyl ring [dihedral angle φ_{CCCC} = –64.2(4)°] consistent with deconjugation of the π-cinnamoyl chromophore in the product *Z*-isomer to minimize $A^{1,3}$-strain. The *contra*-thermodynamic nature of the title transformation was validated by computational investigation of the geometric isomers ***E*-/*Z*-1** and ***E*-/*Z*-3** at the [DG298/(kcal/mol)] (PWPB95-D3+CPCM(MeCN)//TPSS-D3) level of theory (Figure 4). For the model system containing a β-substituent, ***E*-1** → ***Z*-1**, the net isomerization was calculated to be modestly *contra*-thermodynamic (ΔG = +1.48 kcal•mol^{-1}). Deletion of the ethyl group (***E*-3** → ***Z*-3**) augments this difference (ΔG = +6.12 kcal•mol^{-1}). Further analysis of the triplet states for ***E*-2** and ***Z*-2** revealed that spin density is concentrated in the alkene fragment. This is in stark contrast to styrenyl silanes where the deconjugated product *Z*-isomer has spin density localized in the aryl ring.

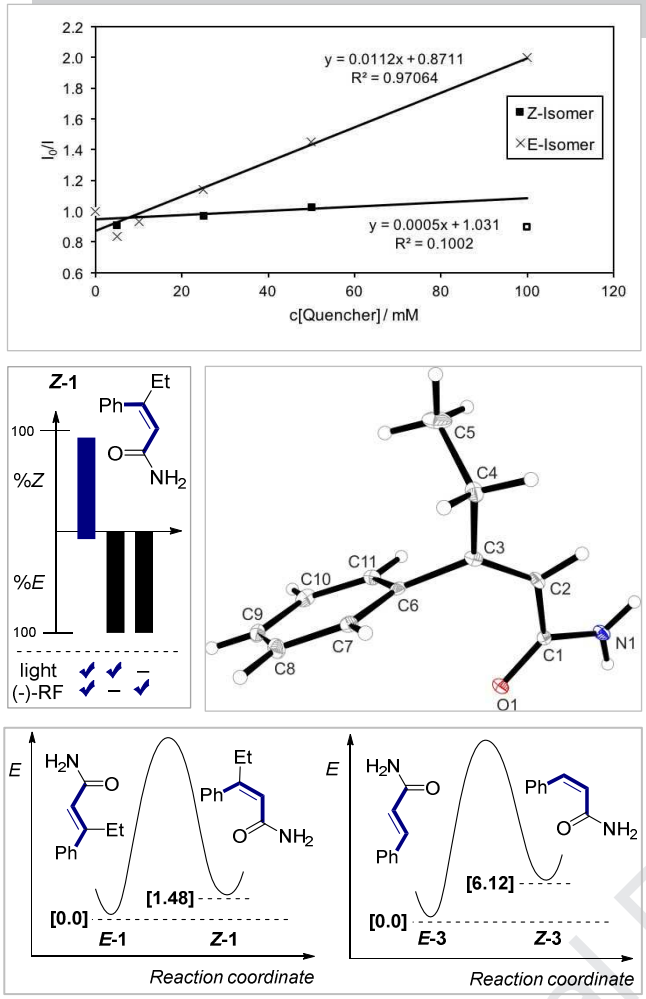

Figure 4. Top: Stern-Volmer photo-quenching study of ***E*-1** and ***Z*-1**; Center left: Control experiments. Center right: X-ray crystal structure of ***Z*-1** showing 1,3-allylic strain and intermolecular hydrogen bonding in the dimer (CCDC 1951608). Bottom: Lowest energy conformations of ***E*-1** / ***Z*-1** and ***E*-3** / ***Z*-3** at the [DG298/(kcal/mol)] (PWPB95-D3+CPCM(MeCN)//TPSS-D3) level of theory (please see the Supporting Information).

Finally, to explore the potential of this transformation in influencing peptide conformation, an analog based on the opioid receptor-binding *penta*-peptide Leu-enkephalin (*N*-Tyr-Gly-Gly-Phe-Leu-*C*) was prepared by solid phase peptide synthesis (Figure 6). *E*-alkenes are effective peptide bond isosteres[14,15] and, given the prominence of flavins in bioconjugation,[16] this operationally simple energy transfer strategy to access the corresponding *Z*-isomer might be advantageous. To that end, a short model penta-peptide was conceived in which a novel cinnamamide-based amino acid was introduced into the primary sequence (Figure 6).

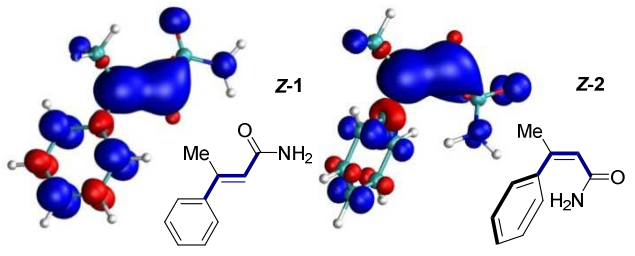

Fig. 5. Calculated spin densities for ***E*-2** (left) and ***Z*-2** (right).

Replacement of the Gly residue in position three with a cinnamide motif proceeded smoothly using conventional Fmoc-based coupling methods. Due to the low solubility of peptide ***E*-15•TFA** in MeCN, the isomerization (***E*-15•TFA** → ***Z*-15•TFA**) was performed under slightly modified conditions: ***E*-15•TFA** (0.020 mmol) and (–)-riboflavin (5 mol %) were dissolved in deuterated dimethyl sulfoxide and irradiated at 402 nm at ambient temperature for 24 h. Gratifyingly, geometric alkene isomerization was observed with a *Z:E* selectivity of 76:24 (Figure 6, lower).

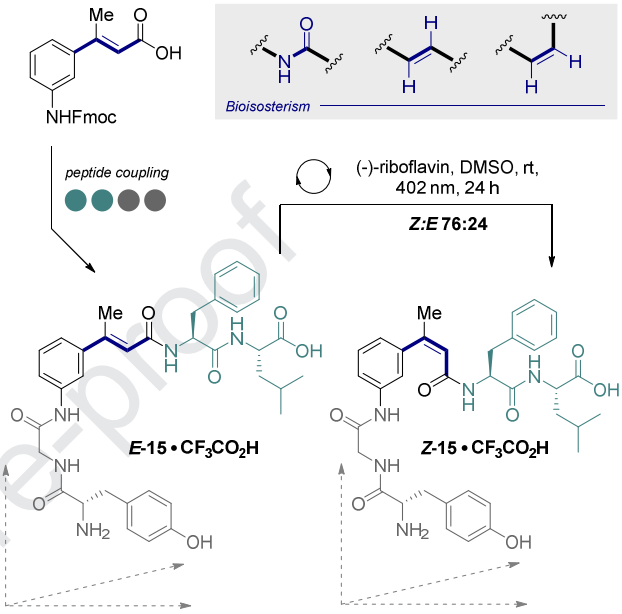

Fig. 6. Isomerization of a model *penta*-peptide.

3. Conclusion

In conclusion, a *contra*-thermodynamic isomerization of cinnamamides has been devised using vitamin photocatalysis. The transformation is compatible with a broad range of amide derivatives including -NR_2, -$NHSO_2R$ and $N(Boc)_2$ (up to 99:1 *Z:E*). The importance of allylic strain in governing selectivity is supported by structural probes and X-ray analysis, and selective energy transfer is operational based on Stern-Volmer photo-quenching studies. Preliminary validation of this bio-compatible strategy to regulate structure is also disclosed in a model Leu-enkephalin peptide.

4. Experimental section

4.1. General Information

All chemicals were purchased as reagent grade and used without further purification. Solvents for purification (extraction and chromatography) were purchased as technical grade and distilled on the rotary evaporator prior to use. For column chromatography SiO_2 (40−63 µm for flash chromatography, VWR Chemicals) was used as stationary phase. Analytical thin layer chromatography (TLC) was performed on aluminum foil precoated with SiO_2-60 F254 (Merck) and visualized with a UV-lamp (254 nm) and KMnO4 solution. Concentration in vacuo was performed at ~10 mbar and 45 °C, drying at ~10^{-2} mbar and room temperature. NMR spectra were measured by the NMR service of the Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster on a *Bruker AV300*, *Bruker*

AV400 or an *Agilent DD2 600* spectrometer at rt. ^{1}H NMR spectra are reported as follows: chemical shift (δ) in ppm (multiplicity, number of protons, coupling constant J in Hz; assignment of proton). ^{13}C NMR spectra are reported as follows: chemical shift (δ) in ppm (multiplicity, coupling constant J_{C-F} in Hz; assignment of carbon). ^{19}F NMR spectra are reported as follows: chemical shift (δ) in ppm (multiplicity, coupling constant J in Hz; assignment of fluorine). Chemical shifts are referenced to the ^{1}H and ^{13}C signal of the respective deuterated solvent. The resonance multiplicity is described as: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), b (broad). Unknown compounds were assigned by 2D NMR spectra (gCOSY, gHMBC, gHSQC) and NOESY spectra. High resolution mass spectometry was performed by the mass spec service of the Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster. Melting points were determined using a *Büchi B-545* melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a *Perkin-Elmer 100* FT-IR spectrometer and are reported in wavenumbers (cm^{-1}) with the following abbreviations: w (weak), m (medium), s (strong), br (broad). Emission spectra for the Stern-Volmer photoquenching study were measured on a *Jasco Spectrofluorometer FP8300*. Optical rotations were determined on a *Jasco P-2000* polarimeter. Isomerization reactions were performed utilizing an ACULED VHL (ACL01-SC-UUUU-E05-C01-L-0000) by LED Solutions. The forward current per chip was set to 350 mA, the resulting forward voltage was 14 V while the resulting radiants flux was 1150 mW. Further isomerization reactions were performed utilizing a set-up of four Winger WEPUV3-S2 UV Power LED Star (Schwarzlicht) 1.2 W lamps. The forward current per chip was set to 700 mA, the resulting forward voltage was 3.4 V while the resulting radiant flux was 1200 mW. The reaction flask was placed approximately 1 cm above the UV lamp.

4.2. General Procedure (GP) for the Isomerization of α,β-Unsaturated Amides

The respective α,β-unsaturated amide (0.1 mmol, 1 eq.) and (–)-riboflavin (1.9 mg, 0.005 mmol, 0.05 eq.) were dissolved in MeCN (1.5 mL) and stirred under UV-light irradiation (402 nm) at rt until completion (monitored by TLC). Residual catalyst was removed by filtration through a SiO_2-plug and the products were eluted by Et_2O or EtOAc. The eluate was concentrated *in vacuo* and purified by flash column chromatography. The *E*-/*Z*-isomer ratio was determined by integration of the crude ^{1}H NMR spectra.

4.2.1. ***Z*-1**

Prepared according to GP, ***E*-1** (18 mg, 0.1 mmol, 1.0 eq.) was converted to ***Z*-1** in 6 h yielding a white solid (13 mg, 74%) after separation by flash column chromatography (50% EtOAc/cyclohexane). The spectroscopic data obtained were in accordance with those described in the literature.[4d]

R_f = 0.11 (50% EtOAc/cyclohexane); M.p.: 96–100 °C; ^{1}H NMR (600 MHz, CD_3OD): δ = 7.39 – 7.35 (m, 2H; H8), 7.34 – 7.30 (m, 1H; H9), 7.27 – 7.24 (m, 2H; H7), 5.96 (t, J = 1.4 Hz, 1H; H2), 2.50 (qd, J = 7.4, 1.4 Hz, 2H; H4), 1.05 (t, J = 7.4 Hz, 3H; H5) ppm; ^{13}C NMR (151 MHz, CD_3OD): δ = 172.2 (C1), 156.5 (C3), 141.2 (C6), 129.2 (H8), 128.8 (H9), 128.6 (C7), 120.4 (C2), 33.7 (C4), 12.6 (C5) ppm; IR (ATR): ν = 3476 (m), 3293 (m), 3057 (w), 2932 (w), 2885 (w), 1661 (s), 1634 (s), 1606 (s), 1597 (s), 1491 (m), 1423 (m), 1330 (m), 1307 (m), 1208 (m), 1052 (m), 906 (w), 887 (s), 766 (s), 738 (m), 699 (s) cm^{-1}; HR-ESI-MS: *m*/*z* calcd. for $C_{11}H_{13}NONa^+$ $[M+Na]^+$: 198:0889, found: 198.0891.

4.2.2. ***Z*-2**

Prepared according to GP, ***E*-2** (16 mg, 0.1 mmol, *E*:*Z* >20:1) was converted to ***Z*-2** in 24 h yielding a white solid (16 mg, quant., *Z*:*E* 93:7) after filtration over a SiO_2-plug. The spectroscopic data obtained were in accordance with those described in the literature.[4d]

R_f = 0.06 (10% Et_2O/*n*-pentane); M.p.: 88.2 – 89.3 °C; ^{1}H NMR (600 MHz, CD_3OD): δ = 7.39 – 7.34 (m, 2H; H6), 7.31 (tt, J = 8.0, 1.5 Hz, 3H; H7/8), 5.99 (q, J = 1.5 Hz, 1H; H2), 2.18 – 2.17 (m, 3H; H4) ppm; ^{13}C NMR (151 MHz, CD_3OD): δ = 172.0 (C1), 150.7 (C3), 141.9 (C5), 129.2 (2C; C6), 128.9 (C8), 128.3 (2C; C7), 121.7 (C2), 26.6 (C4) ppm; IR (ATR): $\tilde{\upsilon}$ = 3326(w), 3080(w), 3057(w), 3046(w), 3023(w), 2999(w), 2957(w), 2906(w), 2556(m), 2464(w), 2391(m), 2341(w), 1988(w), 1962(w), 1938(w), 1885(w), 1764(w), 1666(m), 1640(m), 1609(s), 1597(s), 1572(s), 1492(m), 1442(m), 1402(m), 1346(s), 1312(m), 1289(m), 1266(m), 1217(w), 1144(m), 1079(w), 1035(w), 1025(w), 1011(w), 995(w), 964(w), 916(m), 879(m), 853(m), 841(m), 769(s), 750(m), 722(m), 698(s), 670(m) cm^{-1}; HR-ESI-MS: *m*/*z* calcd. for $C_{10}H_{11}NONa^+$ $[M+Na]^+$: 184.0738), found: 184.0737.

4.2.3. ***Z*-3**

Prepared according to GP, ***E*-3** (15 mg, 0.1 mmol, *E*:*Z* >20:1) was converted to **Z-3** in 24 h yielding a white solid (14 mg, 98%., *Z*:*E* 68:32) after filtration over a SiO_2-plug. The spectroscopic data obtained were in accordance with those described in the literature.[4d]

R_f = 0.05 (10% Et_2O/*n*-pentane); M.p.: 132.3 – 134.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 – 7.45 (m, 2H; H5), 7.39 – 7.29 (m, 3H; H6/7), 6.84 (d, J = 12.6 Hz, 1H; H3), 5.98 (d, J = 12.6 Hz, 1H; H2), 5.77 (s, 1H; N-H), 5.49 (s, 1H; NH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.1 (C1), 137.7 (C3), 135.0 (C4), 129.0 (2C; C5), 128.9 (C7), 128.7 (2C; C6), 124.0 (C2) ppm; IR (ATR): $\tilde{\upsilon}$ = 3319(m), 3146(m), 3085(m), 3023(w), 1949(w), 1837(w), 1663(s), 1614(s), 1575(m), 1494(s), 1456(m), 1433(s), 1345(s), 1320(m), 1240(w), 1189(w), 1156(w), 1134(m), 1078(w), 1031(w), 1002(w), 987(w), 976(w), 925(m), 800(s), 762(s), 752(s), 711(m), 688(s) cm^{-1}; HR-ESI-MS: *m*/*z*: calcd. for $C_9H_9NONa^+$ $[M+Na]^+$: 170.0576; found 170.0577.

4.2.4. ***Z*-4**

Prepared according to GP, ***E*-4** (19 mg, 0.1 mmol, 1.0 eq.) was converted to ***Z*-4** in 6 h yielding a white solid (16 mg, 86%) after separation by flash column chromatography (50% EtOAc/cyclohexane).

R_f = 0.15 (50% EtOAc/cyclohexane); M.p.: 98–100 °C; ^{1}H NMR (600 MHz, CD_3OD): δ = 7.37 – 7.33 (m, 2H; H2), 7.33 – 7.28 (m, 1H; H1) 7.25 – 7.21 (m, 2H; H3), 5.93 (s, 1H; H8), 2.57 (d, J = 2.0 Hz, 3H; H10), 2.49 (q, J = 7.3 Hz, 2H; H6), 1.04 (td, J = 7.5, 2.0 Hz, 3H; H7) ppm; ^{13}C NMR (151 MHz, CD_3OD): δ = 170.6 (C9), 155.2 (C5), 141.3 (C4), 129.1 (C2), 128.7 (C1/C3), 120.7 (C8), 33.3 (C10), 26.1 (C6), 12.7 (C7) ppm; IR (ATR): ν = 3324 (m), 3058 (w), 2973 (w), 2939 (w), 2887 (w), 2478 (w), 1661 (m), 1627 (s), 1532 (s), 1492 (m), 1456 (m), 1403 (m), 1318 (m), 1259 (s), 1195 (m), 1156 (m), 1082 (m), 866 (s), 752 (s), 697 (s) cm^{-1}; HR-ESI-MS: *m*/*z* calcd. $C_{12}H_{15}NONa^+$ for $[M+Na]^+$: 212.1046, found: 212.1054.

4.2.5. ***Z*-5**

Prepared according to GP, E-5 (20 mg, 0.1 mmol, 1.0 eq.) was converted to Z-5 in 22 h yielding a colorless oil (16 mg, 79%) after separation by flash column chromatography (50% EtOAc/cyclohexane).

R_f = 0.17 (50% EtOAc/cyclohexane); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.33 – 7.28 (m, 2H; H2), 7.28 – 7.24 (m, 3H; H1/H3), 5.91 – 5.90 (m, 1H; H8), 2.76 (s, 3H; H10/H11), 2.62 (s, 3H; H10/H11), 2.50 (qd, J = 7.4, 1.3 Hz, 2H; H6), 1.07 (t, J = 7.4 Hz, 3H; H7) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 169.24 (C9), 148.71 (C5), 139.76 (C4), 128.15 (C2), 127.78 (C1), 127.21 (C3), 119.32 (C8), 37.70 (C10/C11), 34.25 (C10/C11), 30.60 (C6), 12.50 (C7) ppm; IR (ATR): ν = 3460 (br), 2966 (w), 2933 (w), 1610 (s), 1493 (m), 1442 (m), 1394 (s), 1266 (m), 1176 (m), 1153 (m), 1101 (w), 1083 (w), 1055 (m), 1028 (m), 989 (m), 917 (w), 848 (m), 771 (s), 749 (m), 700 (s) cm^{-1}; HR-ESI-MS: *m/z* calcd. for $C_{13}H_{17}NONa^+$ $[M+Na]^+$: 226.1202, found: 226.1209.

4.2.6. ***Z-6***

Prepared according to GP, *E*-6 (32 mg, 0.1 mmol, 1.0 eq.) was converted to *Z*-6 in 8 h yielding a white solid (24 mg, 74%) after separation by flash column chromatography (10% EtOAc/cyclohexane).

R_f = 0.28 (20% EtOAc/cyclohexane); M.p.: 137–140 °C; ^{1}H NMR (600 MHz, CD_3OD): δ = 7.54 (d, J = 8.6 Hz, 2H; H11), 7.50 – 7.48 (m, 2H; H12), 7.33 – 7.29 (m, 2H; H2), 7.28 – 7.24 (m, 1H; H1), 7.24 – 7.21 (m, 2H; H3), 6.08 (t, J = 1.4 Hz, 1H; H8), 2.52 (qd, J = 7.4, 1.4 Hz, 2H; H6), 1.05 (t, J = 7.4 Hz, 3H; H7) ppm; ^{13}C{^{19}F} NMR (151 MHz, CD_3OD): δ = 167.8 (C9), 158.5 (C5), 143.4 (C10), 141.3 (C4), 129.2 (C2), 128.8 (C1), 128.6 (C3), 126.9 (C12), 126.4 (C13), 125.7 (C14), 120.6 (C12), 120.5 (C8), 33.8 (C6), 12.7 (C7) ppm; ^{19}F NMR (564 MHz, CD_3OD): 63.61 ppm; IR (ATR): ν = 3238 (w), 3052 (w), 2969 (w), 1659 (m), 1604 (s), 1539 (w), 1410 (m), 1314 (s), 1264 (s), 1181 (m), 1151 (s), 1111 (s), 1067 (s), 1015 (m), 995 (m), 866 (m), 840 (s), 785 (m), 769 (s), 699 (s) cm^{-1}; HR-ESI-MS: *m/z* calcd. for $C_{18}H_{16}F_3NONa^+$ $[M+Na]^+$: 342.1076, found: 342.1071.

4.2.7. ***Z-7***

Prepared according to GP, *E*-7 (38 mg, 0.1 mmol, 1.0 eq.) was converted to *Z*-7 in 6 h yielding a colorless oil (32 mg, 86%) after separation by flash column chromatography (5% EtOAc/ cyclohexane).

R_f = 0.44 (20% EtOAc/cyclohexane); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34 – 7.29 (m, 3H; H1/H2), 7.24 – 7.21 (m, 2H; H3), 6.31 (t, J = 1.3 Hz, 1H; H8), 2.51 (qd, J = 7.4, 1.3 Hz, 2H; H6), 1.48 (s, 18H; H12), 1.07 (t, J = 7.4 Hz, 3H; H7). ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 166.3 (C9), 159.4 (C5), 150.0 (C10), 139.8 (C4), 128.2 (C1/C2), 128.0 (C1/C2), 127.5 (C3), 118.7 (C8), 84.3 (C11), 33.1 (C6), 27.8 (C12), 12.3 (C7) ppm; IR (ATR): ν = 2979 (w), 2936 (w), 1776 (m), 1742 (s), 1695 (m), 1626 (m), 1458 (w), 1444 (w), 1394 (w), 1370 (m), 1299 (s), 1245 (s), 1150 (s), 1114 (s), 1005 (m), 998 (m), 845 (s), 790 (m), 772 (m), 698 (s) cm^{-1}; HR-ESI-MS: *m/z* calcd. for $C_{21}H_{29}NO_5Na^+$ $[M+Na]^+$: 398.1938, found: 398.1961.

4.2.8. ***Z-8***

Prepared according to GP, *E*-8 (31 mg, 0.1 mmol, 1.0 eq.) was converted to *Z*-8 in 22 h under oxygen atmosphere yielding a white solid (13 mg, 42%) after separation by flash column chromatography (10%→30% →80% EtOAc/cyclohexane).

R_f = 0.42 (100% EtOAc); M.p.: Decomposition >98 °C; ^{1}H NMR (600 MHz, CD_3OD): δ = 7.35 – 7.30 (m, 2H; H2), 7.30 – 7.25 (m, 1H; H1), 7.23 – 7.18 (m, 2H; H3), 6.01 (d, J = 2.2 Hz, 1H; H8), 2.47 (q, J = 7.4 Hz, 2H; H6), 1.02 (td, J = 7.4, 1.7 Hz, 3H; H7) ppm; ^{13}C{^{19}F} NMR (151 MHz, CD_3OD): δ = 173.8 (C9), 159.0 (C5), 141.7 (C4), 128.9 (C2), 128.6 (C3), 128.4 (C1), 122.8 (C8), 121.5 (C10), 34.1 (C6), 12.7 (C7) ppm; ^{19}F NMR (564 MHz, CD_3OD): –79.61 ppm; IR (ATR): ν = 3609 (w), 3364 (br), 2973 (w), 1708 (w), 1639 (m), 1618 (m), 1599 (w), 1491 (w), 1456 (m), 1384 (m), 1302 (s), 1275 (s), 1176 (s), 1133 (s), 1114 (s), 1042 (m), 948 (w), 869 (m), 760 (m), 699 (s) cm^{-1}; HR-ESI-MS: *m/z* calcd. for $C_{12}H_{11}F_3NO_3S^-$ $[M-H]^-$: 306.0417, found: 306.0421.

4.2.9. ***Z-9***

Prepared according to GP, *E*-9 (33 mg, 0.1 mmol, 1.0 eq.) was converted to *Z*-9 in 23 h yielding a white solid (20 mg, 62%) after separation by flash column chromatography (20% EtOAc/cyclohexane).

R_f = 0.21 (1% MeOH/CH_2Cl_2); M.p.: Decomposition >116 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 – 7.73 (m, 2H; H10), 7.45 – 738 (m, 3H; H1/H2), 7.34 (bs, 1H; H8), 7.28 (d, J = 8.1 Hz, 2H; H11), 7.12 – 7.08 (m, 2H; H3), 5.81 (bs, J = 1.3 Hz, 1H; H6), 2.44 (m, 5H; H13/H14), 1.01 (t, J = 7.4 Hz, 3H; H15) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 163.4 (C7), 158.9 (C5), 144.9 (C9), 138.3 (C4), 135.7 (C12), 129.5 (C11), 129.4 (C1/C2), 129.3 (C1/C2), 128.6 (C10), 127.3 (C3), 119.4 (C6), 33.4 (C14), 21.8 (C13), 12.0 (C15) ppm; IR (ATR): ν = 3202 (br), 2969 (w), 2932 (w), 2872 (w), 1678 (s), 1632 (m), 1438 (s), 1346 (s), 1178 (s), 1138 (s), 1084 (s), 1041 (m), 880 (m), 856 (s), 812 (m), 780 (m), 756 (m), 730 (s), 695 (s), 659 (s) cm^{-1}; HR-ESI-MS: *m/z* calcd. for $C_{18}H_{19}NO_3SNa^+$ $[M+Na]^+$: 352.0983, found: 352.0978; *m/z* calcd. for $C_{36}H_{38}N_2O_6S_2Na^+$ $[2M+Na]^+$: 681.2069, found: 681.2056.

4.2.10. ***Z-10***

Prepared according to GP, *E*-10 (25 mg, 0.1 mmol, 1.0 eq.) was converted to *Z*-10 in 6.5 h yielding a white solid (22 mg, 88%) after separation by flash column chromatography (50% EtOAc/cyclohexane).

R_f = 0.25 (50% EtOAc/cyclohexane); M.p.: Decomposition >141 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.38 – 7.28 (m, 3H; H1/H2), 7.23 – 7.17 (m, 2H; H3), 5.94 (t, J = 1.4 Hz, 1H; H8), 3.10 (s, 3H; H10), 2.51 (qd, J = 7.4, 1.4 Hz, 2H; H6), 1.04 (t, J = 7.4 Hz, 3H; H7) ppm; ^{13}C NMR (101 MHz, CD_3OD): δ = 166.8 (C9), 163.1 (C5), 140.9 (C4), 129.1 (C1/C2), 129.0 (C1/C2), 128.4 (C3), 117.7 (C8), 41.3 (C10), 34.2 (C6), 12.5 (C7) ppm; IR (ATR): ν = 3198 (w), 2972 (w), 2933 (w), 1702 (w), 1683 (s), 1630 (m), 1600 (w), 1449 (s), 1406 (m), 1331 (s), 1323 (s), 1230 (m), 1170 (m), 1122 (s), 1040 (m), 972 (s), 859 (s), 781 (m), 754 (s), 697 (s) cm^{-1}; HR-ESI-MS: *m/z* calcd. for $C_{12}H_{15}NO_3SNa^+$ $[M+Na]^+$: 276.0665, found: 276.0649.

4.2.11. ***Z-11***

Prepared according to GP, E-11 (38 mg, 0.1 mmol, 1.0 eq.) was converted to Z-11 in 24 h yielding a white solid (35 mg, 92%) after separation by flash column chromatography (10%→40% EtOAc/cyclohexane).

R_f = 0.31 (50% EtOAc/cyclohexane); M.p.: 145–148 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.26 (bs, 1H; H10), 7.79 (d, J = 7.1 Hz, 2H; H12), 7.46 (d, J = 7.7 Hz, 2H; H3), 7.30 (d, J = 7.8 Hz, 2H; H13), 7.17 (d, J = 7.8 Hz, 2H; H4), 5.91 (bs, 1H; H8), 2.45 (bs, 3H; H15), 2.12 (bs, 3H; H7) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.9 (C9), 152.9 (C6), 145.3 (C14), 143.0 (C5), 135.6 (C11), 130.5 (q, J_{C-F} = 32.5 Hz; C2), 129.7 (C13), 128.4 (C12), 127.5 (C4), 125.6 (q, J_{C-F} = 3.8 Hz; C3), 124.0 (q, J_{C-F} = 272.3 Hz; C1), 120.0 (C8), 26.5 (C7), 21.8 (C15) ppm; ^{19}F NMR (564 MHz, $CDCl_3$): 62.73 ppm; IR (ATR): ν = 3112 (br), 2878 (w), 1672 (m), 1637 (m), 1615 (w), 1449 (s), 1406 (w), 1344 (s), 1323 (s), 1236 (w), 1143 (s), 1121 (s), 1107 (s), 1089 (s), 1063 (s), 1030 (s), 1018 (s), 863 (s), 835 (s), 814

(s) cm^{-1}; HR-ESI-MS: *m/z* calcd. for $C_{18}H_{16}F_3NO_3SNa^+$ $[M+Na]^+$: 406.0701, found: 406.0702.

4.2.12. ***Z*-12**

Prepared according to GP, *E*-12 (28 mg, 0.1 mmol, 1.0 eq.) was converted to *Z*-12 in 7.5 h yielding a colorless oil (27 mg, 97%) after separation by flash column chromatography (50% EtOAc/cyclohexane).

R_f = 0.11 (20% EtOAc/cyclohexane); $[\alpha]_D^{25}$ = –76.5 (c = 0.8, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 – 7.29 (m, 3H; H1/H2), 7.24 – 7.19 (m, 2H; H3), 5.88 (t, *J* = 1.4 Hz, 1H; H8), 5.55 (d, *J* = 7.6 Hz, 1H; H10), 4.39 (p, *J* = 7.2 Hz, 1H; H11), 4.08 (m, 2H; H14), 2.44 (qd, *J* = 7.2, 1.1 Hz, 2H; H6), 1.20 (t, *J* = 7.1 Hz, 3H; H15), 1.07 – 1.01 (m, 6H; H7/H12) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8 (C13), 166.3 (C9), 154.0 (C5), 139.8 (C4), 128.7 (C1/C2), 128.2 (C1/C2), 127.5 (C3), 121.0 (C8), 61.4 (C14), 47.9 (C11), 32.9 (C6), 18.2 (C12), 14.2 (C15), 12.2 (C7) ppm; IR (ATR): ν = 3297 (m), 2977 (w), 2935 (w), 1743 (s), 1660 (m), 1634 (s), 1539 (s), 1454 (m), 1378 (m), 1347 (m), 1301 (m), 1264 (m), 1185 (s), 1159 (s), 1081 (w), 1026 (m), 989 (w), 888 (m), 776 (m), 697 (s) cm^{-1}; HR-ESI-MS: *m/z* calcd. for $C_{16}H_{21}NO_3Na^+$ $[M+Na]^+$: 298.1414, found: 298.1423.

4.2.13. ***Z*-13**

Prepared according to GP, *E*-13 (29 mg, 0.1 mmol, 1.0 eq.) was converted to ***Z*-13** in 7.5 h yielding a colorless oil (22 mg, 77%) after separation by flash column chromatography (20% EtOAc/ cyclohexane).

R_f = 0.14 (20% EtOAc/cyclohexane); $[\alpha]_D^{25}$ = –49.8 (c = 0.2, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.41 – 7.37 (m, 2H; H2), 7.34 – 7.30 (m, 1H; H1), 7.25 – 7.22 (m, 2H; H3), 5.91 (t, *J* = 1.4 Hz, 1H; H8), 5.56 (d, *J* = 8.6 Hz, 1H; H10), 4.37 (dd, *J* = 8.6, 4.7 Hz, 1H; H11), 3.62 (s, 3H; H16), 2.44 – 2.39 (m, 2H; H6), 1.85 (hd, *J* = 6.9, 4.7 Hz, 1H; H12), 1.04 (t, *J* = 7.4 Hz, 3H; H7), 0.64 (d, *J* = 6.9 Hz, 3H; H13/H14), 0.50 (d, *J* = 6.9 Hz, 3H; H13/H14) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 172.2 (C15), 166.7 (C9), 153.7 (C5), 139.9 (C4), 129.0 (C2), 128.2 (C1), 127.6 (C3), 121.2 (C8), 57.2 (C11), 52.0 (C16), 33.4 (C6), 30.9 (C12), 18.8 (C13/C14), 17.5 (C13/C14), 12.1 (C7) ppm; IR (ATR): ν = 3278 (m), 3055 (w), 2964 (m), 2879 (w), 1745 (s), 1655 (m), 1631 (s), 1539 (s), 1463 (m), 1436 (m), 1372 (m), 1322 (m), 1280 (m), 1253 (m), 1195 (s), 1179 (s), 1153 (s), 885 (m), 767 (m), 670 (s) cm^{-1}; HR-ESI-MS: *m/z* calcd. for $C_{17}H_{23}NO_3Na^+$ $[M+Na]^+$: 312.1574, found: 312.1578.

For comparative determination of the $[\alpha]_D^{25}$ value ***Z*-13** was prepared according to GP-C (for details: see ESI), (*Z*)-3-phenylpent-2-enoic acid (240 mg, 1.4 mmol, 1.0 eq.) was converted to ***Z*-13** in 16 h with L-valine methylester hydrochloride (268 mg, 1.6 mmol, 1.2 eq.) yielding a colourless oil (328 mg, 83%) after flash column chromatography (50% Et_2O/*n*-pentane).

$[\alpha]_D^{25}$ = –45.3 (*c* = 1, MeOH)

4.3. Isomerization of Peptide ***15***

E → *Z* Isomerization of peptide **15** was achieved by following a modified procedure GP: The peptide (15.4 mg, 20.0 µmol, 1.0 eq.) and (–)-riboflavin (0.4 mg, 1.0 µmol, 0.05 eq.) was dissolved in d_6-DMSO and stirred under UV-light irradiation (402 nm) at rt for 24 h. The crude reaction mixture was analyzed by NMR-spectroscopy showing a clean reaction and a *Z*/*E*-ratio of 76/24. An analytically pure sample of the *Z*-isomer for full characterization was obtained by semi-preparative HPLC.

^{1}H NMR (600 MHz, d_6-DMSO): δ = 10.04 (bs, 1H, NH), 9.34 (s, 1H, OH), 8.84 (bs, 1H, NH), 8.14 – 8.02 (bm, 4H, NH), 7.89 (d, *J* = 8.1 Hz, 1H, NH), 7.54 – 7.48 (m, 1H, H20), 7.34 (s, 1H, H22), 7.25 (t, *J* = 7.4 Hz, 2H, H11), 7.21 – 7.16 (m, 3H, H10, H12), 7.11 (t, *J* = 7.9 Hz, 1H, H19), 7.07 (d, *J* = 8.5 Hz, 2H, H29), 6.73 – 6.67 (m, 3H, H30, H18), 5.94 (d, *J* = 1.5 Hz, 1H, H14), 4.46 (td, *J* = 9.2, 4.0 Hz, 1H, H7), 4.20 (q, *J* = 7.7 Hz, 1H, H2), 4.02 (m, 1H, H26), 3.97 (m, 2H, H24), 3.03 (dd, *J* = 14.3, 5.1 Hz, 1H, H27), 3.00 – 2.94 (m, 1H, H8), 2.84 (dd, *J* = 14.2, 8.3 Hz, 1H, H27'), 2.70 (dd, *J* = 13.9, 9.9 Hz, 1H, H8'), 2.01 (d, *J* = 1.4 Hz, 3H, H16), 1.64 – 1.54 (m, 1H, H4), 1.50 (t, *J* = 7.3 Hz, 2H, H3), 0.88 (d, *J* = 6.5 Hz, 3H, H5), 0.83 (d, *J* = 6.4 Hz, 3H, H5') ppm; ^{13}C NMR (151 MHz, d_6-DMSO): δ = 174.0 (C1), 173.4 (C6), 168.6 (C23), 166.9 (C25), 164.6 (C13), 156.6 (C28), 147.2 (C17), 141.4 (C21), 137.9 (C9), 130.5 (C29), 129.1 (C10), 128.0 (C11), 127.9 (C19), 126.2 (C12), 124.8 (C31), 122.7 (C18), 121.1 (C14), 117.9 (C20), 117.7 (C22), 115.4 (C30), 53.7 (C26), 53.4 (C7), 50.3 (C2), 42.7 (C24), 40.1 (C4), 37.4 (C8), 36.3 (C27), 26.3 (C16), 24.2 (C4), 22.8 (C5), 21.4 (C5') ppm; HR-ESI-MS: *m/z*: calcd. for $C_{36}H_{44}N_5O_7^+$ $[M+H]^+$: 658.3236; found 658.3231.

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6. References and notes

1. (a) Dugave, C.; Demange, L. *Chem. Rev*. **2003**, *103*, 2475-2532. (b) Metternich, J. B.; Gilmour, R. *Synlett* **2016**, *27*, 2541–2552; (c) Pearson, C. M.; Snaddon, T. N. *ACS Cent. Sci*. **2017**, *3*, 922-924; (d) Molloy, J. J.; Morack, T.; Gilmour. R. *Angew. Chem. Int. Ed.* **2019**, *58*, 13654-13664.
2. For selected reviews on photocatalysis highlighting energy transfer, see: (a) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. *Angew. Chem. Int. Ed*. **2018**, *57*, 10034-10072; (b) Zhou, Q. -Q.; Zou, Y. -Q.; Lu, L. -Q.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2019**, *58*, 1586–1604. (c) Metternich, J. B.; Mudd, R. J.; Gilmour, R. Flavins in Photochemistry. *Science of Synthesis: Photocatalysis in Organic Synthesis*, **2019**, 391-404.
3. Faßbender, S. I.; Molloy, J. J.; Mück-Lichtenfeld, C.; Gilmour, R. *Angew. Chem. Int. Ed.* **2019**, *59*, 330-334.
4. (a) Singh, K.; Staig, S. J.; Weaver, J. *J. Am. Chem. Soc.* **2014**, *136*, 5275-5278; (b) Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257; (c) Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc*. **2016**, *138*, 1040-1045; (d) Metternich, J. B.; Artiukhin, D. G.; Holland, M. C.; Von Bremen-Kuhne, M.; Neugebauer, J.; Gilmour, R. *J. Org. Chem.* **2017**, 82, 9955-9977; (e) Cai, W.; Fan, H.; Ding, D.; Zhang, Y.; Wang, W. *Chem. Commun.* **2017**, *53*, 12918 – 12921; (f) Kurzawa, T.; Harms, K; Koert, U. *Org. Lett.* **2018**, *20*, 1388-1391. (g) Molloy, J. J.; Metternich, J. B.; Daniliuc, C. G.; Watson, A. J. B.; Gilmour, R. *Angew. Chem. Int. Ed.* **2018**, *57*, 3168-3172; (h) Hostmann, T.; Molloy, J. J.; Bussmann K.; Gilmour, R. *Org. Lett.* **2019**, *21*, 10164-10168; (i) Neveselý, T.; Daniliuc, C. G.; Gilmour, *R. Org. Lett.* **2019**, *21*, 9724-9728; (j) Onneken, C.; Bussmann, K.; Gilmour, R. *Angew. Chem. Int. Ed.* **2020**, *59*, 330-334.
5. Hoffmann, R. W. *Chem. Rev*. **1989**, *89*, 1841-1860.
6. Arai, T.; Tokumaru, K. *Chem. Rev*. **1993**, *93*, 23-39.
7. Gozem, S.; Luk, H. L.; Schapiro, I.; Olivucci, M. *Chem. Rev.* **2017**, *117*, 13502-13565.
8. For examples of photo-isomerization of cinnamamides, see (a) Lewis, F. D.; Elbert, J. E.; Upthagrove, A. L; Hale, P. D. *J. Am. Chem. Soc*. **1988**, *110*, 5191-5192; (b) Lewis, F. D.; Elbert, J. E.; Upthagrove, A. L.; Hale, P. D. *J. Org. Chem*. **1991**, *56*, 553-561; (c) Shu, P.; Xu, H.; Zhang, L.; Li, J.; Liu, H.; Luo, Y.; Yang, X.; Ju, Z.; Xu, Z. *SynOpen* **2019**, *3*, 103-107.
9. Walker, A. G.; Radda G. K. *Nature* **1967**, *215*, 1483.
10. Ultrafast laser pulse and time-resolved fluorescent measurements gave a quantum yield for ISC of φ_T = 0.375 with a relatively long phosphorescence lifetime of τ_P = 27 µs, which makes riboflavin

suitable for the application as a triplet sensitizers. Please see, Zhao, J.; Wu, W.; Sun, J.; Guo, S. *Chem. Soc. Rev*. **2013**, *42*, 5323-5351.
11. Morack, T.; Metternich, J. B.; Gilmour, R. *Org. Lett.* **2018**, *20*, 1316-1319.
12. Mazzier, D.; Crisma, M.; De Poli, M.; Marafon, G.; Peggion, C.; Clayden, J.; Moretto, A. *J. Am. Chem. Soc*. **2016**, *138*, 8007-8018.
13. Cai, S.; Saito, T.; Fuji, N. *Free Radic. Biol. Med*. **2013**, *65*, 1037-1046.
14. Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, J. B. *J. Chem. Soc., Chem. Commun*. **1980**, 234-235. (b) Jenkins, C. L.; Vasbinder, M. M.; Miller, S. J.; Raines, R. T. *Org. Lett*. **2005**, *7*, 132619-132622.
15. Kumar, M. G.; Thombare, V. J.; Katariya, M. M.; Veeresh, K.; Raja, K. M. P.; Gopi, H. N. *Angew. Chem. Int. Ed*. **2016**, *55*, 7847-7851.
16. Bloom, S.; Liu, C.; Kölmel, D. K.; Qiao, J. X.; Zhang, Y.; Poss, M. A.; Ewing, W. R.; MacMillan, D. W. C. *Nat. Chem*. **2018**, *10*, 205-211.

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7. Supporting Information

Supporting Information including experimental protocols, NMR and X-ray data is available (PDF file).

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: