Communication

A Bio-Inspired, Catalytic E#Z Isomerization of Activated Olefins

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A Bio-Inspired, Catalytic *E*→*Z* Isomerization of Activated Olefins

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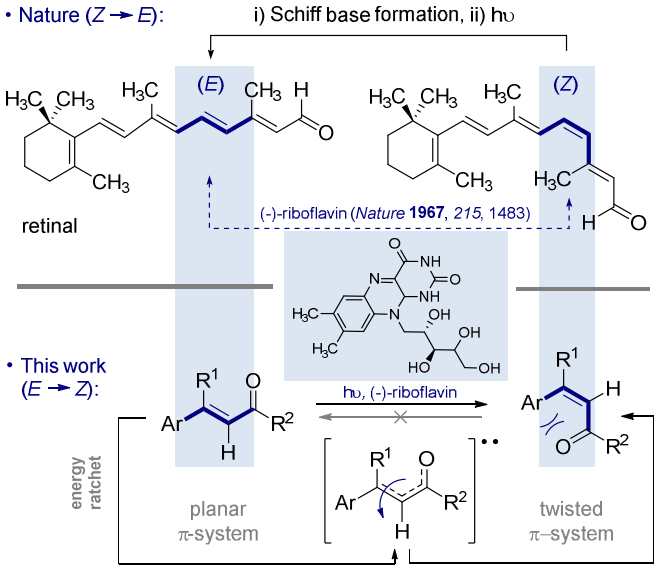
Supporting Information Placeholder

ABSTRACT: Herein, *Nature's* flavin-mediated activation of complex (poly)enes has been translated to a small molecule paradigm culminating in a highly (*Z*)-selective, catalytic isomerization of activated olefins using (−)-riboflavin (up to 99:1 *Z*:*E*). In contrast to the prominent *Z* → *E* isomerization of the natural system, it was possible to invert the directionality of the isomerization (*E*→*Z*) by simultaneously truncating the retinal scaffold, and introducing a third olefin substituent to augment A1,3-strain upon isomerization. Consequently, conjugation is reduced in the product chromophore leading to a substrate / product combination with discrete photophysical signatures. The operationally simple isomerization protocol has been applied to variety of enone-derived substrates and showcased in the preparation of the medically relevant 4-substituted coumarin scaffold. A correlation of sensitizer triplet energy (E_T) and reaction efficiency, together with the study of additive effects and mechanistic probes, is consistent with a triplet energy transfer mechanism.

Of the plethora of fundamental reactions that can be achieved by (organo)-catalysis,[1] a strategy for the selective *E*→*Z* isomerization of olefins remains conspicuously absent. Indeed, the development of a generic catalyst to realize this pinnacle of atom economy[2] has yet to be reported.[3] Despite the value of *Z*-olefins in contemporary organic synthesis,[4] the development of a highly selective transformation remains formidable on account of the "*uphill*" energetics of the net process.[5] To circumvent this obstacle, a strategy relying on an energy ratchet mechanism is necessary; this has proven to be highly successful in the design of functional supramolecular systems.[6] By translating the notion of an (irreversible) energy ratchet to the paradigm of olefin isomerization, concerns pertaining to microscopic reversibility, and the undesired formation of thermodynamic mixtures, are mitigated.

Photochemical activation via a sensitiser[7] is a logical energy ratcheting tactic that is ideally suited to catalytic olefin isomerisation. Not only does the initial excitation ensure that all subsequent steps are energetically "*downhill*", the principle of microscopic reversibility does not apply to transformations initiated by photochemical excitation. Hammond's pioneering stilbene photoisomerization studies[8] and Arai's β-alkylstyrene isomerization[9] beautifully exemplify this notion. However, the synthetic utility of this isomerization strategy has been limited by an extremely narrow substrate scope. In an effort to extend the substrate scope of photosensitized isomerizations beyond electron rich styrenes and stilbenes, *Nature's* photochemical (*Z*→*E*) isomerization of retinal[10] was taken as a blueprint for reaction design (Scheme 1, upper). Whilst the overall directionality of the natural system favors the *E*-isomer, an elegant study by Walker and Radda in 1967 described the qualitative observation that riboflavin catalyzes the reverse *E*→*Z* photoisomerization of retinal.[11]

Scheme 1 Reaction design considerations. Upper: the *Z*→*E* photoisomerization of retinal. Lower: a bio-inspired catalytic, *Z*-selective isomerization.



To improve this reversal to useful levels, and thus translate biological photo-isomerization into a small molecule paradigm, a process of substrate re-engineering was applied. In retinal, isomerization about the 1,2-disubstituted olefin induces a change in conformation and photo-physical properties. By simultaneously truncating the retinal scaffold, and introducing a third olefin substituent to augment A1,3-strain upon *E*→*Z* isomerization, it was envisaged that this same phenomenon might be exploited to discriminate the substrate and product based on de-conjugation of the π-system.

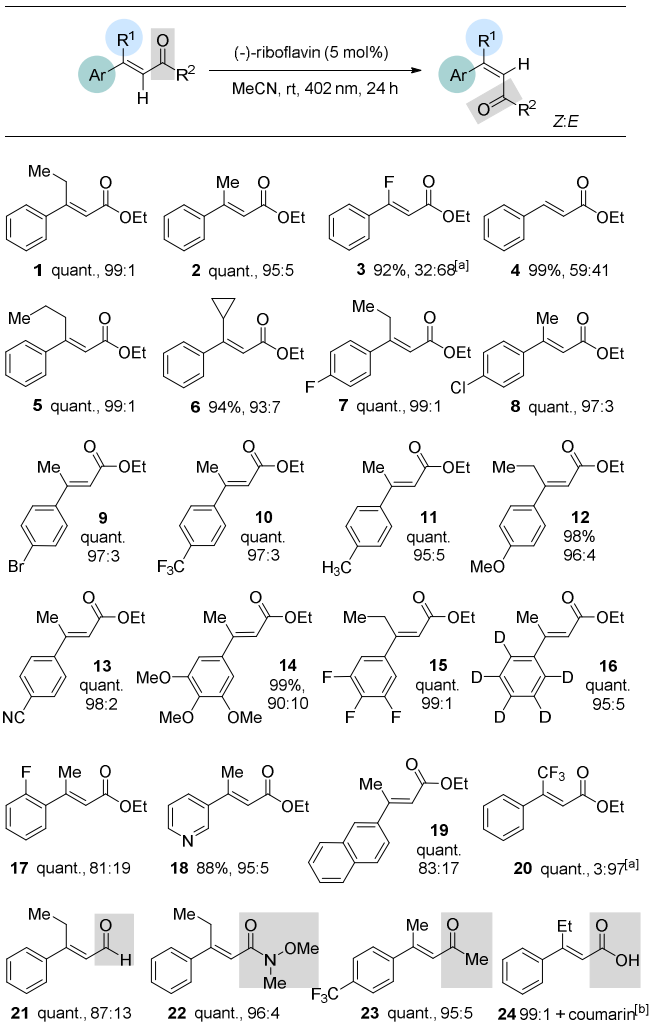
This in turn would ensure that only the starting *E*-isomer interacts with the photo-catalyst, thus ultimately resulting in a *Z*-selective transformation. It was expected that the excited state species generated by an initial energy transfer process would induce cleavage of the π-bond to generate a delocalized biradical intermediate[12] where C-C bond rotation is possible (*cf* Paterno-Büchi reaction[13]). This species could, in theory, be transposed to the corresponding radical cation or anion depending on the environment (Scheme 1, lower). For simplicity, activated olefins based on cinnamaldehyde were selected as substrates for investigation. (−)-Riboflavin was investigated as a cheap, commercially available photocatalyst (25g, 27.50 USD, Sigma-Aldrich).[14-16] Inspection of the respective triplet energies of cinnamaldehyde and riboflavin indicate a productive match for this partnership (full details in the SI).

As a start point for this investigation, the isomerization of α,β-unsaturated esters was investigated (Table 1). To the best of our knowledge, this transformation has only been achieved with modest selectivities using sub-stoichiometric loadings of Lewis-acids.[17] A screen of common solvents and catalysts loadings quickly identified acetonitrile with 5 mol% (−)-riboflavin to be the optimal conditions. The *E*→*Z* isomerization of ethyl (*E*)-3-phenylpent-2-enoate (**1**) proceeded smoothly within 24 h under UV-light irradiation. Quantitative material recovery was achieved by simple filtration, and analysis of the crude mixture revealed a *Z*:*E* mixture of 99:1.

Encouraged by the first results obtained for **1**, a variety of substrates were successively modified at i) the β-substituent (R^1), ii) the aryl ring and iii) the carbonyl functionality (R^2), and investigated under the standard reaction conditions. Substituting R^1=Et by Me led only to a very minor erosion of selectivity (**1** and **2**, *Z*:*E* 99:1 and 95:5, respectively). However, the installation of F or H at R^1 led to a decrease in selectivity (**3** and **4**, *Z*:*E* 32:68 and 59:41, respectively), thus implicating a steric parameter in influencing the reaction outcome. The higher selectivity of the vinyl fluoride **3** compared to **4** may be attributed to the improved α-radical stabilizing ability of fluorine as compared to hydrogen.[18] Modification of R^1 was found to be well tolerated as is demonstrated by compounds **5** (*Z*:*E* 99:1) and **6** (*Z*:*E* 93:7). Interestingly, a slight erosion of the isolated yield was observed in the cyclopropyl derivative (94%), possibly due to ring opening. This observation would later prove to be useful in formulating a working mechanistic hypothesis.

Electronic modulation of the aryl ring was found to have a negligible effect on stereoselectivity for both the ethyl and methyl derivatives (**7** and **8**, *Z*:*E* 99:1 and 97:3, respectively; **9**-**15** *Z*:*E* up to 99:1). To probe for radical abstraction phenomena, the deuterated analogue **16** was subjected to the standards reaction conditions. No exchange was observed and the isolated yield and geometric ratio was identical to that of **2** (quant. *Z*:*E* 95:5). To explore the effect of breaking conjugation of the π-system, the *ortho*-fluorophenyl derivative **17** was explored to subtly tilt the ring out of plane. This small modification led to a notable decrease in stereoselectivity (*Z*:*E* 81:19). Replacing the phenyl ring by pyridyl resulted in a slightly lower yield but with high *Z*:*E* selectivity (95:5). Interestingly a slight decrease in the geometric ratio was noted for substrate **19** bearing a larger naphthyl substituent. Finally, exposure of the highly electron deficient system **20** to (−)-riboflavin resulted in quantitative conversion and with a 3:97 ratio. Having confirmed a general tolerance for modifications at R^1 and the aryl substituent, attention was focused on the carbonyl group. Aldehyde **21**, Weinreb amide **22** and ketone **23** (Figure 1, lower) all proved to be excellent substrates for this isomerization, with *Z*:*E* ratios of up to 96:4 having been observed.

Table 1 The (−)riboflavin-catalyzed isomerization of activated olefins

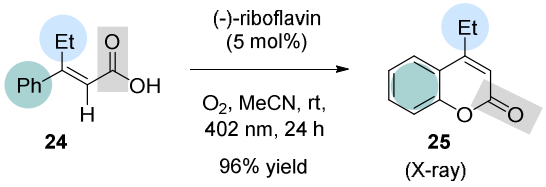


Standard reactions conditions: Reactions were performed with 0.1 mmol substrate (*E*:*Z* >20:1) at ambient temperature in MeCN using 5 mol% catalyst loading under 24 hours of UV-light irradiation (402 nm). *Z*:*E* ratios were determined by ^{1}H NMR spectroscopy and HPLC analysis. [a] N.B. product *E*:*Z* ratio is inverted to reflect the higher IUPAC priority of F than C. [b] Under standard conditions the product distribution was 24% cinnamic acid (*Z*:*E* 99:1) plus coumarin (76%).

By extension, the behavior of (*E*)-cinnamic acid **24** was also explored under the optimized reaction conditions. Again, this substrate furnished the expected (*Z*)-isomer with excellent levels of geometric control (*Z*:*E* 99:1) but in a lower yield (24%): the major product of this process was found to be the corresponding 4-substitued coumarin (**25**). By performing the reaction under an oxygen atmosphere, the intramolecular cyclisation of the (*Z*)-isomer could be driven to comple-

tion (Scheme 2, 96% yield): this constitutes a facile route to an important drug scaffold.[19] The isomerization reaction also proved amenable to scale-up with the (*Z*)-isomer of **1** having been isolated in 82% yield on a 1 mmol scale. The slightly lower yield is attributable to the low intensity of the UV-lamp (1150 mW), thus preventing the photo-stationary state from being reached.[20] When performing the isomerization of (*E*)-**1** with a catalyst loading of only 1 mol%, the product was isolated in quantitative yield and with excellent levels of stereocontrol (*Z*:*E* 99:1).

Scheme 2 A one-pot isomerization/cyclization strategy to generate the 4-substituted coumarin scaffold

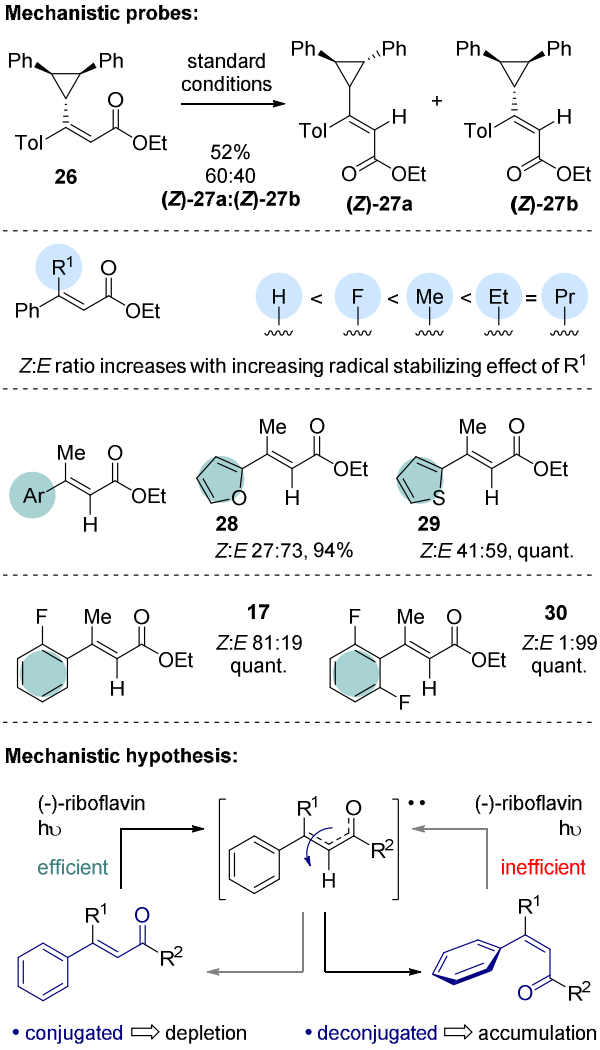


Left: The *E*→*Z* photoisomerization of cinnamic acid **24** by (−)-riboflavin led to the formation of the corresponding coumarin **25** (96% yield). X-ray structural data for coumarin **25** is provided in the SI.

Pursuant to Hammond's mechanistic analyses, correlation of the sensitizer triplet energies (E_T) of various photocatalysts with reaction efficiency,[8] together with the study of additive effects and mechanistic probes, and a Stern-Volmer photoquenching experiment, indicated that a mechanism consistent with triplet energy transfer was operational (full details are provided in the SI). The Stern-Volmer analysis revealed that increased quenching of the photoexcited state of (-)-riboflavin by the *E*-isomer (*E*)-**1** is at least one order of magnitude more effective than with the corresponding *Z*-isomer (*Z*)-**1**, thus a photostationary state with constant *Z*:*E* ratios might be expected. Consequently, pure *E*-(**1**), *Z*-(**1**) and a 1:1 mixture of both isomers were independently subjected to the standard photocatalysis conditions for validation. In all cases, quantitative formation of the expected product was observed with a *Z*:*E*-ratio of 99:1. A time-course analysis of the isomerization of (*E*)-**1** revealed that the photostationary state was reached after 4 hours (full details provided in the SI). Moreover, by correlating the triplet state energy (E_T) of (−)-riboflavin and other common photocatalysts, a clear guideline can be deduced and translated to related isomerization paradigms: Sensitizers with an E_T below that of the excited state of the substrate[21] lead to little or no isomerisation. In contrast, sensitizers with E_T values greater than that of the (*E*)-isomer, but less than that of the (Z)-isomer, result in effective isomerisation (i.e. (−)-riboflavin).

To provide experimental support for the delocalized radical intermediate outlined in Scheme 1, the cyclopropyl-based radical clock **26** was prepared and subjected to the standard conditions used throughout this study. Both diastereoisomers (*Z*)-**27a** and (*Z*)-**27b** were isolated as a 60:40 mixture (52% yield). Stereomutation in (*Z*)-**27a** is consistent with configurational scrambling via a benzylic radical. The retention of stereochemical information in (*Z*)-**27b** suggests that the lifetime of the postulated biradical is comparable to the radical-induced ring opening and closure of the trans-2,3-diphenyl substituted cyclopropane.[22] Repeating this reaction in the absence of (−)-riboflavin led to the quantitative recovery of **26** with no loss of stereochemical information. Additional support for the intermediary benzylic radical is reflected in the increasing *Z*:*E* ratio when improving the stabilizing auxiliary R^1 (H < F < Me < Et ≈ Pr).[18]

Figure 1 Mechanistic investigations of the title reaction.



The initial supposition that a deconjugation-induced change in photophysical signature facilitates selective excitiation was then examined. Probing the effect of ring size (Ar) indicates that (i) distortion (deconjugation) in the product and (ii) planarity (conjugation) in the substrate are key to ensuring high levels of stereocontrol. To illustrate the first condition, substrates **28** and **29** were investigated, where the 5-membered rings retain the requisite aromatic character, but reduce A1,3-strain in the (*Z*)-isomer. In both cases, the (*E*)- and (*Z*)-isomers are conjugated and planar,[23] and the subsequent selectivity is low (*Z*:*E* 27:73 and 41:59 for **28** and **29**, respectively). To validate the second condition, substrates **17** and **30** were investigated which subtly introduce allylic strain by virtue of *ortho*-fluoro substituents. In both cases, where the aryl ring is distorted from planarity,[24] a decrease in selec-

tivity was noted: this was most pronounced in the disubstituted system **30** (*Z*:*E* 1:99).

By emulating the flavin-mediated activation of complex (poly)enes, an operationally simple, highly (*Z*)-selective isomerization of activated olefins has been developed employing inexpensive, commercially available (−)-riboflavin as the photo-catalyst. In contrast to the signature $Z \rightarrow E$ isomerization of the natural system, the directionality of the isomerization ($E \rightarrow Z$) was inverted by truncating the retinal scaffold, and introducing a third olefin substituent to augment A1,3-strain upon isomerization. The transformation is generally applicable to substrates in which the cinnamyl motif is embedded: this includes esters, aldehydes, ketones, Weinreb amides and carboxylic acids. In this latter case the method can be extended to generate 4-substituted coumarins directly. Correlation of sensitizer triplet energy (E_T) and reaction efficiency, together with the study of additive effects and mechanistic probes (see SI), has allowed a mechanistic hypothesis to be formulated based on selective excitation. It is envisaged that the guidelines delineated from this study will facilitate the rapid development of a (photo)-catalyst tool box[25] to address the need for highly selective, generic isomerization catalysts.

ASSOCIATED CONTENT

Supporting Information

NMR spectra, absorption spectra, experimental procedures and mechanistic studies. Supporting information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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