Photocatalytic *E*→*Z* Isomerization of β-Ionyl Derivatives

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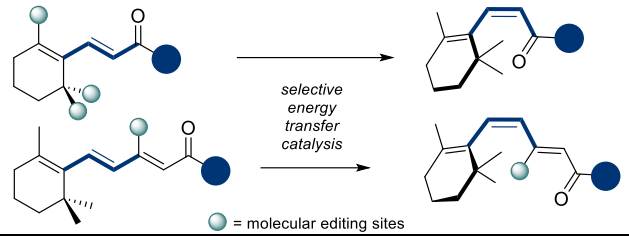
Supporting Information Placeholder



ABSTRACT: An operationally simple *E* → *Z* isomerization of activated dienes, based on the β-ionyl motif intrinsic to retinal, is reported using inexpensive (-)riboflavin (vitamin B_2) under irradiation at 402 nm. Selective energy transfer from photo-excited (−)-riboflavin to the starting *E*-isomer enables geometrical isomerization. Since the analogous process with the *Z*-isomer is inefficient, microscopic reversibility is circumvented, thereby enabling a directional isomerization to generate the *contra*-thermodynamic product (up to 99% yield, up to 99:1 *Z:E*). Prudent choice of photo-catalyst enables chemoselective isomerization to be achieved in both inter- and intramolecular systems. The principles established from this study, together with a molecular editing approach, have facilitated the development of a regioselective isomerization of a truncated triene based on the retinal scaffold.

Retinal isomerization in the mammalian visual cycle is an exemplar of biological precision.[1] Centred on the regioselective geometrical isomerization of a complex polyene,[2] Nature´s efficiency masks the intrinsic challenges associated with manipulating cross-conjugated alkene units. Consequently, general solutions to enable the site-selective isomerization of polyenes using small molecule catalysts remain challening.[3] The discovery that flavins are effective photosensitizers in manipulating retinal geometry by Walker and Radda,[4a] together with seminal studies from Liu and co-workers on the regioselective isomerization of cross conjugated polyenes[4b] provide valuable guidelines on how to reconcile the strategic value of this goal with the current lack of synthetically viable methods. Inspired by these blueprints, and given the ubiquity of the β-ionyl scaffold in human medicine (e.g. vitamin A),[5] the 2,6,6-trimethylcyclohexene core of the retinoids provided a versatile starting point for this study (Figure 1). Specifically, the truncated diene inherent to β-ionone would allow the photochemical isomerization[6] to be explored under biomimetic, flavin-catalysed conditions. It is pertinent to note that studies by Liu and co-workers have established that formation of the *Z*-isomer of β-ionol can be achieved when employing an appropriate triplet sensitizer with a broadband Hg lamp.[3a,6,7] NMR spectroscopic evidence from the same group implicates limited planarity of the strained *Z*-alkene as being an important factor in stereoselection.[8]

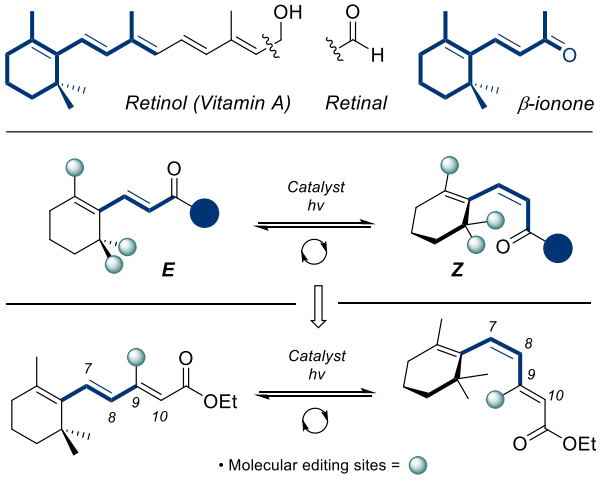


Figure 1. Truncating the complex retinoid template to explore the isomerization of simple dienes based on the β-ionyl system.

Encouraged by these reports, and with the ultimate goal of devising guidelines to enable the regioselective isomerization of larger, naturally occurring polyenes, (-)-riboflavin was evaluated as a biomimetic photosensitizer for *contra*-thermodynamic

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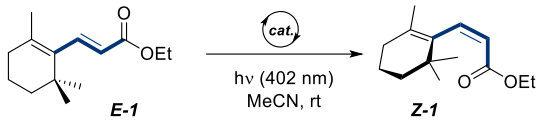
alkene isomerization. Herein, we report molecular editing studies together with the conceptual extension to model triene systems based on truncated retinal. This vitamin catalysis approach[9] enables orthogonality relative to reactions using Ir(III)–based photosensitizers.[10,11] Moreover, the structural editing process allows speculation to be cast on the importance of fractional bond distances, as reported by Dunitz,[12] in selective alkene isomerization following excitation.

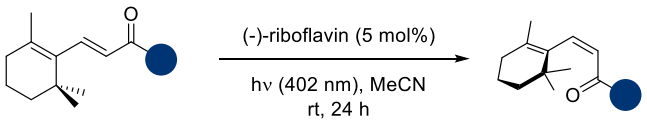
Table 1: Reaction optimization for *E*-1 → *Z*-1.[a,b]



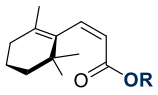
Entry	Catalyst	Time (h)	Conversion (%)	*Z*/*E* Ratio
1	Thioxanthone	14	87	59:41
2	Benzil[c]	14	76	92:8
3	Ir(ppy)$_3$	14	99	99:1
4	(–)-riboflavin	14	99	99:1
5	-	14	>99	10:90
6	(–)-riboflavin	14	>99	0:100[d]

[a]Reactions were performed on a 0.1 mmol scale under an argon atmosphere, using 5 mol % of the specified catalyst at a concentration of 0.05 M. [b]Conversion and *Z*/*E* ratios were determined using ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. [c]365 nm LED used [d]Reaction performed in the dark. [e]Isolated yield.

Table 2: Exploring substrate scope[a]



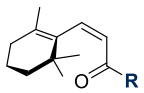
a) Acids/Esters



***Z*-1, 99%** >99:1 R = Et
***Z*-2, 65%[b]** >99:1 R = H

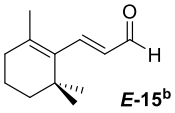
***Z*-3, 85%** >99:1 R = Me
***Z*-4, >99%[c]** 96:4 R = ^{t}Bu
***Z*-5, 98%** 96:4 R = C(Me)$_2$Et
***Z*-6, 85%** 95:5 R = Adamantyl
***Z*-7, >99%** 98:2 R = 2,6-di-OMePh
***Z*-8, >99%** 99:1 R = Bn
***Z*-9, 79%** 80:20 R = 2,6-di-^{t}BuPh

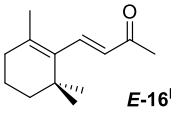
b) Amides



***Z*-10, 98%** >99:1 R = NH$_2$
***Z*-11, 95%** >99:1 R = NHMe
***Z*-12, 97%** 99:1 R = NMe$_2$
***Z*-13, 87%** 98:2 R = NHBn
***Z*-14, 50%** 96:4 R = N(OMe)Me

c) Control Substrates





Opportunity for chemoselectivity

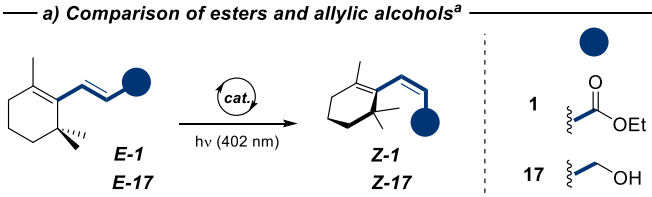
[a]Reactions were performed under an argon atmosphere at a 0.2 mmol scale, at 0.05 M concentration. [b]Significant decomposition observed [c]5 mol % lumichrome was used as the catalyst.

An initial optimisation employing conditions developed previously in this laboratory[10b] validated (–)-riboflavin as being a competent photosensitizer for the *E* → *Z* isomerisation of β-ionyl ester ***E*-1** to ***Z*-1** under irradiation at 402 nm using a narrow-band LED (Table 1, entries 1-4). Control experiments established the need for both a light source and photocatalyst (entries 5 and 6). Having identified general reaction conditions the scope of the transformation was investigated. To complement the studies by Liu and co-workers, focus was placed on esters and amides. Gratifyingly, the steric footprint of the ester functionality had little influence on the reaction outcome (Table 2a). Starting from the benchmark carboxylic acid ***Z*-2**, which was itself a competent isomerization substrate (>99:1 *Z*:*E*), augmenting steric bulk had little effect on stereoselectivity with ratios of >99:1, >99:1 and 96:4 being observed for the OMe (***Z*-3**), OEt (***Z*-1**) and O^{t}Bu (***Z*-4**) derivatives, respectively. In the case of ***Z*-4**, lumichrome proved to be the superior photocatalyst. Further enlargement of the ester such as ***Z*-5** and ***Z*-6** did not erode selectivity (96:4 and 95:5), nor did the inclusion of the phenol motif (***Z*-7**, 98:2). Similarly, the benzyl derivative ***Z*-8** proved to be a highly effective substrate (99:1, *Z*:*E*) as did the di-*tert*-Bu derivative (80:20, ***Z*-9**). This latter example would likely be challenging to prepare in a stereoselective manner by conventional olefination methodology. Having explored the efficiency of (−)-riboflavin in enabling geometrical isomerization of esters via selective energy transfer catalysis, the methodology was extended to amide derivatives (Table 2b). Primary, secondary and tertiary systems were all found to furnish the desired *Z*-isomer with excellent selectivity. Primary amide ***Z*-10** showed comparable isomerization efficiency to carboxylic acid ***Z*-2**, but with a significant improvement in yield (98% *versus* 65%). Methyl ester ***Z*-3** and methyl amide ***Z*-11** behaved comparably (>99:1). By extension, the benzyl derivative ***Z*-13** was isolated with essentially the same *Z*:*E* ratio as its ester counterpart (98:2 and >99:1). Synthetically versatile Weinreb amides such as ***Z*-14** could be accessed using this approach with a *Z*:*E* ratio of 96:4, but with a reduction in yield. Intrigued by the sensitivity of isomerization efficiency to the seemingly innocuous installation of the N(OMe)Me group (cf NMe$_2$), the aldehyde and ketone substrates originally examined by Liu under different conditions were investigated. Surprisingly, no isomerization was observed in ***E*-15** and ***E*-16** (Table 2c). This result indicates that chemoselective isomerization of activated alkenes may be achievable through simple molecular editing processes. To formalize this notion, and cognisant of their differing triplet energy, ester ***E*-1** was directly compared with the corresponding allylic alcohol ***E*-17** (Scheme 1a). As anticipated, the allylic alcohol proved recalcitrant to energy transfer-mediated isomerization (entry 1). The introduction of thioxanthone as a photocatalyst generated ***Z*-17** with >99:1 *Z*:*E* selectivity (entry 2). An intermediate triplet energy sensitizer [Ir(ppy)$_3$, entry 3] facilitated isomerization of both ***E*-17** and ***E*-1**, enabling near-quantitative isomerization of both substrates (*Z*:*E* 99:1). As a final proof of concept, an intramolecular variant of this concept was investigated. The first protocol utilizing (–)-riboflavin furnished ***Z*-18a**, with the α,β-unsaturated ester unit selectively isomerized in the presence of the masked allylic alcohol (37%, *Z*:*E* 97:3). In contrast, switching the photocatalyst to Ir(ppy)$_3$ isomerized both alkenes to furnish ***Z*-18b**. While the isolated yield of ***Z*-18a** was considerably lower than the

analogous *Z*,*Z* species, the majority of the remaining mass balance was comprised of the ***E*-18** starting material, which was easily separated from the desired reaction product.

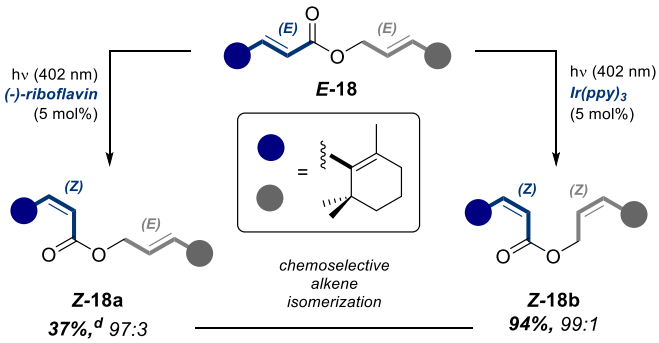
Scheme 1: a) Exploring photosensitizer E_T; b) An intramolecular example.

a) Comparison of esters and allylic alcohols[a]



Entry	Catalyst	E_T (kJmol^{-1})	Isolated Yield (*Z*:*E*)	
			1	**17**
1	(–)-riboflavin	209[13a]	99 (>99:1)	96 (<1:99)
2	thioxanthone	265[13b]	87(59:41)[b]	90 (>99:1)
3	$Ir(ppy)_3$	236[13c]	72 (99:1)	92 (>99:1)

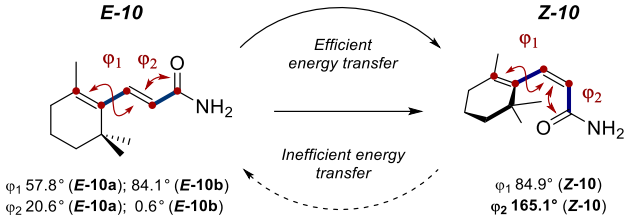
b) Selective Intramolecular Isomerization[c]



[a]Reactions were performed under an argon atmosphere on a 0.1 mmol scale, using MeCN (0.05 M) as the solvent and 5 mol % of photocatalyst for 14 hours. [b]Conversion determined by ^{1}H NMR with an internal standard. [c]Reactions were performed under argon on a 0.2 mmol scale, using MeCN (0.05 M) for 24 hours. [d]An additional 5 mol % (-)-riboflavin was added after 24 h.

To further interrogate the origin of stereoselectivity, crystals of both ***E*-10** and ***Z*-10** were isolated and subject to X-ray crystallographic analysis (Scheme 3). The *E*-isomer was found to have two independent molecules in the asymmetric unit (**10a/b**). Inspection of the dihedral angles φ_1 and φ_2, representing the diene and α,β-unsaturated carbonyl π-systems, reveal differences in the substrate structures (φ_1 = 57.8° and 84.1°, and φ_2 = 20.6° and 0.6° for **10a/b**, respectively). In ***Z*-10**, the φ_1 is similar to the *E*-isomer (84.9°) but the φ_2 value is 165.1° (see SI). To explore the origin of selectivity further, the impact of the three methyl groups were assessed by systematic deletion. (Scheme 3). Using model substrate ***E*-1** as a template, this molecular editing approach revealed a sequential erosion of selectivity.

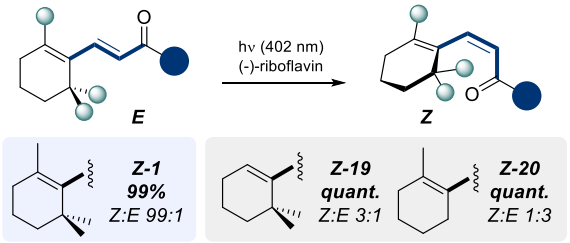
Scheme 2: Structural analysis of *E*- and *Z*-10.[a]



[a]Data extrapolated from crystal structures of ***E*-10a/b** (CCDC 1951892) and ***Z*-10** (CCDC 1951893). See SI for further details.

Finally, the regioselective isomerization of substrates ***E*-21** (R=Me) and ***E*-22** (R = H) was investigated (Table 3). Exposure of ***E*-21** to the standard reaction conditions yielded a complex mixture, with decreased selectivity relative to Liu's earlier work (Table 3, entries 1 and 2).[6d] Interestingly, deletion of the 9-methyl group improved selectivity. This structural alteration together with a switch in photocatalyst to eosin Y (E_T = 190 kJmol^{-1})[13a] enabled the highly selective and exclusive isomerization of the 7-position (Table 3, entries 3 and 4).

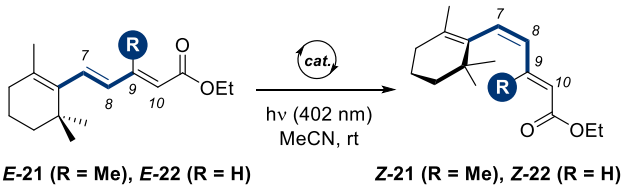
Scheme 3: Molecular editing study[a]



[a]Reactions were performed under an argon atmosphere on a 0.1 mmol scale, using MeCN (0.05 M) as the solvent and 5 mol % of photocatalyst for 14 hours.

Inspired by the efficiency with which flavins photoisomerize complex polyenes in the visual cycle, *E*→*Z* isomerization of dienes based on the ubiquitous 2,6,6-trimethylcyclohexene core of retinal was accomplished via a vitamin catalysis approach. Variation in the alkene substituent enables α,β-unsaturated carbonyl sytems to be selectively manipulated in the presence of allylic alcohol derivatives Moreover, molecular editing studies confirmed the structural importance of the pendant methyl groups of ionoid derivatives in achieving high *Z*-selectivity. These structural insights were then synergistically matched to the triplet energy of the photocatalyst to enable the site selective isomerization of a model triene based on retinal (90% selective for the 7Z isomer). This approach that builds on the seminal Walker/Radda[4a] and Liu[4b] studies provides a foundation from which to further expand the π-system to address the challenge of selective polyene isomerization.

Table 3: Regioselective isomerization of a model triene.[a,b]



Entry	Catalyst [E_T (kJmol^{-1})]	triene	Conversion (%) (*E*,*E*:7*Z*:9*Z*:*Z*,*Z*)
1[6d]	benzanthrone (192)[13d]	**21 (Me)**	n.r. (0:56:0:44)
2	(–)-riboflavin (209)[13a]	**21 (Me)**	>99 (16:44:14:26)
3	(–)-riboflavin (209)[13a]	**22 (H)**	99 (33:60:0:7)
4	eosin Y (190)[13a]	**22 (H)**	62[c] (0:**90**:0:10)

[a]Reactions performed on a 0.1 mmol scale under Ar, using 5 mol % of the specified catalyst (0.05 M). [b]Conversion and *Z*/*E* ratios were determined using ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental protocols and selected NMR spectra (PDF).
X-ray crystallographic data for compounds ***E*-10** and ***Z*-10**.

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Notes

The authors declare no competing financial interest.

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