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Selective Synthesis of *Z*-Cinnamyl Ethers and Cinnamyl Alcohols via Visible Light Promoted Photocatalytic *E* to *Z* Isomerization

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Abstract: A photocatalytic *E* to *Z* isomerization of alkenes using an iridium photosensitizer under mild reaction conditions is disclosed. This method provides scalable and efficient access to *Z*-cinnamyl ether and allylic alcohol derivatives in high yields with excellent stereoselectivity. Importantly, this method also provides a powerful strategy for the selective synthesis of *Z*-magnolol and honokiol derivatives possessing potential biological activity.

Alkenes are versatile building blocks in biologically active entities and serve as universal precursors for numerous chemical transformations to generate important organic compounds in chemical, natural product, material, and pharmaceutical fields.^[1] Cinnamyl ethers and derivatives have analogous fundamental properties as important alkenes. Furthermore, they are also important starting materials for a variety of organic reactions, including the allylic substitution reactions,^[2] aziridoarylation, bromocarbocyclization,^[3] and Claisen rearrangement (Scheme 1a).^[4] To date, the common ways to access cinnamyl ethers are transition-metal-catalyzed etherification^[5] and palladiumcatalyzed Mizoroki-Heck reaction (Scheme 1a).^[6] However, all of these strategies have been established to obtain the thermodynamically favorable E-cinnamyl ethers. By contrast, the stereoselective generation of Z-cinnamyl ethers are quite limited, which has been restricted to a limited number of available synthetic methods. Hence, there is a high demand for developing methods for the facile synthesis of stereochallenging Zalkenes.^[2a,7]

Indeed, a number of conceptually diverse strategies have been introduced to address this issue, including Wittig reactions,^[8] cross-coupling of alkenyl halides,^[9] stereoselective semihydrogenation of alkynes,^[10] *Z*-selective metathesis^[11] and Peterson olefinations.^[12] However, the highlighted reactions lack high *Z*-configuration selectivity and often require high energy reagents and expensive transition-metal based catalysts. Consequently, the alternative solution for this problem would allow preparation of the *Z*-isomer from the more readily available *E*-isomer and permit divergence from a common and easily accessed intermediate.

During the past decade, visible-light photoredox catalysis in organic synthesis has witnessed a surge in research activity by

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Scheme 1. Realization of a photocatalyzed isomerization for the synthesis of cis-cinnamyl ethers.

utilizing either its electron-transfer or energy-transfer reactivity.^[13] Of which, visible-light-mediated $E \rightarrow Z$ isomerization of simple alkenes can be achieved by using photosensitizers as a safe and clean energy source (Scheme 1b).[14] This approach has significant appeal both in terms of atom economy and environmentally benign nature. In recent years, photocatalysts such as iridium-base triplet photosensitisers,[15] organic dyes such as riboflavin,[16] aromatic keto compounds such as 2-iodo-9fluorenone, $^{\left[17\right] }$ and covalent organic frameworks (COF) $^{\left[18\right] }$ have been employed to promote the E to Z isomerization of alkenes (Scheme 1b). Detailed investigations by Weaver, Rueping, Gilmour, Wang, Balaraman and others, carefully delineated the sensitized isomerization mechanisms and delivered the E to Z stilbenes,^[15b,17,18] isomerization of allylamines,^[15a] α.βunsaturated esters,[15d,16a] cinnamonitriles,[16c] allylic alcohols,[19] styrenyl boron species^[15f] and vinyl silanes.^[20] Inspired by these seminal investigations, we aim to realize stereoselective synthesis of cis-cinnamyl ethers via photocatalytic isomerization of the easily accessed trans-isomers with high fidelity (Scheme 1c). Due to the planar starting material (E-cinnamyl ether) and 1,3-allylic strain^[21] of the product (Z-cinnamyl ether), it was expected that the excited state species generated by an initial energy transfer process would contribute to generate a

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delocalized biradical intermediate $^{\left[15a,16a,16c\right]}$ where C-C bond rotation is possible.

Inspired by our recent work on a highly efficient palladiumcatalyzed one-pot reaction for building up E-cinnamyl ethers from simple and readily available aryl halides, phenols and allyl chloride (Scheme 1a),^[6b] our initial investigation was conducted using E-cinnamyl phenyl ether 1a as a model substrate for the synthesis of Z-isomer through photocatalytic isomerization. We were pleased to find that E-1a could be converted to the expected Z-1a in the presence of fac-Ir(ppy)₃ (2 mol%) with a good selectivity of Z/E 84:16 under irradiation by blue LED (Table 1, entry 1). Various photocatalysts were then tested in this process, and the triplet sensitizer fac-lr(ppy)3 still proved to be highly effective (Table 1, entries 1-5 and Table S1, entries 1-3). With fac-Ir(ppy)₃ as the photocatalyst, the solvent screening (Table 1 and Table S1) revealed that THF served as the best solvent for this reaction, providing the best efficiency and Z/E ratio of the product. Remarkably, the photochemical isomerization worked well in a number of solvents (1,4-dioxane, toluene, DMA, or CH₃CN) with the exception of methanol which may be due to the solubility of the cinnamyl ether or the photosensitizer in the corresponding solvent (Table 1, entries 6-10). Although there was no obvious influence noticed on the prolonged reaction time (Table1, entry 11), lowering the reaction temperature had a positive effect on the reaction performance (Table1, entries 1, 12 and 13, Z/E = 84:16► 87:13). Control experiments were conducted and the results showed that both visible light and the photosensitizer are essential for this reaction (Table1, entries 14 and 15). Furthermore, performing the reaction at 70 °C in absence of blue

 $\mbox{Table 1.}$ The screening of reaction conditions for the photocatalytic isomerization $^{[a]}.$

	OPh photocatalysis (2 mol%)				
	sol	vent, Ar, 24	۔ h, blue LED		OPh
<i>E</i> -1a				Z-1a	
entry	catalyst	solvent	temp (℃)	scale (mmol)	Z/E ratio ^[b]
1	fac-Ir(ppy)₃	THF	50	0.1	84:16
2	lr(ppy) ₂ (bpy)PF ₆	THF	50	0.1	11:89
3	lr(ppy)₂(dtbbpy) PF ₆	THF	50	0.1	17:83
4	Ru(bpy) ₃ (PF ₆) ₂	THF	50	0.1	2:98
5	Rose bengal	THF	50	0.1	3:97
6	<i>fac</i> -Ir(ppy)₃	1,4- dioxane	50	0.1	83:17
7	fac-Ir(ppy)₃	toulene	50	0.1	80:20
8	<i>fac</i> -Ir(ppy)₃	CH₃CN	50	0.1	78:22
9	<i>fac</i> -Ir(ppy)₃	DMA	50	0.1	83:17
10	fac-Ir(ppy)₃	CH₃OH	50	0.1	13:87
11 ^[c]	<i>fac</i> -Ir(ppy)₃	THF	50	0.1	84:16
12	<i>fac</i> -Ir(ppy)₃	THF	35	0.1	87:13
13 ^[c]	fac-Ir(ppy)₃	THF	25	0.1	87:13
14	none	THF	35	0.1	0:100
15 ^[d]	<i>fac</i> -Ir(ppy)₃	THF	35	0.1	0:100
16 ^[d]	<i>fac</i> -Ir(ppy)₃	THF	70	0.1	0:100
17 ^[e]	<i>fac</i> -Ir(ppy)₃	THF	35	0.2	90:10

[a] Reaction conditions: *E*-1a (0.1 mmol) and photocatalysis (2 mol%) in the indicated degassed solvent (1.0 mL) were irradiated by blue LED bulb for 24 h under argon, unless otherwise noted. [b] Z/E selectivity was determined by ¹H NMR spectroscopy of the crude product. [c] 48 h. [d] Reaction was performed in darkness. [e] *E*-1a (0.2 mmol) and *fac*-lr(ppy)₃ (1 mol%) in THF (1.5 mL).

LED light did not lead to the product *Z*-1a, which again suggests the visible-light driven photosensitization pathway (Table 1, entry 16). Notably, the better result was obtained in the presence of 1 mol % of *fac*-Ir(ppy)₃ with the concentration of substrate at 0.2 M. (Table 1, entry 17, Z/E = 90:10).

Having established the reaction conditions to achieve the efficient E to Z isomerization of cinnamyl ethers, we proceeded to explore the scope of this transformation (Scheme 2). It is noteworthy that the isolated yields of the Z-isomers were reported for the reactions with the use of the pure E-isomers as the substrates. To our delight, the reaction works well for a number of cinnamyl ether analogues (Scheme 2). For aryl cinnamyl ether substrates with electron-rich (E-1b, E-1c), electron-deficient (E-1d, E-1h, E-1i), and halogenated (E-1e-1g) substituents at the para-position of the phenol ether, the reactions proceeded well with high Z-alkene conversion (Z-1b-1i, 74-93%). Good results were also obtained for the substrates bearing the substituted groups at the ortho position (Z-1i-10, 76-85%). While an amino at ortho-position led to the isomerization futile, exchanging NH₂ with NHBoc provided a good yield (Z-11, 76%). Furthermore, naphthalene substrates (Z-1g, 65% and Z-1r, 60%) as well as heterocyclic aromatic substrates (Z-1s, 82% and Z-1t, 71%) were well tolerated with good to excellent selectivities albeit with increasing the amount of fac-lr(ppy)₃. The structure of Z-1r was confirmed by X-ray crystallographic analysis,^[22] which clearly



Scheme 2. Photocatalytic *E*-to-*Z* isomerization of aryl cinnamyl ethers. [a] Standard reaction conditions: Reactions were performed with 0.2 mmol of substrate *E*-1 (*E*/*Z* > 20:1) at 35 °C in THF (1.5 mL) using *fac*-Ir(ppy)₃ (1 mol%) under 24 h of blue LED irradiation, unless otherwise noted. [b] Isolated yields of the *Z*-isomer was reported. [c] Determined by ¹H NMR spectroscopy of the crude product. [d] *fac*-Ir(ppy)₃ (2 mol%) and DMA (1.5 mL) were required for isomerization. [e] *fac*-Ir(ppy)₃ (2 mol%) was used. [f] *E*/Z ratio of the substrate **1z** was 83:17.

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showed the cis-configuration of the double bond for 1r. Meanwhile, the photochemical isomerization of E-aryl cinnamyl ethers was applicable to substrates with electron-rich and electron-deficient substituents on the cinnamyl chain (Z-1u-1x, 75-91%). Moreover, the same seems to be applicable for the unsaturated bonds such as allyl and propenyl in ortho-position of the phenol ether, which resulted in very good yields of 90% (Z-1y) and 90% (Z,Z-1z), respectively. It is of particular note that the isomerization of the double bonds in two positions of the substrate E,E-1z was observed, which indicating the photochemical isomerization reaction is also wellsuited to alkyl-substituted alkenes. Finally, the magnolol and honokiol derivatives (E,E-2 and E,E-3) which possess antitumoral, antiangiogenic, and anxyolitic activities^[23] were also suitable substrates to deliver Z,Z-isomers in high yields (Z,Z-2, 80% and Z,Z-3 60%).

Encouraged by these results obtained for cinnamyl ethers, a variety of allylic alcohol substrates were successively modified at the arvl ring (R^1) and the double bond (R^2) and investigated under the standard conditions, as shown in Scheme 3. Unsubstituted Zcinnamyl alcohol 4a was obtained in 78% yield. Gratifyingly, substituting $R^2 = H$ by Me or CH_2CI led to a significant improvement in the geometric ratios (Z-4b, 91% and E-4c, 92%). This is likely a consequence of augmenting 1,3-allylic strain in the product. Testing the scope of electronic modulation revealed various cinnamyl alcohol substrates with electron-withdrawing and electron-donating groups at the para- or meta-position were all amenable to generate Z-isomer products in good to high yields (Z-4e-4j, 4o, 4p, 68-90%). When the substituted group was introduced at the ortho position, a significant increase in the reaction efficiency was observed (Z-4k-4n, 93-99%, Z/E = 78:22-93:7). This observation may be attributable to severely congested and highly twisted conformation inducing by the Z-isomers bearing ortho-substituted groups.[16] However, a reduction of selectivity was observed with ortho-substituents allyl alcohols (R² = Me, Z-4q, Z/E = 26:74 and Z-4r, Z/E = 48:52). As reported by Gilmour in their seminal work,^[16] this is presumably caused by the fact that the deconjugation of the starting material as it compromises the efficiency of the initial excitation of the trans-allyl alcohols. The Z/E selectivity was slightly increased with the rising of the temperature and the extension of the photoisomerization time (Z-4q and Z-4r). The replacement of the benzene ring with a larger naphthalene ring led to a slight decrease in the geometric ratio (Z-4s, 80%), possibly due to resonance forms partially facilitating bond rotation and relaxation to the starting Eisomer.^[16e] What's more, heterocyclic aromatic substrates were also tolerated with good to excellent selectivities (Z-4t, 91% and Z-4u, 72%). However, an obvious decrease in the geometric ratio was noted for substrate *E*-4u bearing a thiophene ring. Although the 5-membered ring retains the requisite aromatic character, 1.3allylic strain in both isomers of the thiophene (E-4u and Z-4u) is significantly reduced compared to the 6-membered ring analogs.^[16,21] These results indicate that distortion in the Z-isomer product and planarity in the E-isomer substrate are key to ensuring high levels of stereocontrol.

To demonstrate the synthetic utility of this method, the photochemical isomerization reaction also proved amenable to scale-up with the Z-isomer of **1a** having been isolated in 82% vield on a 1 mmol scale using only 0.2 mol% of fac-lr(ppy)₃ (Scheme 4a). Finally, several control experiments to confirm the origin of the Z-selectivity are shown in scheme 4. In the presence of 1 equiv of a radical scavenger TEMPO in the reaction medium, the yield of Z-configured product decreases significantly under the



Scheme 3. Scope of photocatalytic isomerization of allylic alcohol derivatives. [a] Standard reaction conditions: Reactions were performed with 0.2 mmol of substrate *E*-4 (*E*/*Z* > 20:1) at 35 °C in THF (1.5 mL) using *fac*-Ir(ppy)₃ (1 mol%) under 24 h of blue LED irradiation. [b] Isolated yields of the Z-isomer was reported. [c] Determined by ¹H NMR spectroscopy of the crude product. [d] Isolated yields of Z/E mixtures and the Z/E ratio were determined by ¹H NMR spectroscopy. [e] at 50 $^\circ\!\!\mathbb{C}$ for 36 h.



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standard conditions ($Z/E = 90:10 \rightarrow 33:67$). Substituting methyl by cyclopropyl on the double bond led only to a very minor erosion of selectivity (Z-4b and Z-4v, Z/E = 95:5 and 93:7, respectively). However, the installation of cyclopentyl or cyclohexyl led to a remarkable decrease in selectivity (Z-4w and Z-4x, Z/E = 33:67and 12:88, respectively). This is probably due to 1,3-allylic strain in the starting material (E-4w and E-4x) distorting the phenyl ring of the plane and reducing conjugation. Moreover, Stern-Volmer fluorescence quenching experiments of fac-lr(ppy)₃ with substrates E-1a, E-4a and E-4b were performed (Scheme 4c and Figure S1-S3). According to Hammond's mechanistic analyses,^[24] together with the study of control experiments and mechanistic probes, the Stern-Volmer analysis indicated that the isomerization reaction mechanism consistent with triplet energy transfer was operational. Interestingly, from the slope of the line generated by plotting of *I*^o/*I* vs concentration of the quencher, and comparison with the Z/E selectivities reported in Scheme 2 and Scheme 3 (Z-4b 91%. Z-1a 87%. Z-4a 78%), shows that selectivity correlate with guenching efficiency. Additional support for the biradical intermediate is reflected in the increasing Z/E ratio when improving the stabilizing auxiliary groups.

In conclusion, we have established an efficient and operationally simple protocol to access thermodynamically less stable *cis*-alkenes through a photochemical isomerization. Many *cis*-cinnamyl ethers and cinnamyl alcohols, which are not readily accessible via classic methods, can thus be achieved in synthetically useful ratios and yields. This reaction is remarkably clean and tolerates a wide range of functional groups with regard to both the cinnamyl ethers and cinnamyl alcohols. In addition, *Z*-configured magnolol and honokiol derivatives, which possess potential biological activity, could be easily obtained in good yields and selectivity by this straightforward photocatalysis isomerization.

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COMMUNICATION

Entry for the Table of Contents



An efficient geometrical $E \rightarrow Z$ isomerization of cinnamyl ethers and cinnamyl alcohols is disclosed via energy transfer using an iridium photosensitizer. A series of contra-thermodynamic *cis*-cinnamyl ether and alcohol derivatives were achived through a photoisomerization of the readily available *trans*-isomer. This simple reaction system shows satisfactory *Z*-selectivity, broad substrate scope, and functional group tolerance.

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Selective Synthesis of Z-Cinnamyl Ethers and Cinnamyl Alcohols via Visible Light Promoted Photocatalytic E to Z Isomerization