Stereodivergent Synthesis | *Very Important Paper* |

Photocatalytic Isomerization of Styrenyl Halides: Stereodivergent Synthesis of Functionalized Alkenes

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Abstract: An efficient and general method for the isomerization of styrenyl halides under different photocatalytic conditions (*fac*-Ir(ppy)$_3$ in methanol for *E* to *Z* isomerization and fluorescein in 1,4-dioxane for *Z* to *E* isomerization, respectively) is disclosed. A series of stereospecific transformations constitute preliminary validation of this strategy in the synthesis of functionalized alkenes, including two diaryl alkenes, a styrenyl boronic ester and an enyne. The photocatalytic isomerization and subsequent cross coupling reaction can be run in a one-pot manner. The stereodivergent synthesis of all four isomers of a conjugated diene, as well as the antitumor agent DMU-212 and its (*Z*)-isomer highlights the synthetic applicability of this method.

Introduction

Functionalized alkenes are frequently encountered in natural compounds, pharmaceuticals[1] and optical materials.[2] They are also valuable units in chemical synthesis.[3] Since the configuration of C=C double bonds affects physical, chemical, biological and physiological properties of alkenes significantly, synthesis of the stereochemistry-defined functionalized alkenes is quite important and highly demanded. One of the most efficient and reliable method for synthesis of functionalized alkenes is transition metal-catalyzed cross couplings of vinyl halides with organometallics (Scheme 1a).[4] Given that these cross couplings are stereochemistry conservative, stereoselective synthesis of vinyl halides is crucial to preparation of the functionalized alkenes. Hence, the development of a controllable and facile method for synthesizing stereo-defined vinyl halides is of great value.
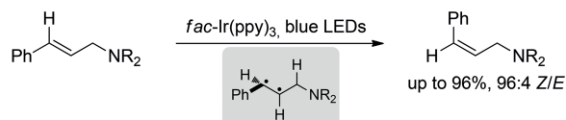
The control of the geometry of alkenes is often a challenging problem in organic synthesis.[5] In particular, there is a paucity of routes to the thermodynamically less stable *Z*-alkenes.[6] To date, *E*-styrenyl haildes can be stereoselectively obtained by Hunsdiecker reaction of cinnamic acid derivatives,[7] halogenation of alkynes[8] or dehalogenation of 1,1-dihaloalkenes[9] while the common ways to access *Z*-styrenyl haildes have been largely restricted to Wittig reaction.[10] Despite these significant
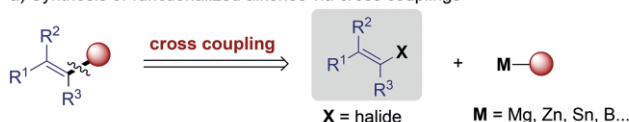
Scheme 1. Photocatalytic isomerization of functionalized alkenes.

advances, there is a lack of a general strategy for the synthesis of both *E* and *Z*-isomers.

With the renaissance of photocatalysis in recent years, a feasible idea for visible-light-mediated selective isomerization of

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alkenes has been provided.[11] Although the rotation of the C=C double bond is usually hindered by the high rotational energy barrier in the ground state reaction, photochemical excitation at an appropriate wavelength can alleviate this constraint.[12] As early as the 1950s, Wyman, Hammond and others demonstrated that direct irradiation or sensitized excitation via energy transfer can result in photoisomerization of symmetrical alkenes,[13] which provided a very powerful guiding principle for the realization of geometric isomerization of alkenes. Recently, this concept has been applied to more substrate scopes and reactions, even under visible light irradiation.[14] Weaver and co-workers reported a remarkable *E* to *Z* photoisomerization of cinnamyl derived amines with *fac*-Ir(ppy)$_3$ as the triplet sensitizer (Scheme 1b).[15] This mild energy transfer activation mode enables the thermodynamically unstable *Z*-isomer to be generated under kinetic control. Subsequently, Gilmour and co-workers disclosed the bio-inspired photoisomerization of diverse activated alkenes using the flavin derivative (–)-riboflavin as an energy transfer catalyst (Scheme 1b).[16] More recently, the same group has demonstrated that styrenyl boron species could also undergo this contra-thermodynamic isomerization process.[17] Good functional-group tolerance and application in contemporary cross-coupling technologies emphasize the synthetic utility of this strategy.
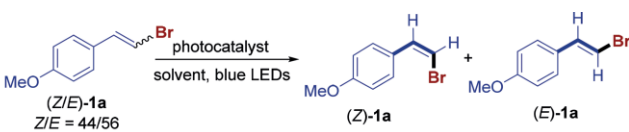
Inspired by these works, and deeply recognized the general lack of efficient methods for the formation of polysubstituted *Z*-configuration styrenyl halides, we have attempted to provide a strategy for the synthesis of both *E*- and *Z*-styrenyl halides with high stereoselectivity from an *E/Z* mixture through visible light-induced isomerization (Scheme 1c). As indicated by Gilmour and co-workers,[16,17] in general, the alkenes with a conjugated π system can be activated effectively by the excited state of a photosensitizer via an energy-transfer mechanism.[18] The formed diradical intermediate can lead to the re-generation of both the *E* and *Z*-isomers through C–C bond rotation. In general, the energy gap between the ground state and the excited state of acyclic styrenoids is the main influencing factor for its photostationary state. Specifically, this gap is more pronounced in *Z*-alkenes due to the allylic strain disrupting conjugation. Thus, the re-excitation of *Z*-configured product is inefficient and only the *E*-styrenyl halides can be excited. This intrinsic directionality is in favor of the contra-thermodynamic isomerization, resulting in gradual accumulation of the *Z*-styrenyl halides.

Results and Discussion

A *Z/E* mixture of 1-(2-bromovinyl)-4-methoxybenzene (*Z/E*)-**1a** as a model substrate to investigate the optimal reaction conditions of geometric isomerization (for detailed optimization of isomerization conditions, see the Supporting Information). When Methanol was chosen as the solvent, several photocatalysts were preferentially explored under 90 W blue LEDs irradiation (Table 1). The triplet sensitizer *fac*-Ir(ppy)$_3$ has been proved to be effective for the geometric isomerization of (*E*)-**1a** to the contra-thermodynamic product (*Z*)-**1a** (*Z/E* = 93:7) in nearly quantitative yield (entry 2). The *Z/E* ratio of the mixture did not affect this isomerization significantly. When pure (*E*)-**1a** was

employed, (*Z*)-**1a** was also isolated as the major isomer in 93:7 *Z/E* ratio (entry 3). Several other solvents, such as Ethanol and Acetonitrile, were also tested, but none of them gave better results (entries 5 and 6). Interestingly, when organic dyes eosin Y and fluorescein were used as the photosensitizers, *Z* to *E* isomerization was observed and (*E*)-**1a** was isolated as the major product (entries 7 and 8). 1,4-dioxane proved to be optimal solvent for *Z* to *E* isomerization (*Z/E* = 7:93, entry 9). Thus, both direction *Z/E* isomerization was achieved under different photocatalytic conditions (*fac*-Ir(ppy)$_3$ in Methanol for *E* to *Z* isomerization and fluorescein in 1,4-dioxane for *Z* to *E* isomerization, respectively).

Table 1. Optimization of the isomerization.[a]

Entry	Catalyst	Solvent	Z/E[b]	Yield/%[c]
1	-	MeOH	62/38	> 99
2	Ir(ppy)$_3$	MeOH	93/7	> 99 (99[d])
3[e]	Ir(ppy)$_3$	MeOH	93/7	> 99 (99[d])
4[f]	Ir(ppy)$_3$	MeOH	44/56	> 99
5	Ir(ppy)$_3$	EtOH	85/15	> 99
6	Ir(ppy)$_3$	CH$_3$CN	90/10	> 99
7	eosin Y	MeOH	20/80	91
8	fluorescein	MeOH	17/83	91
9	fluorescein	dioxane	7/93	> 99 (99[d])
10[g]	fluorescein	dioxane	7/93	> 99 (99[d])
11	–	dioxane	49/51	> 99
12[f]	fluorescein	dioxane	44/56	> 99

[a] Reactions were performed in specified degassed solvents (2.0 mL) on 0.1 mmol scale at ambient temperature under 90 W blue LEDs irradiation in the presence of 2 mol-% photocatalyst. The *Z/E* ratio of (*Z/E*)-**1a** is 44:56. [b] The *Z/E* ratio was determined by ^{1}H NMR spectroscopy. [c] Yield determined by ^{1}H NMR using dibromomethane as the internal standard. [d] Isolated yield based on (*Z/E*)-**1a** after column chromatography. [e] 100 % of (*E*)-**1a** was used. [f] No light. [g] 100 % of (*Z*)-**1a** was used.

Having established a set of general reaction conditions to achieve the efficient isomerization of styrenyl haildes, the scope and limitations of this isomerization were then established. *E* to *Z* isomerization was first investigated (Scheme 2). Electronic of the aryl ring was found to have a negligible effect on *E* to *Z* isomerization. Moreover, the *meta*-substituent did not hinder the reaction, yielding the isomerization product ((*Z*)-**1d**, (*Z*)-**1m** and (*Z*)-**1r**) in good yield. (*Z*)-**1a**–**1e** could be isolated (86:14 to 93:7 *Z/E* ratios) from the corresponding *E/Z* mixtures. The α-substituent (R^2) of styrenyl bromides had a positive effect on *E* to *Z* isomerization. Increasing the steric hindrance of α-substituent led to higher stereoselectivity (up to 99:1 *Z/E* ratios). Styrenyl chloride (**1u**) and iodide (**1v**) also underwent this isom-

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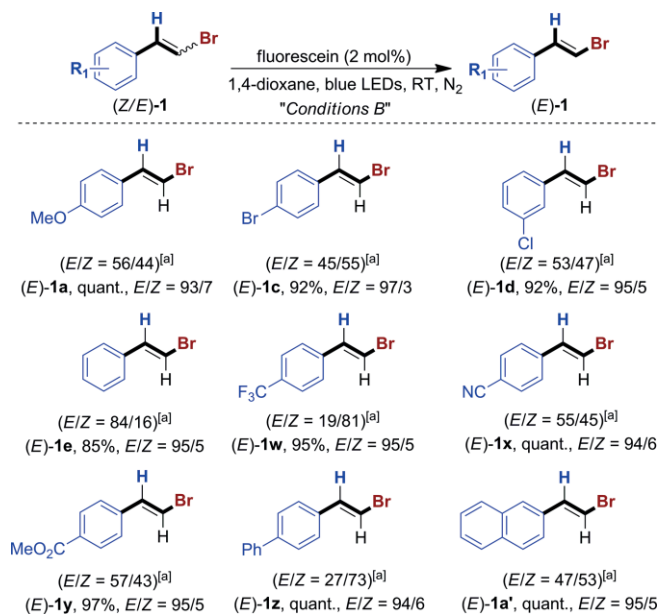of Organic Chemistry

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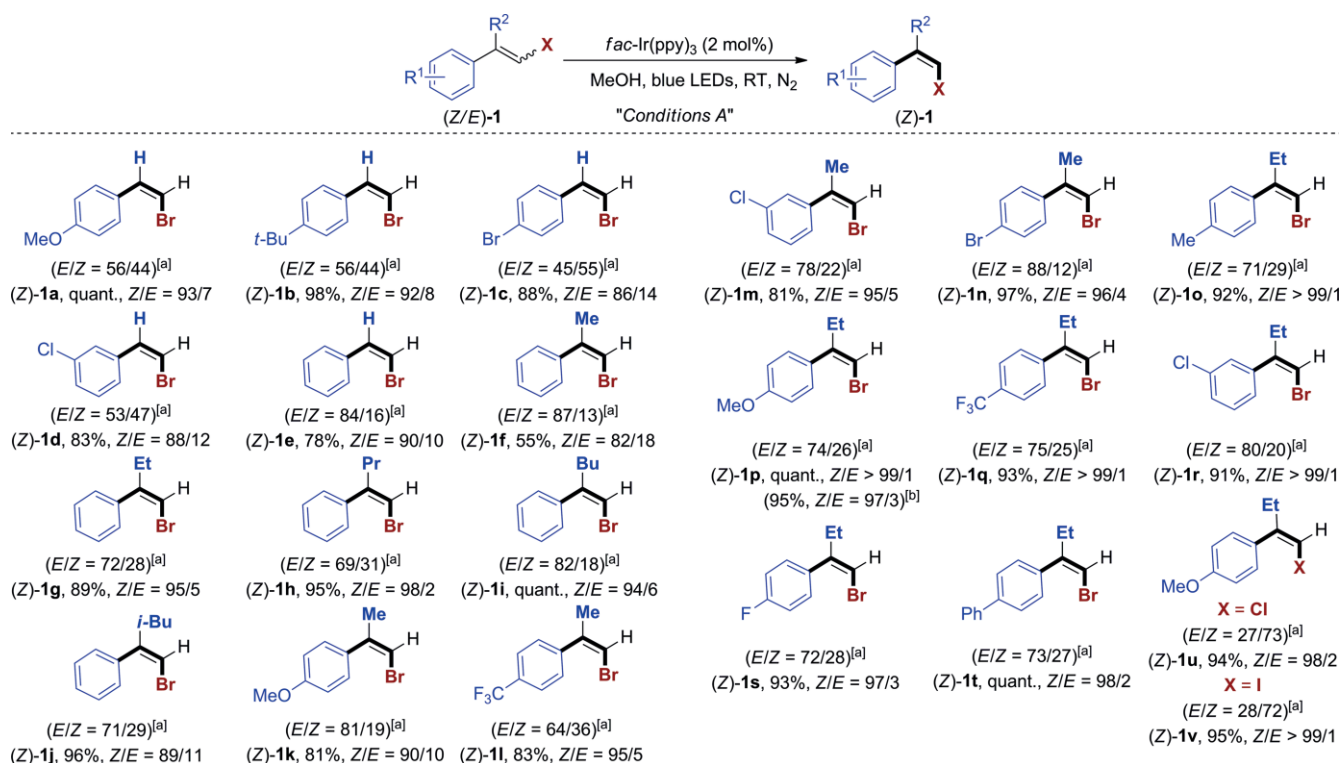
Scheme 2. Photocatalytic *E* to *Z* isomerization of styrenyl halides. Reactions were performed with 0.1 mmol substrate at ambient temperature in degassed methanol (2.0 mL) using 2 mol-% *fac*-Ir(ppy)$_3$ under 90 W blue LEDs irradiation. *Z/E* ratios were determined by ^{1}H NMR spectroscopy of the crude products using dibromomethane as the internal standard. Isolated yields based on (*Z/E*)-**1** after silica gel column chromatography. [a] The initial *E/Z* ratio of the starting materials. [b] 5.0 mmol scale (1.15 g).

erization smoothly give (*Z*)-**1u** and (*Z*)-**1v** in 98:2 and > 99:1 *Z/E* ratios, respectively. This photocatalytic *E* to *Z* isomerization could be easily scaled up to gram scale without influencing yield and stereoselectivity significantly (**1p**).

We next investigated the generality of geometric isomerization of the *Z/E* mixtures of styrenyl haildes to (*E*)-styrenyl haildes. As shown in Scheme 3, (*E*)-styrenyl bromides could be isolated as the major geometric isomers regardless of the electronic and steric effects when the corresponding *Z/E* mixtures were irradiated by blue LEDs in 1,4-dioxane in the presence of fluorescein. Unfortunately, *Z* to *E* isomerization of α-substituted styrenyl bromides was unsuccessful. The mechanism for this *Z* to *E* isomerization is not clear at this stage.

To understand the conversion between the *E* and *Z* configurations in this photocatalytic isomerization reaction, kinetic experiments were carried out under specified conditions (Figure 1). The relative compositions of substrates and isomerization products were monitored over time by ^{1}H NMR under the standard conditions of 2 mol-% of photosensitizer. In the case of the substrate (*E*)-**1a**, almost complete *Z*-selective isomerization was observed over the course of 10 h, and after that, the reaction ultimately reached a photostationary state (Figure 1a). For (*Z*)-**1a**, the equilibration was reached within 10 h smoothly with 97:3 *E/Z* ratio (Figure 1b). Both (*E*)-**1a** and (*Z*)-**1a** are stable under photocatalytic conditions and decomposition of styrenyl bromides (*E*)-**1a** and (*Z*)-**1a** was not observed. In addition, the slow consumption of the α-substituted substrates leads to a

Scheme 3. Photocatalytic *Z* to *E* isomerization of styrenyl bromides. Reactions were performed with 0.1 mmol substrate at ambient temperature in degassed 1,4-dioxane (2.0 mL) using 2 mol-% fluorescein under 90 W blue LEDs irradiation. *Z/E* ratios were determined by ^{1}H NMR spectroscopy of the crude products using dibromomethane as the internal standard. Isolated yields based on (*Z/E*)-**1** after silica gel column chromatography. [a] The initial E/Z ratios of the starting materials.

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slight decrease in the rate of photoisomerization (Figure 1c). The (E)-**1p** isomer is completely consumed in 24 h. However, the continuous decline in product yield is caused by competitive photocatalytic decomposition. In a case of (Z)-**1p** (Figure 1d), a short induction period was recorded during which the composition of (Z)-**1p** almost stayed the same. Although the E-selectivity will be improved to some degree with the extension of the reaction time, the yield of the product will also decrease due to competitive decomposition.
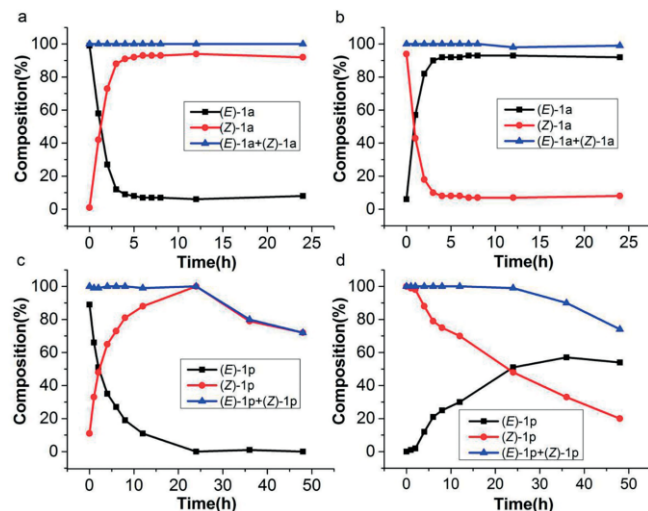

Figure 1. Kinetic experiments: reaction progress monitoring starting from the E and Z isomers of **1a** and **1p**: (a) (E)-**1a** with 2 mol-% fac-Ir(ppy)₃. (b) (Z)-**1a** with 2 mol-% fluorescein. (c) (E)-**1p** with 2 mol-% fac-Ir(ppy)₃. (d) (Z)-**1p** with 2 mol-% fluorescein.

In order to preliminary demonstrate the synthetic value of this photocatalytic isomerization strategy, the resultant styrenyl bromide (Z)-**1p** was applied to the following experiments of stereospecific transformation (Scheme 4a). Bromide (Z)-**1p** could undergo Suzuki–Miyaura cross coupling[19] and Sonogashira reaction[20] to give diaryl alkenes **3** and enyne **7** in a stereochemically conservative manner, respectively. The reaction with boronic acid pinacol ester also proceeded smoothly to generate another important coupling partner **5**. What is more, this photocatalytic isomerization method and Suzuki–Miyaura cross coupling reaction can be achieved successively in a one-pot manner without affecting the chemical yield and stereoselectivity, even in a gram scale (Scheme 4b).

The linear (E)-s-trans-2,4-dienone can provide cyclohexene derivatives through visible-light-mediated cascade rearrangement reaction, wherein the regioselective E→Z isomerization of more dienophilic double bond is the key to the success of this pathway.[21] It can be seen that construction of the stereodefined conjugated diene is extremely important. Thus, the successful stereodivergent synthesis of all four stereoisomers of conjugated dienes further emphasizes the synthetic utility of this photocatalytic isomerization strategy (Scheme 5). The Suzuki–Miyaura cross couplings of styrenyl bromide (E)-**1p** with boronic esters (E)-**8a** and (Z)-**8a**, respectively, affording (3E, 5E)- and (3E, 5Z)-isomers of conjugated diene **9**. (3Z, 5E)- and (3Z, 5Z)-isomers of conjugated diene **9** could be accessed by the couplings of photocatalytic isomerization product (Z)-**1p** with
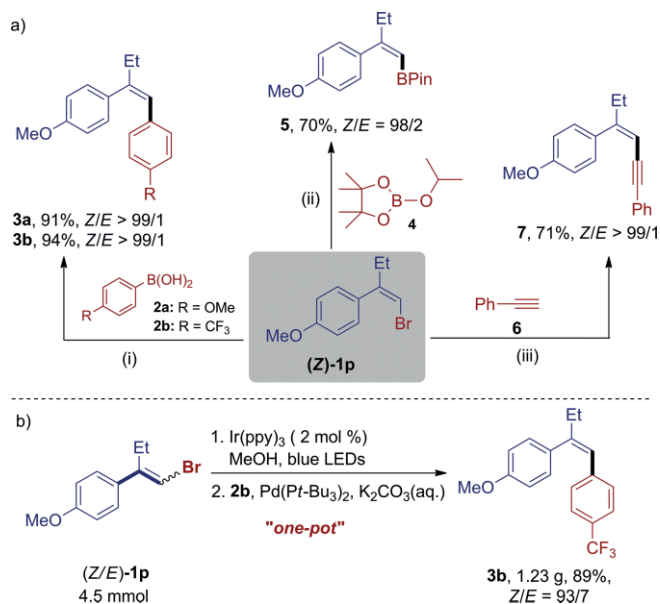
Scheme 4. Stereospecific transformations of (Z)-**1p**. (i) (Z)-**1p** (1.0 equiv.), boronic acid (1.2 equiv.), Pd(PtBu₃)₂ (2 mol-%), an aqueous solution of K₂CO₃ (3 equiv.), toluene, r.t.; (ii) (Z)-**1p** (1.0 equiv.), nBuLi (1.1 equiv.), **4** (3.0 equiv.), THF, r.t.; (iii) (Z)-**1p** (1.0 equiv.), **6** (1.1 equiv.), Pd(PPh₃)₄ (3 mol-%), CuI (5 mol-%), Et₂NH.

boronic esters (E)-**8a** and (Z)-**8a**, respectively. Except (3Z, 5Z)-**9**, the other three stereoisomers were isolated with the retention of the stereochemistry. (3Z, 5Z)-**9** was isolated as the major product with slightly loss of stereochemistry (90:2:8:0).
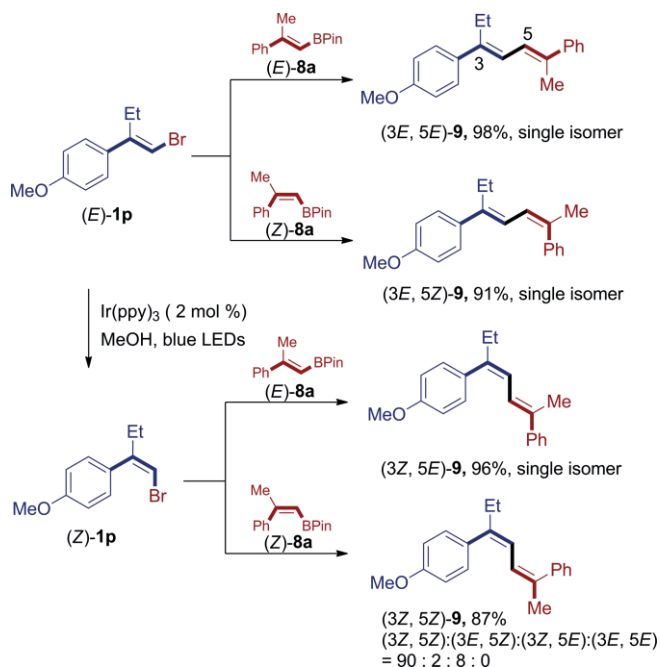
Scheme 5. Stereodivergent synthesis of conjugated dienes.

Finally, the highly stereoselective synthesis of the antitumor agent DMU-212 (**11**),[22] a synthetic analogue of resveratrol with high activity and selectivity against cancer cell,[23] has been achieved through the Suzuki–Miyaura cross coupling of (E)-**1a**

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with boronic acid **10** (Scheme 6, 80 % yield in single stereoisomer). Its *Z*-isomer **12**, which effectively induces the rapid polymerization of perinuclear mitochondrial and the apoptosis of p53-independent cells in cancer cells,[24] could also synthesized in 86 % yield and 94:6 *Z/E* ratio using (*Z*)-**1a** as the coupling partner.
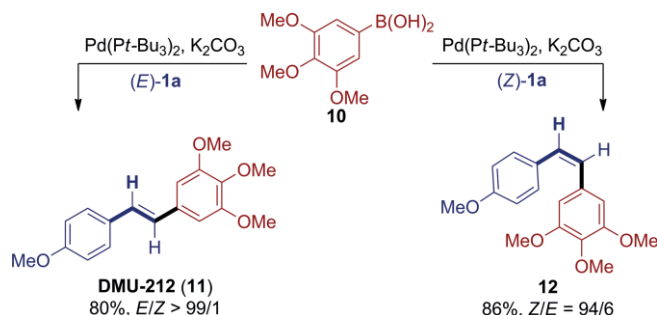
Scheme 6. Synthesis of the antitumor agent **DMU-212** and its *Z*-isomer.

Conclusions

In summary, we have developed an efficient method for photocatalytic isomerization of styrenyl halides. Both (*E*)- and (*Z*)-styrenyl halides can be accessible with high stereoselectivity respectively from the *E/Z*-mixtures of styrenyl halides. A series of stereospecific transformations in the synthesis of functionalized alkenes, such as diaryl alkenes, styrenyl boronic esters and enynes, which make this chemistry a practical protocol complementary to traditional methods. Furthermore, the photocatalytic isomerization and subsequent cross coupling reaction can be run in a one-pot manner. The stereodivergent synthesis of all four isomers of a conjugated diene, as well as the antitumor agent DMU-212 and its (*Z*)-isomer, highlight the synthetic applicability of this method.

Experimental Section

Isomerization leading to (*Z*)-styrenyl halides: A *Z/E* mixture of styrenyl halide (0.1 mmol, 1.0 equiv.) and *fac*-Ir(ppy)$_3$ (1.3 mg, 0.002 mmol, 0.02 equiv.) were added in a 10-mL reaction tube. The tube was evacuated and backfilled with nitrogen 3 times. Degassed Methanol (2.0 mL) was then added via a syringe under nitrogen. The mixture was then irradiated by 90 W blue LEDs for 8 h. After the reaction was completed, the residual catalyst was removed by filtration through a SiO$_2$-plug, subsequent elution of the products with Et$_2$O (6.0 mL) and concentration in vacuo yielded the mixture of the *Z* and *E*-isomer. The *Z/E* ratio of the mixture was determined by the ^{1}H NMR spectra and the crude product was purified by flash chromatography on silica gel to afford the desired product.

Isomerization leading to (*E*)-styrenyl halides: A *Z/E* mixture of styrenyl halide (0.1 mmol, 1.0 equiv.) and fluorescein (0.7 mg, 0.002 mmol, 0.02 equiv.) were added in a 10-mL reaction tube. The tube was evacuated and backfilled with nitrogen 3 times. Degassed 1,4-dioxane (2.0 mL) was then added via a syringe under nitrogen. The mixture was then irradiated by 90 W blue LEDs for 24 h. After the reaction was completed, the residual catalyst was removed by filtration through a SiO$_2$-plug, subsequent elution of the products with Et$_2$O (6.0 mL) and concentration in vacuo yielded the mixture

of the *Z* and *E*-isomer. The *Z/E* ratio of the mixture was determined by the ^{1}H NMR spectra and the crude product was purified by flash chromatography on silica gel to afford the desired product.

Conflict of Interest

The authors declare no conflict of interest.

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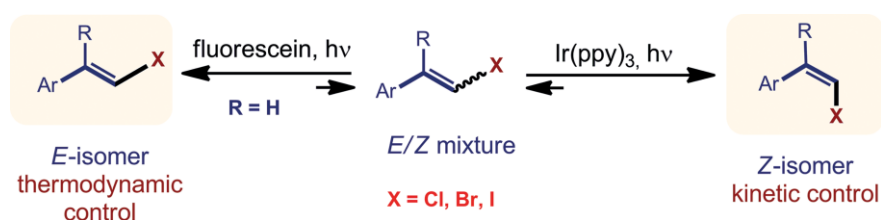[24] A. Gosslau, S. Pabbaraja, S. Knapp, K. Y. Chen, *Eur. J. Pharmacol.* **2008**, *587*, 25–34.

Stereodivergent Synthesis

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Photocatalytic Isomerization of Styrenyl Halides: Stereodivergent Synthesis of Functionalized Alkenes

An efficient and general method for the isomerization of styrenyl halides under photocatalytic conditions is reported. A series of stereospecific transformations constitute preliminary validation of this strategy in the synthesis of functionalized alkenes, including two diaryl alkenes, a styrenyl boronic ester, and an enyne.