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Photocatalytic *E*→*Z* isomerization of *gem*-bromofluoroalkenes: Stereospecific synthesis of β-fluorostyrene derivatives

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Photocatalytic *E*→*Z* isomerization of *gem*-bromofluoroalkenes: Stereoselective synthesis of β-fluorostyrene derivatives

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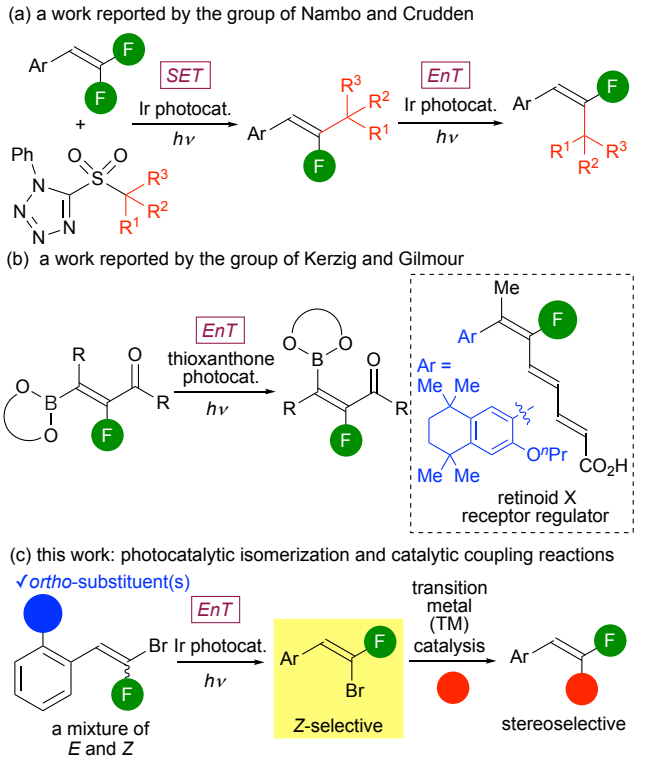
Stereoselective synthesis of β-fluorostyrene derivatives has been developed. Selective isomerization of *gem*-bromofluoroalkenyl benzenes bearing various *ortho*-substituent(s) is enabled by use of Ir photocatalysts with high triplet energy. Subsequent one-pot transition-metal (TM)-catalyzed reactions achieves pot-economical synthesis of monofluoroalkenes in a stereoselective manner.

Monofluoroalkene motifs have attracted a myriad of attention in drug design because the scaffold is regarded as a bioisostere of the biologically valuable amide functionality.[1] In addition, fluorinated alkenes have been frequently found in bioactive molecules.[2] Thus, the development of new protocols for efficient and selective synthesis of monofluoroalkenes has become an important topic in synthetic organic chemistry. While a large number of strategies have been implemented for the synthesis of monofluoroalkenes,[3,4] stereoselective strategies, especially for thermodynamically unfavorable isomers have been still limited. In recent years, photochemical energy transfer (EnT)-driven *E*/*Z* isomerization of the C=C bond has been widely applied to stereoselective access to such elusive isomers.[5] Separately, the group of Nambo and Crudden reported on photocatalytic radical alkylation of *gem*-difluoroalkenes with alkyl sulfone derivatives.[6] In their reaction system, the Ir photocatalyst is effective for both single electron transfer (SET) and EnT processes. The resultant *E*-isomer is obtained in a selective manner (Scheme 1a). More recently, the isomerization of fluorinated β-borylacrylates by thioxanthone photocatalyst was reported by the group of Kerzig and Gilmour.



Scheme 1. Photocatalytic strategies for stereoselective synthesis of thermodynamically unfavorable monofluoroalkene isomers.

They have proved their reaction system could be applied to synthesis of the retinoid X receptor derivative (Scheme 1b).[7] On the other hand, we paid our attention to *gem*-bromofluoroalkenes because they are readily available[8] and undergo a variety of debrominative functionalization to afford valuable monofluoroalkenes.[9] Herein, we will report on *Z*-selective isomerization of *gem*-bromofluoroalkenes by Ir photocatalysis. Furthermore, subsequent transition-metal

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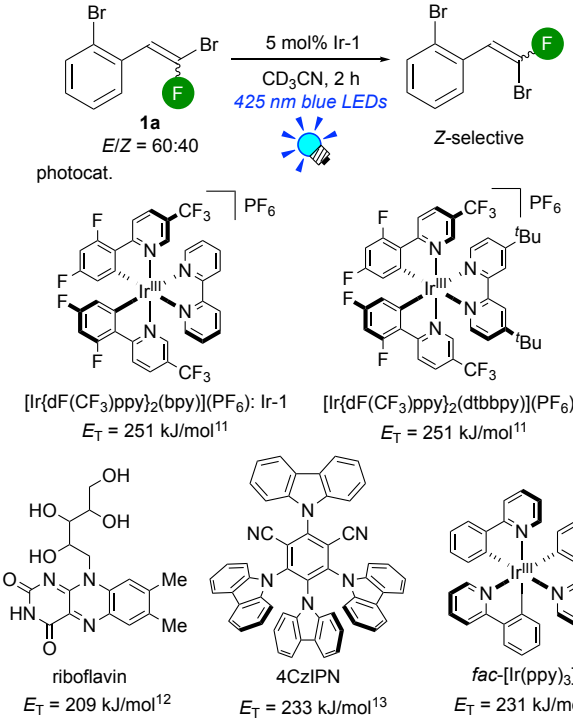
Table 1 Photocatalytic isomerization of 1-bromo-2-(2-bromo-2-fluoroethenyl)benzene[a]



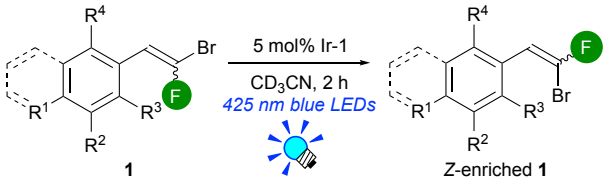
Entry	Deviations from the above	*E*/Z ratios after irradiation[b]
1	–	16:84, 93% NMR yield
2	Ir-2 instead of Ir-1	15:85
3	Riboflavin instead of Ir-1	72:28
4	4CzIPN instead of Ir-1	70:30
5	*fac*-[Ir(ppy)$_3$] instead of Ir-1	65:35
6	dmso-d_6 instead of CD_3CN	16:84
7	acetone-d_6 instead of CD_3CN	16:84
8	no photocat	60:40
9	In the dark	60:40

[a]General reaction conditions: a mixture of **1a** (0.24 mmol), photocatalyst (0.012 mmol, 5 mol%), CD_3CN (0.50 mL), and an internal standard ($C_6H_5CF_3$ or dimethyl sulfone (0.0030 mmol)) was irradiated by 425 nm blue LEDs at 25–27 ˚C. E_T: triplet energy. [b]Determined by ^{19}F NMR spectroscopy.

(TM)-catalyzed reactions lead to β-fluorostyrene derivatives in a stereoselective manner.[10]

We commenced the reaction of 1-bromo-(2-bromo-2-fluoroethenyl)benzene (**1a**) (*E*/*Z* mixture = 60:40) in CD_3CN in the presence of [Ir(dF(CF_3)ppy)$_2$(bpy)](PF_6) (Ir-1) (dF(CF_3)ppy: 2-(2,4-difluorophenyl)-5-(trifluomethyl)pyridine, bpy: 2,2'-bipyridine) (5 mol%) under visible light irradiation (425 nm blue LEDs). As a result, the isomerization reaction proceeded to attain a ratio of *E* to *Z* of 16:84 after 2 h irradiation (93% NMR yield) (entry 1 in Table 1). Even after irradiation for an additional 3 hours, the ratio did not change, *i.e.*, it is the photostationary state (PS). Photocatalysts with a higher triplet energy (E_T) proved to be effective, suggesting that the excited triplet species is involved in the reaction (entries 2–5). In addition, the use of CD_3CN, dmso-d_6, and acetone-d_6 as the solvent did not make a marked difference (entries 6 and 7). Furthermore, the isomerization reaction did not proceed very well in the absence of the photocatalyst and under dark conditions (entries 8 and 9).

Table 2 Photocatalytic isomerization of (2-bromo-2-fluoroethenyl)arenes[a]



Entry	alkene	Aromatic ring				*E*/*Z* ratios	*E*/*Z* ratios NMR yields	
		R^1	R^2	R^3	R^4	before irradiation[b]	at PS[b]	(%)[b]
1	**1b**	MeO	H	H	H	51:49	29:71	95
2	**1c**	CF_3	H	H	H	53:47	30:70	91
3	**1d**	Ph	H	H	H	60:40	36:64	94
4	**1e**	H	MeO	H	H	42:58	35:65	91
5	**1f**	2-naphthyl				45:55	40:60	94
6	**1g**	H	H	Me	H	64:36	17:83	92
7	**1h**	H	H	I	H	44:56	10:90	95
8	**1i**	H	H	TfO	H	61:39	14:86	94
9[c]	**1j**	H	H	Me	Me	57:43	<5:>95	94

[a]The reaction conditions were identical to those of entry 1 in Table 1. [b]Determined by ^{19}F NMR spectroscopy using $C_6H_5CF_3$ as an internal standard. [c]22 h irradiation.

Next, the influence of substituents on the aromatic ring on the present isomerization reaction was investigated. The *para*-positioned substituents of electron-donating (MeO (**1b**)) and -withdrawing (CF_3 (**1c**)) and electronically moderate Ph (**1d**) groups, the MeO group at the *meta* position (**1e**), and the naphthyl scaffold (**1f**) afforded *Z*-enriched ratios (*E*/*Z* = 40:60–29:71, 91–95% NMR yields) but lower selectivity compared to that of **1a** (entries 1–5 in Table 2). In contrast, the *ortho*-positioned substituents, Me (**1g**), I (**1h**), and TfO (**1i**) groups, gave *Z*-selective results (*E*/*Z* = 17:83–10:90, 92–95% NMR yields) in a manner similar to that of **1a** (entries 6–8). To our surprise, 2,2-dimethyl-(2-bromo-2-fluoroethenyl)benzene (**1j**) (*E*/*Z* = 57:43) underwent highly selective isomerization to the *Z*-isomer (*E*/*Z* = <5:>95, 94% NMR yield) but with a longer reaction time of 22 h (entry 9).

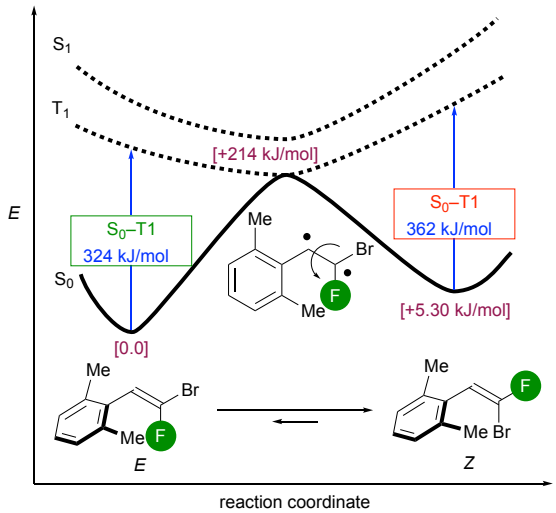
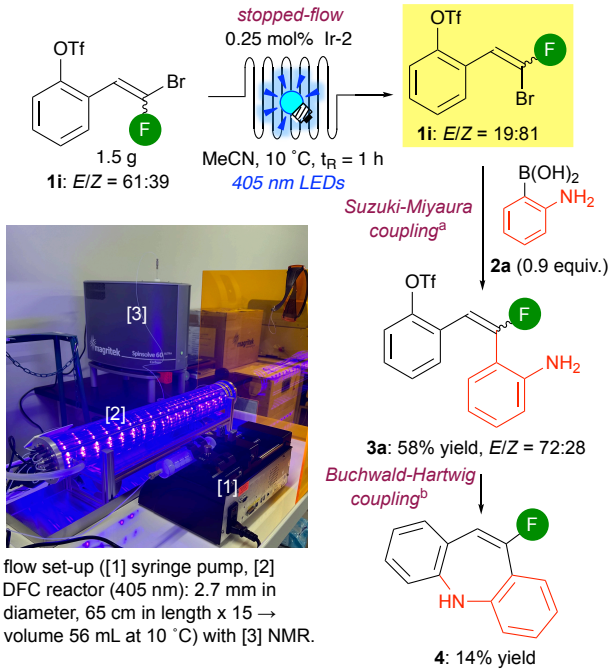


Figure 1. Energy profiles for isomerization of **1j**.

It should be noted that the obtained isomer *Z*-**1j** was not subject to deterioration of stereoselectivity at room temperature in the dark without photocatalyst for at least one week. These results showed that the steric factor at the *ortho* position(s) significantly affects the stereoselectivity.[14]

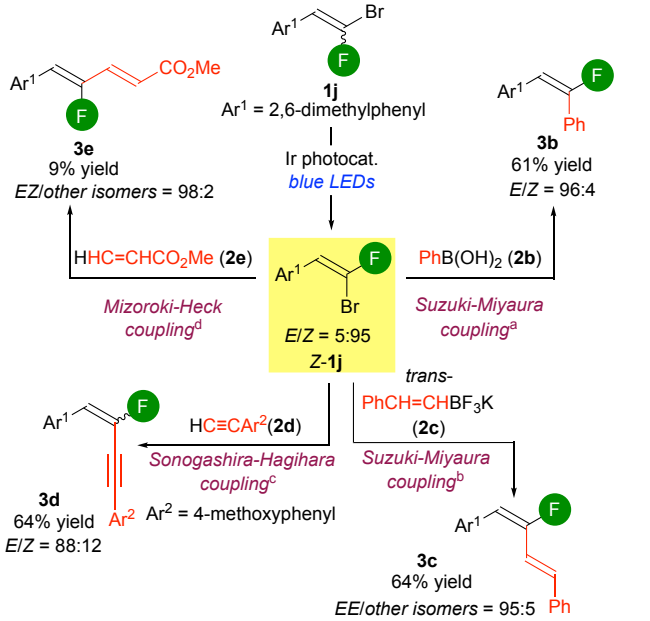
TD-DFT calculations (BLYP/def2-TZVP) revealed that the S_0–T_1 energies of each *E* and *Z* isomers depend significantly on the structure of **1**. In the case of **1j**, the S_0–T_1 energies of the *E* and *Z* isomers are calculated to be 324 and 362 kJ/mol, respectively (Figure 1), indicating that the excitation of the *Z* isomer requires higher energy than that of the *E* isomer. Thus, use of a photocatalyst with an appropriate triplet energy can promote selective EnT toward one isomer, *i.e.*, the *E* isomer in the present case. Then, the excited isomer can undergo isomerization to the opposite isomer through the C–C bond rotation of the biradical intermediate, resulting in enrichment of the thermodynamically unfavored *Z* isomer.[15]

Next, the scalability of the present reaction system was studied. Flow technologies have been usually applied to scale-up and high-speed photocatalytic reactions.[16] We also set up the flow reactor with *built-in* desktop NMR system for in-line analysis (Figure 2). An MeCN solution of **1i** (4.20 mmol, 1.47 g) and [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)](PF$_6$) (dtbbpy: 4,4′-di-*tert*-butyl-2,2′-bipyridine) (Ir-2), (0.25 mol%) was pumped into the flow reactor around blue LEDs (405 nm visible light) at 10 ˚C (refrigerant temperature) while monitoring ratios of isomers by ^{19}F NMR spectroscopy. After 1 h of irradiation (residence time: t_R), the isomerization reaction gave a highly *Z*-enriched mixture (*E*/*Z* = 19:81) at PS. The obtained *Z*-enriched **1i** was used for the synthesis of fluorinated 5*H*-dibenzo[*b,f*]azepine **4**.



flow set-up ([1] syringe pump, [2] DFC reactor (405 nm): 2.7 mm in diameter, 65 cm in length x 15 → volume 56 mL at 10 ˚C) with [3] NMR.

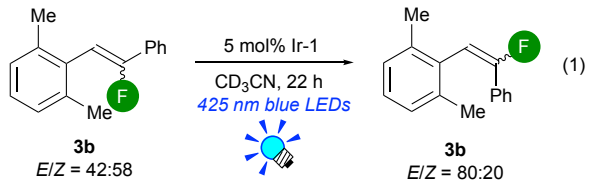
Figure 2. Gram-scale photocatalytic isomerization and application to synthesis of fluorinated 5*H*-dibenzo[*b,f*]azepine derivative. For detailed reaction conditions, see the Supporting Information. The *E*/*Z* ratio of **1i** was determined by in-line ^{19}F NMR analysis. (a) Pd(PPh$_3$)$_4$ (10 mol%), K$_2$CO$_3$ (3 equiv.), toluene/EtOH/H$_2$O, reflux, 22 h. (b) Pd(OAc)$_2$ (3.0 mol%), XPhos (4.5 mol%), NaO*t*Bu (1.2 equiv.), toluene, 100 ˚C, 24 h.



Scheme 2. Pot-economical stereoselective synthesis of fluoroalkenes. For detailed reaction conditions, see the Supporting Information. (a) Pd(PPh$_3$)$_4$ (15 mol%), **2b** (2 equiv.), K$_2$CO$_3$ (3 equiv.), toluene/EtOH/H$_2$O, reflux, 22 h. (b) Pd(PPh$_3$)$_4$ (10 mol%), **2c** (1.4 equiv.), Cs$_2$CO$_3$ (4 equiv.), toluene/H$_2$O, 80 ˚C, 23 h. (c) Pd(PPh$_3$)$_2$Cl$_2$ (0.5 mol%), CuI (10 mol%), **2d** (1.5 equiv.), Et$_3$N, r.t., 48 h. (d) Pd(OAc)$_2$ (2 mol%), **2e** (8 equiv.), K$_2$CO$_3$ (5 equiv.), Bu$_4$NCl (1 equiv.), r.t., 24 h.

The related *N*-heterocycles have been actively studied as bioactive ring systems.[17] After the photocatalytic isomerization, the solvent was removed. Then, without further purification, Suzuki-Miyaura coupling with 2-aminophenylboronic acid (**2a**) afforded the *cis*-type stilbene derivative **3a** as a major product (*E*/*Z* = 72:28). Subsequent intramolecular Buchwald-Hartwig reaction produced fluorinated 5*H*-dibenzo[*b,f*]azepine **4** in 14% yield. These results suggest that the present photocatalytic isomerization is scalable and allows us to design modular flow reaction systems[18] followed by TM-catalyzed coupling reactions.

Finally, we studied synthetic applications of *Z*-*gem*-bromofluoroalkene **1j** (Scheme 2). As mentioned above, the Ir photocatalyst is potentially compatible with subsequent Pd-catalyzed reactions. Thus, pot-economical synthetic strategies, *i.e.*, one-pot two-reactions: (i) photocatalytic isomerization and (ii) Pd-catalyzed coupling reactions were applied to **1j**. After photocatalytic isomerization, volatiles were removed *in vacuo*. Then, the coupling partner **2**, catalyst(s), reagent(s), and solvent(s) were added to the reaction vessel. The reactions of *Z*-enriched **1j** (*E*/*Z* = 5:95) with phenylboronic acid (**2b**), potassium *trans*-styryltrifluoroborate (**2c**), and 4-ethynylanisole (**2d**) under appropriate reaction conditions afforded the corresponding stereocontrolled fluoroalkenes, stilbene derivative **3b** (61% yield, *E*/*Z* = 96:4), conjugated diene derivative **3c** (64% yield, *EE*/*other isomers* = 95:5), and enyne derivative **3d** (64% yield, *E*/*Z* = 88:12), respectively. These results show that the stereochemistry of **1j** is almost retained under these coupling reaction conditions. Additionally, Mizoroki-Heck-type reaction with methyl acrylate (**2e**) could also be applied to the present pot-economical strategy. According to the related literature[9b],



the coupling product **3e**, of which stereochemistry is (2*E*,4*Z*)-structure, could be isolated, albeit in low yield (9%). It should be noted that the photocatalytic isomerization turned out to be less effective for the stilbene derivative **3b**, which was prepared from the coupling reaction prior to isomerization. Considering the fact that the isomerization of **3b** (*E*/*Z* = 42:58) under the reaction conditions given in Table 2 afforded an *E*/*Z* mixture (80:20) in 22 h (Eq. 1), the present reaction sequence is the key to successful stereoselective synthesis. These results underscore that the one-pot strategy using *gem*-bromofluoroalkenes as starting materials is feasible for the stereoselective synthesis of monofluoroalkenes, which cannot be achieved directly by photocatalytic isomerization *via* EnT.

In conclusion, we have developed the pot-economical strategy for the stereoselective synthesis of trisubstituted β-fluorostyrene derivatives. The photocatalytic isomerization of *gem*-bromofluoroalkenyl benzenes bearing *ortho*-substituent(s) to thermodynamically unfavored isomers using $[Ir(dF(CF_3)ppy)_2(bpy)](PF_6)$ or $[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$ with a high triplet energy is the key process. The subsequent appropriate transition-metal catalysis for debrominative coupling reactions realizes the production of stereocontrolled β-fluorostyrene derivatives. In addition, *Z*-isomers of the *gem*-bromofluoroalkenyl benzenes bearing halogen and TfO groups, which serve as potential handles for additional transformations, at the *ortho*-position can be useful scaffolds for fluoroalkenyl cyclic structure. Further synthesis and transformation of monofluoroalkene derivatives are in progress in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the Supplementary Information

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September 23rd, 2024

Dear the Editors of the *Chemical Communications*,

Title: Photocatalytic *E*→*Z* isomerization of *gem*-bromofluoroalkenes: Stereoselective synthesis of β-fluorinated aromatic alkenes
Authors: Hayato Kato, Prof. Dr. Yoshihito Kayaki, and Prof. Dr. Takashi Koike*

A data availability statement
The data supporting this article have been included as part of the Supplementary Information.

Dr. Takashi Koike, Associate Prof.