

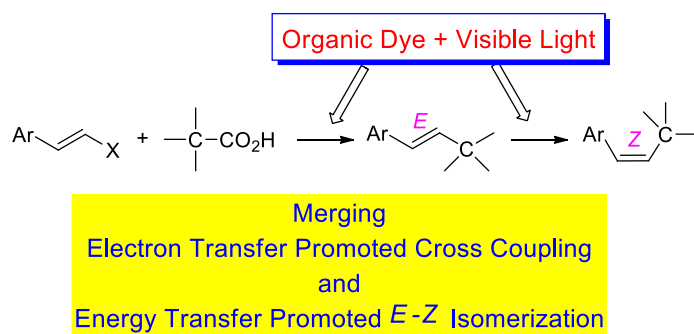
## Graphical abstract

# Organophotocatalyzed *E* and *Z* Stereoselective C<sub>sp3</sub>-C<sub>sp2</sub> Bond Forming Cross Coupling Reactions of Carboxylic Acids with $\beta$ -Aryl-Vinyl Halides

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Organic dye photocatalyzed divergent *E* and *Z* stereoselective C<sub>sp3</sub>-C<sub>sp2</sub> bond forming cross coupling reactions of carboxylic acids with  $\beta$ -aryl-vinyl halides.

# Organophotocatalyzed *E* and *Z* Stereoselective C<sub>sp3</sub>-C<sub>sp2</sub> Bond Forming Cross Coupling Reactions of Carboxylic Acids with $\beta$ -Aryl-Vinyl Halides

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## ABSTRACT

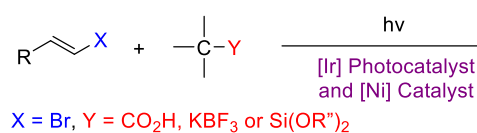
Owing to their importance in organic synthesis, transition metal catalyzed cross-coupling reactions have been the focus of many studies. Recently, it was recognized that merged transition metal and photoredox catalysis is a powerful strategy for the design of challenging C<sub>sp3</sub>-C<sub>sp2</sub> bond forming cross coupling reactions. However, these reactions require metals (e.g., Ni) to activate C<sub>sp2</sub>-halogen bonds. In the current investigation, we developed a new, photocatalysis based, metal free approach to accomplish C<sub>sp3</sub>-C<sub>sp2</sub> bond formation between an alkyl fragment, derived from a carboxylic acid, and a vinyl moiety of  $\alpha,\beta$ -aryl-substituted vinyl halide. The cross coupling process, which is activated by using the simple organic dye 4CzIPN, acting as a single electron transfer type photocatalyst, and visible light, is chemoselective, *E*-stereoselective and efficient. Moreover, upon prolonged irradiation of the reaction mixture, 4CzIPN serving as an energy transfer photocatalyst, promotes isomerization of the initially formed alkenes into mixtures enriched in the *Z*-isomers.

The advent of cross-coupling reactions has revolutionized the synthesis of organic compounds. These reactions, which generally require the use of transition metals (TM) as catalysts, are among those most used for carbon-carbon and carbon-heteroatom bond formation.[1] Perhaps the most important challenge in this area is the development of cross coupling reactions that generate bonds to sp<sup>3</sup> hybridized carbons. Recently, a new paradigm for designing cross coupling reactions of this type was revealed in independent studies by Doyle and MacMillan and Molander.[2] The new approaches devised by them (Scheme 1a) involve the use of dual photoinduced single electron transfer (SET) and nickel catalysis to promote direct C<sub>sp3</sub>-C<sub>sp2</sub> cross-coupling between alkyl-carboxylates, -silicates and -trifluoroborates and aryl-vinyl-halides.[3] Moreover, the results of additional studies by Molander and MacMillan led to the development of C<sub>sp3</sub>-C<sub>sp2</sub> bond forming [Ni] free reactions between alkyl potassium fluoroborates or carboxylic acids, and vinyl sulfones that utilize metal containing photoredox catalysts or Na<sub>2</sub>-Eosin Y (Scheme 1b).[4] In addition, impressive studies of photoredox decarboxylative couplings of alkenyl carboxylic acids or active esters for alkene formation have been reported. These processes generally are also carried out with metal containing photoredox catalysts and/or other TM as co-catalysts (Scheme 1c).[5] It is noted that in many cases, thermodynamically favored (*E*) products are formed.

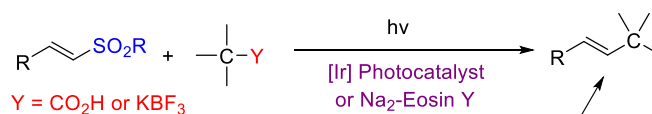
In a recent study, the results of which are described below, we developed a simple photoredox catalyzed C<sub>sp3</sub>-C<sub>sp2</sub> bond forming cross coupling reaction that utilizes  $\beta$ -aryl substituted haloalkenes and alkyl carboxylic acids (Scheme 1d). Importantly the new process does not require the use of vinylsulfones, and it is photocatalyzed by the simple metal free organic dye, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN).[6] Notably, the initially formed *E*-alkene products can be converted in situ into mixtures enriched in the *Z*-isomers via a process in which 4CzIPN serves as an energy transfer photocatalyst.[5d, 7]

Therefore, the process can deliver both *E* and *Z* alkenes in a divergent manner.[7b]

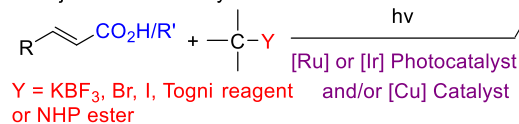
(a) Molander's, Doyle's & MacMillan's Work



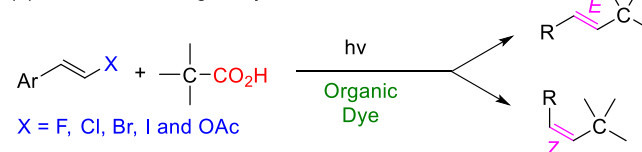
(b) Molander's & MacMillan's Work



(c) Chen's, Zhu's, Liu's, Noel's, Wang's, Duan's, Nakajima and Nishibayashi's Work



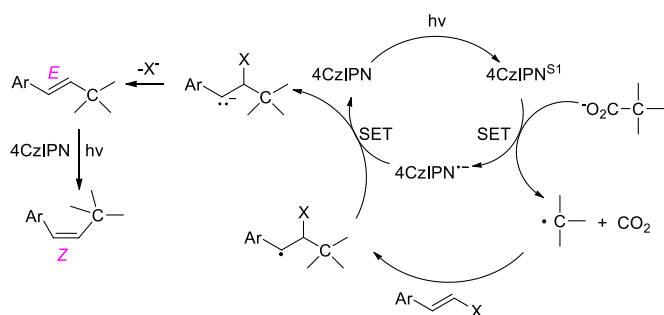
(d) This work - divergent synthesis of *E* and *Z* olefins



**Scheme 1.** Novel Cross Coupling Reactions.

At the outset of our studies, we questioned if it would be possible to design a simple photoredox promoted, free radical based C<sub>sp3</sub>-C<sub>sp2</sub> bond forming cross coupling reaction that utilizes the simple organic dye 4CzIPN as the photocatalyst, an alkyl-carboxylic acid as the radical precursor and a vinyl halide as C<sub>sp2</sub> component, and that does not require the use of a Ni catalyst. We reasoned that alkyl free radicals, produced by single electron induced decarboxylation of

alkyl-carboxylates, would add in a chemoselective manner to  $\beta$ -aryl substituted haloalkenes to produce aryl stabilized radicals. SET to this radical from the radical anion of 4CzIPN, formed in the initial step of the process, followed by halide ion loss would then produce the cross coupling product (Scheme 2). Arguing well for the success of this process is the fact that the reduction potential of the photoexcited state of 4CzIPN ( $E^{*ox} = +1.35$  V vs. SCE)[6] should be sufficiently high to promote a SET induced decarboxylation of an alkyl-carboxylates ( $E^{ox} = \text{ca } 1.0$  V vs SCE).[8]



**Scheme 2.** Proposed 4CzIPN photoinduced Csp<sup>3</sup>-Csp<sup>2</sup> bond forming cross coupling reaction.

An exploratory effort designed to assess the validity of this proposal began with a study of the 4CzIPN photocatalyzed decarboxylative cross-coupling reaction of *E*- $\beta$ -bromostyrene (**2a**) and Boc-Abu-OH (**1i**). We observed that blue LED irradiation of a mixture of these substrates and 4CzIPN in DMF containing Cs<sub>2</sub>CO<sub>3</sub> under N<sub>2</sub> leads to efficient (85%) formation of the *E*-stereoisomer of the cross coupling adduct *E*-**3i**.

**Table 1**  
Exploration and Optimization

Reaction scheme showing the cross-coupling of **2a** (Ph-CH=CH-Br) and **1i** (BocHN-CH(Et)-COOH) to form **E-3i** (BocHN-CH(Et)-CH=CH-Ph) and **Z-3i** (BocHN-CH(Et)-CH=CH-Ph). Conditions: 4CzIPN 5 mol%, Cs<sub>2</sub>CO<sub>3</sub>, DMF (1.5 mL), N<sub>2</sub>, blue LED, rt. Time: 4 h (E-3i) or 6 d (Z-3i).

Chemical structure of **4CzIPN** (4,4'-bis(phenyl)-2,2'-bipyridine) is shown in the inset.

| entry | reaction time | deviation from "standard conditions" <sup>a</sup>                       | % yield <sup>b</sup> | Z/E <sup>c</sup>           |
|-------|---------------|---|----------------------|----------------------------|
| 1     | 4 h           | none  | 85                   | <1:99                      |
| 2     | 24 h          | without N <sub>2</sub> protection                                       | 27                   | 37:63                      |
| 3     | 24 h          | dark  | 0                    | -                          |
| 4     | 24 h          | no 4CzIPN   | <5                   | -                          |
| 5     | 4 h           | using (Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbpy))PF <sub>6</sub> | 9                    | -                          |
| 6     | 6 d           | none  | 81                   | 81:19 (86:14) <sup>d</sup> |
| 7     | 90 min        | 10.98g of <b>2a</b> <sup>e</sup>  | 87                   | <1:99                      |

<sup>a</sup> Standard conditions: see SI for details.

<sup>b</sup> Isolated yields.

<sup>c</sup> Z/E values were determined by using <sup>1</sup>H NMR spectroscopic analysis of the crude product mixture obtained by extraction and concentration of the photolysate.

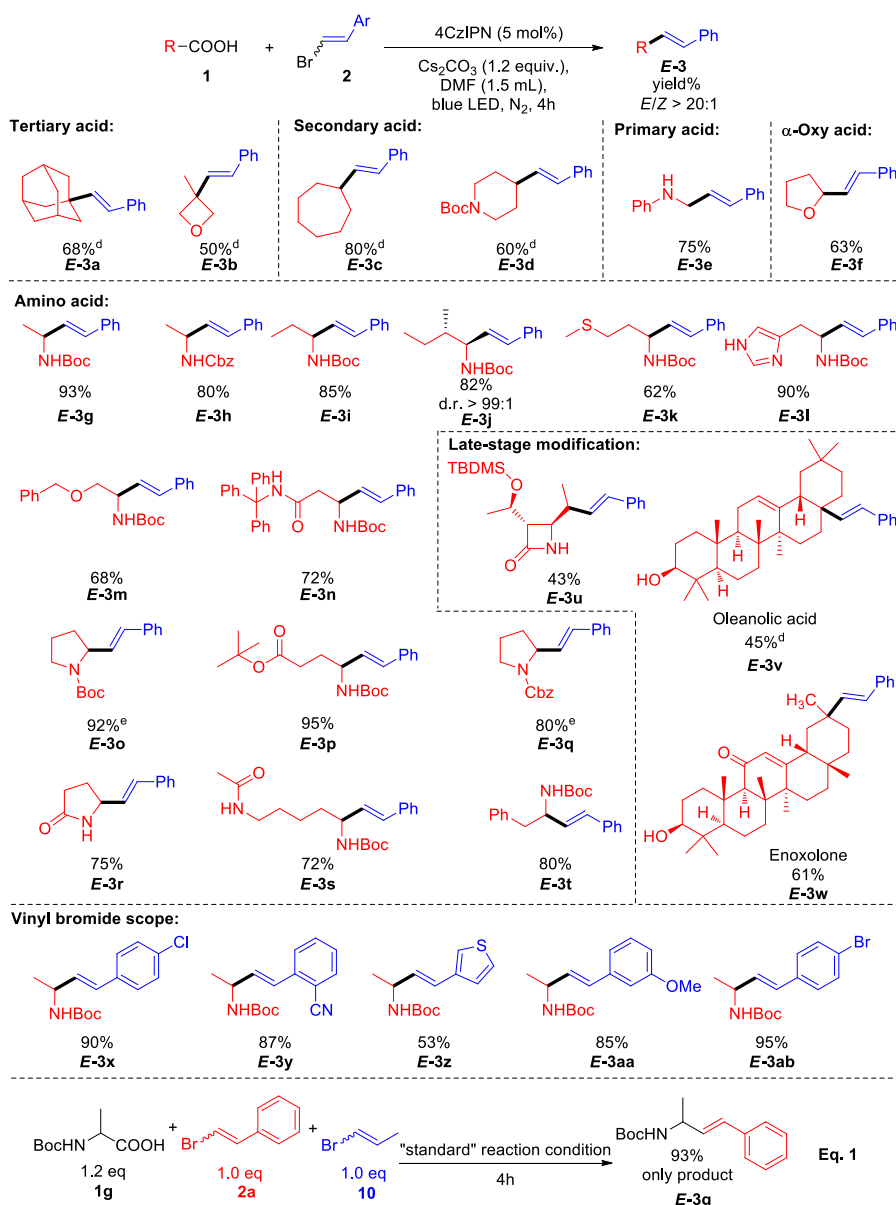
<sup>d</sup> Z/E values in parentheses were determined by quantitative analysis of the isolated product.

<sup>e</sup> Flow conditions: see SI for detail

To gain information about this stereocontrolled process, we probed the effects of several parameters including substrate ratio, photosensitizer (PS), base, reaction time and solvent (Table 1 and Table S1 in the Supporting Information (SI)). The results show that the yield of the cross coupling reaction decreases when O<sub>2</sub> is present, suggesting that the process involves radical intermediates (entry 2). Moreover, both LED irradiation and the photosensitizer are essential for the process (entries 3-4). Surprisingly, reaction using a common Ir photocatalyst was less efficient than the one promoted by 4CzIPN under otherwise identical conditions (entry 5). We also found that it is possible to alter the stereochemical outcome of this reaction by simply controlling the irradiation time (see below). For example, blue light irradiation of the solution of **2a**, **1i** and 4CzIPN for 6 d leads to formation of **Z-3i** in a 86:14 Z/E ratio (entry 6). Finally, a 10.98 g scale reaction, carried out using continuous flow conditions [8a, 8b, 9] with a residence time of 90 min and using only 2.5 mol% of 4CzIPN, generates 13.65g of **E-3i** in 87% yield.

The scope of the photocatalyzed cross coupling reaction forming *E*-arylalkene was probed (Scheme 3). The results show that, under the optimized reaction conditions and, especially using a 4 h irradiation period, *E*-isomers of the alkenes (*E*/*Z* > 20:1) are produced in moderate to high yields (43-95%). An extensive variety of carboxylic acids, including those containing primary, secondary and tertiary alkyl groups (**1a-e**) can be employed as substrates for the process. Also, a number of biologically relevant amino acids (**1g-t**) and complex, highly functionalized acids (**1u-w**) serve as effective coupling partners. Furthermore, a variety of aryl-substituted *E*-vinyl bromides (**2x-ab**) participate in the cross coupling reaction, even ones containing halogen substituted phenyl groups (**2x** and **2ab**) which are troublesome in metal promoted cross coupling reactions. It should be noted that no reaction occurred with simple primary alkyl carboxylic acid substrates presumably due to the difficulty of oxidative SET decarboxylation. Finally, when a mixture 1-bromo-1-propene and the blocked amino acid **1g** is subjected to the optimized conditions, no cross coupling reaction takes place.

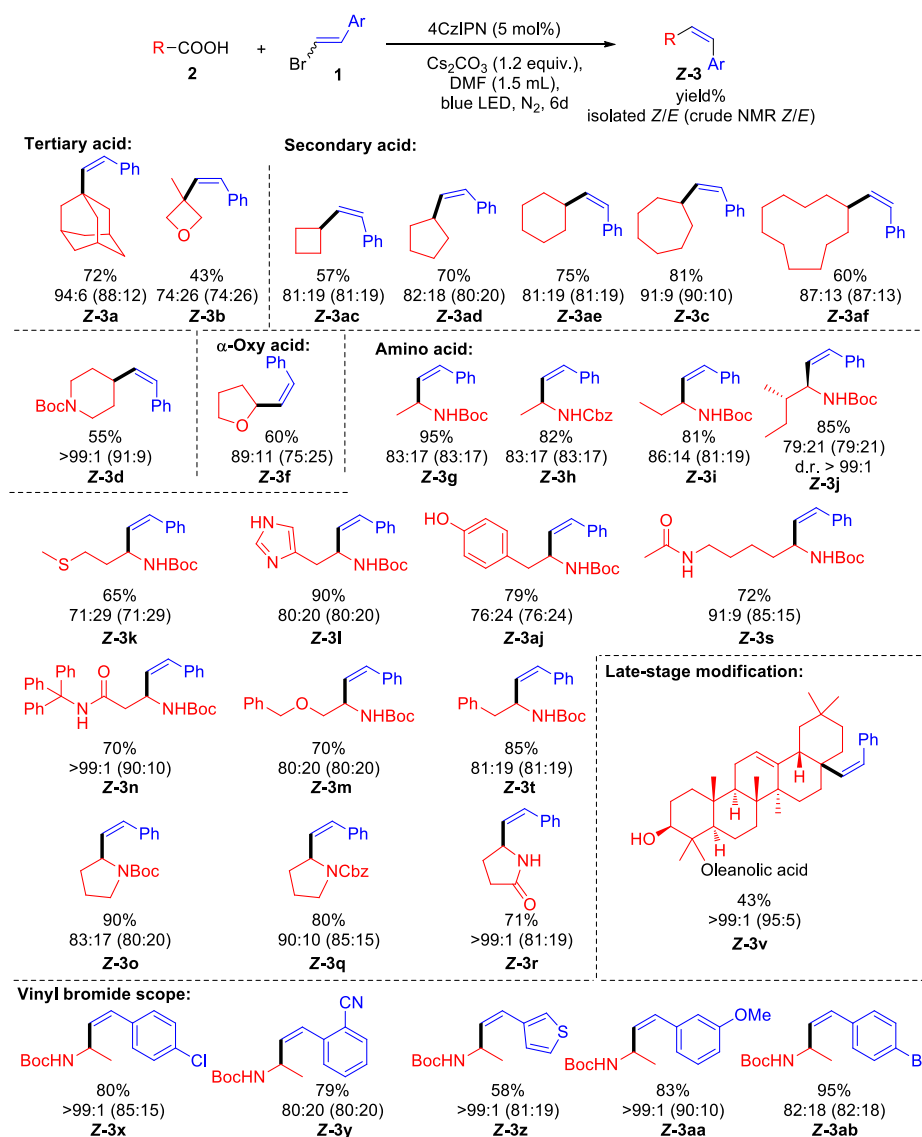
As can be readily seen by viewing the data in Scheme 3, 4CzIPN photocatalyzed cross coupling reactions between alkyl-carboxylic acids and  $\beta$ -aryl substituted bromoalkenes carried out for 4-6 h time periods generate the corresponding *E*-products nearly exclusively. We were interested in determining whether this process could also be employed to produce the corresponding *Z*-isomers without resorting to the use of two photocatalysts or an additional separate isomerization step. Although *E*→*Z* isomerization reactions of styrene derivatives promoted by typical photoredox catalysts have been observed earlier, they are either limited to specific substrate types, or require careful manipulation of reaction conditions to achieve optimal levels of stereoselectivity. [5d, 7] In the current effort, we observed that by using the same photocatalyst and conditions used to carry out the cross coupling process and simply lengthening the reaction time, *Z*-alkenes are generated as predominant products. As can be seen by viewing the examples displayed in Scheme 4, blue LED irradiation induced 4CzIPN photocatalyzed reactions of a wide variety of alkyl carboxylic acids **1** with aryl-haloalkenes **2** carried out for 6 d form *Z*-products in Z:E ratios up to 99:1.



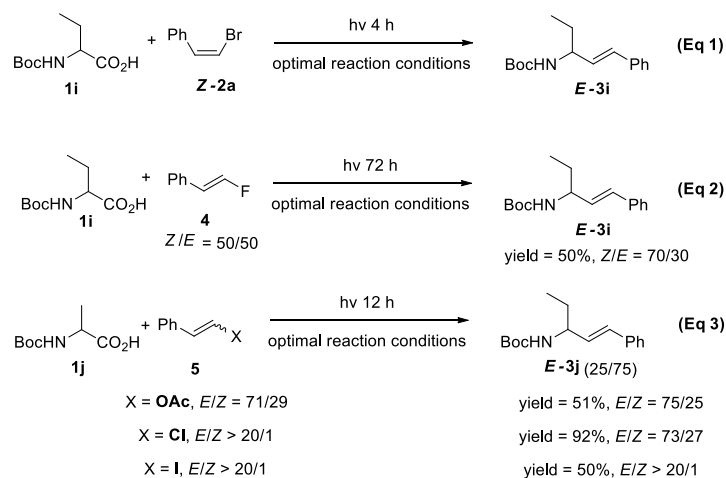
**Scheme 3.** Substrate Scope for the photocatalyzed C<sub>sp3</sub>-C<sub>sp2</sub> bond forming cross coupling reaction producing *E*-products. <sup>a</sup> See SI for detailed procedures. <sup>b</sup> Isolated yields. <sup>c</sup> *E/Z* values were monitored and determined by using <sup>1</sup>H NMR spectroscopic analysis of the residue obtained by extraction and concentration of the reaction. <sup>d</sup> reaction for 6 h. <sup>e</sup> reaction for 3 h

Information about the mechanistic details of the photocatalyzed cross coupling reaction comes from observations made in additional studies. First, 4CzIPN photocatalyzed cross coupling of carboxylic acid **2i** and *Z*- $\beta$ -bromostyrene for 4 h produces the corresponding *E*-product **3i** exclusively. Thus, the stereochemical outcome of the process is not dictated by the stereochemistry of the haloalkene. In addition,  $\beta$ -fluorostyrene (**4**) and the  $\beta$ -styryl acetate (**5**) serve as substrates for the cross coupling reaction (Eq. 2 and 3) although in these cases the reactions require longer times for completion and are, thus, complicated by formation of mixtures of *E* and *Z* products. Although we are uncertain about the efficiency diminishing effect of the fluorine and acetoxy substitution, the fact that reaction takes place with these substrates hints at the possible pathway followed in production of the cross coupling products.

In earlier studies of reactions of this type, it was postulated that the radical formed by addition of an alkyl radical to an arylvinyl-sulfone forms a radical that directly fragments to produce the alkene product along with a sulfonyl radical [4]. An alternative pathway for product formation, as proposed in Scheme 2, in the current cross coupling process involves SET to the radical, formed by addition of an alkyl radical to an arylvinyl-halide, from the radical anion of the photocatalyst, generated in the initial activation step. This process produces the corresponding anion, which upon loss of halide or acetate ion would yield the alkene product. This route is particularly relevant to reactions of **4** and **5** where the large C-F (ca 130 kcal/mol) [10] and ester C-O (ca 106 kcal/mol) [11] bond dissociation energies could cause the radical fragmentation process to occur slowly. These studies further validated the mechanism (Scheme 2).



**Scheme 4.** Photocatalyzed C<sub>sp3</sub>-C<sub>sp2</sub> bond forming cross coupling reactions producing Z-products <sup>a</sup>See SI for detailed procedures. <sup>b</sup>Isolated yields. <sup>c</sup> Z/E values were monitored and determined by using <sup>1</sup>H NMR spectroscopic analysis of the residue obtained by extraction and concentration of the reaction. <sup>d</sup> Z/E values in parentheses were determined by quantitative analysis of the isolated product.



**Scheme 5.** Reactions designed for understanding of reaction mechanistic aspects

The investigation described above led to the development of an organic dye photocatalyzed C<sub>sp3</sub>-C<sub>sp2</sub> bond forming cross coupling reaction between aryl-substituted haloalkenes and alkyl-carboxylic acid. The process has a wide substrate scope and, when conducted using short irradiation times, produces E-coupling products exclusively independent of the double bond configuration of the starting haloalkene. Moreover, the corresponding Z-isomers of the products can be generated predominantly by simply increasing the irradiation time.

## Acknowledgments

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