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Cross-Coupling Reactions of Alkenyl Halides with 4-Benzyl-1,4-Dihydropyridines Associated with *E* to *Z* Isomerization under Nickel- and Photoredox-Catalysis**

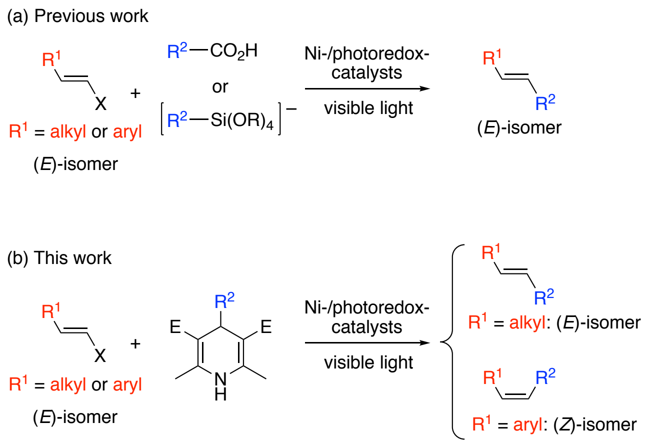
Kazunari Nakajima, Xifeng Guo, and Yoshiaki Nishibayashi**

***Abstract**: Cross-coupling reactions of alkenyl halides with 4-alkyl-1,4-dihydropyridines as alkylation reagents have been achieved by combination of nickel and photoredox catalysts. Alkenyl halides bearing alkyl and aryl substituents are available. Particularly, in the use of aryl-substituted alkenyl halides, cross-coupling reactions are associated with E to Z isomerization of alkenes. Thus, Z-isomers of the products are obtained as major products. The present strategy provides a novel synthetic method to control the stereochemistry around alkenes.*

Alkene is a fundamental molecular skeleton found in various natural products, pharmaceuticals and other useful molecules.[1] In the synthesis of alkenyl compounds, controlling the formation of *E*- and *Z*-isomers is generally unavoidable concern. Among the vast range of methods to synthesize alkenyl compounds, transition metal-catalyzed cross-coupling reactions of alkenyl halides with nucleophilic reagents have been one of the most powerful strategies in the last decades.[2] In this strategy, control of the stereochemistry around alkenes is premised of retention of the starting *E*- or *Z*-isomer, that is, the stereochemistry around the alkenes is usually retained throughout the transformation.[2,3]

Besides the classical cross-coupling reactions under thermal conditions, recently, combination of a nickel catalyst and a photoredox catalyst has emerged as a new method to achieve cross-coupling reactions, where generation of alkyl radicals via single electron transfer is a key step.[4] Actually, reactions of alkenyl halides with alkylation reagents such as aliphatic carboxylic acids and alkyl silicates have been reported to date (Scheme 1a).[5] In previously reported nickel- and photoredox-catalyzed cross-coupling reactions of alkenyl halides,[5,6] limited attention has been paid to the use of aryl-substituted alkenyl halides.

Recently, our group and others have reported the synthetic utilization of dihydropyridine skeletons as formal nucleophilic alkylation reagents in photoredox-catalyzed molecular transformations.[7-9] We have succeeded in the nickel- and photoredox-catalyzed cross-coupling reactions of aryl halides with 4-alkyl-1,4-dihydropyridines.[7b,8d,8g,8j] In the course of our study to expand the utility of dihydropyridines, herein, we have developed cross-coupling reactions of alkenyl halides with 4-alkyl-1,4-dihydropyridines, where not only alkyl-substituted alkenyl halides but also aryl-substituted alkenyl halides were applicable (Scheme 1b). Furthermore, in reactions of aryl-substituted alkenyl halides, the corresponding *Z*-isomers were obtained as major products, and the preferential formation of the *Z*-isomer is independent from the stereochemistry of the starting alkenyl halides. In this paper, the experimental results on this reaction system are described.



Scheme 1. Cross-coupling reactions of alkenyl halides with alkylation reagents.

At the onset of this research, we carried out reactions of (*E*)-1-iodooct-1-ene (*E*-**1a**) with 4-benzyl-3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridine (**2a**) to investigate detailed reaction conditions (Table 1).[10] In the presence of *fac*-Ir(ppy)$_3$ (1 mol%), anhydrous NiCl$_2$ (10 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridyl (dtbbpy; 15 mol%), and sodium acetate (1.5 equiv), the reaction of **1a** (1 equiv) with **2a** (3 equiv) was carried out in various solvents under visible light illumination. When the reaction was performed in *N*,*N*-dimethylimidazolidinone (DMI) as solvent, which was the best solvent in our previous reaction system,[7b] the desired (*E*)-1-phenylnon-2-ene (**3a**) was obtained in 61% yield without formation of the corresponding *Z*-isomer (Table 1, Entry 1). After investigation of other solvents such as dimethylsulfoxide (DMSO), acetonitrile, tetrahydrofuran (THF), and toluene, we found that THF

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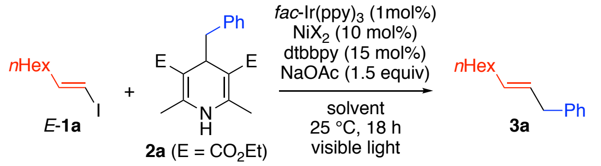
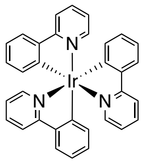
was the best solvent (Table 1, Entries 2-5). Changing $NiCl_2$ to $Ni(acac)_2$ (acac = acetylacetonato) gave the product in only a lower yield (Table 1, Entry 6). Reducing the amount of **2a** to 2 equiv was successful to obtain **3a** in a comparable yield, but further reduction to 1.5 equiv. gave **3a** in a lower yield (Table 1, Entries 4, 7, and 8). We confirmed that photoredox catalyst such as nickel catalyst and visible light are inevitable to this reaction system (Table 1, Entries 9-11). Both dtbbpy as a ligand and sodium acetate as a base were also necessary to obtain the product in high yields (Table 1, Entries 12 and 13). It is noteworthy that the aromatized pyridine derivative **2a'** was observed in 92% yield under the optimized conditions (Table 1, Entry 7).

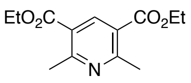
Table 1. Reactions of (*E*)-1-iodooct-1-ene (**1a**) with 4-benzyl-3,5-bis(ethoxycarbonly)-2,6-dimethyl-1,4-dihydropyridine (**2a**).[a]



Entry	**2a** (equiv)	NiX_2	solvent	yield (%)[b]
1	3	$NiCl_2$	DMI	61
2	3	$NiCl_2$	DMSO	22
3	3	$NiCl_2$	MeCN	3
4	3	$NiCl_2$	THF	90
5	3	$NiCl_2$	toluene	16
6	3	$Ni(acac)_2$	THF	60
7	2	$NiCl_2$	THF	87
8	1.5	$NiCl_2$	THF	77
9[c]	2	$NiCl_2$	THF	trace
10[d]	2	$NiCl_2$	THF	0
11	2	–	THF	trace
12[e]	2	$NiCl_2$	THF	6
13[f]	2	$NiCl_2$	THF	24



fac-Ir(ppy)$_3$



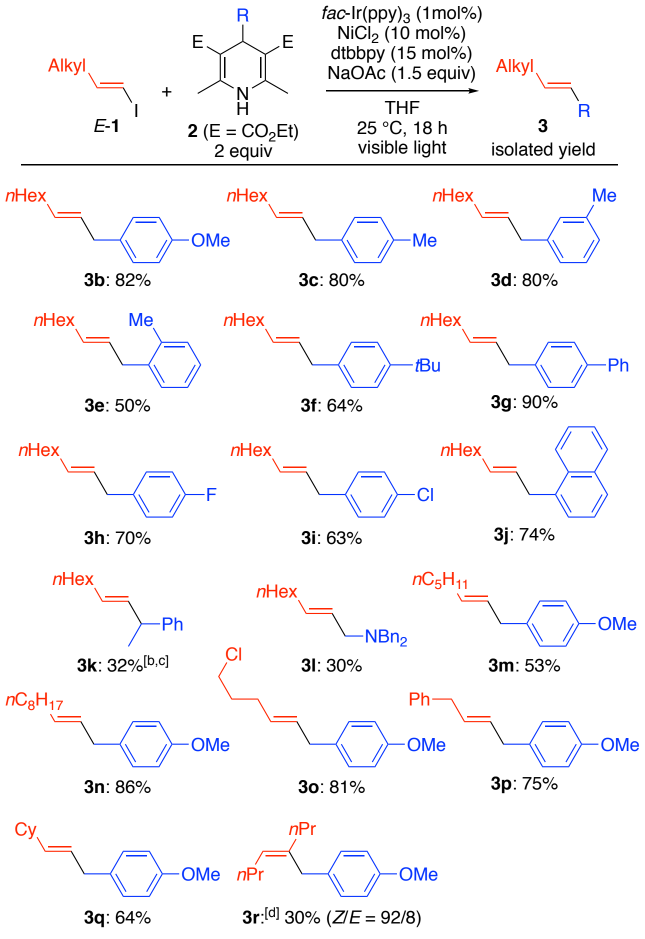
2a'

[a] Reactions of **1a** (0.25 mmol) with **2a** (0.75 or 0.50 mmol) were carried out in the presence of *fac*-Ir(ppy)$_3$ (0.0025 mmol), NiX_2 (0.025 mmol), dtbbpy (0.038 mmol), and NaOAc (0.38 mmol) in solvent (2.5 mL) with 14 W white LED illumination at 25 °C for 18 h. [b] Isolated yield. [c] In the absence of *fac*-Ir(ppy)$_3$. [d] No light. [e] In the absence of dtbbpy. [f] In the absence of NaOAc.

With the optimized reaction conditions in hand, we investigated reactions of alkenyl iodides bearing alkyl substituents with dihydropyridines (Table 2). As for the dihydropyridines, transformations with benzylic type alkyl groups bearing a variety of substituents were successful to give the corresponding products (**3b-3j**). Introduction of a methyl group into the *para*-, *meta*-, and *ortho*-positions of the benzene ring was also successful (**3c-e**). The transformations with a secondary alkyl-type benzylic group and a heteroatom-substituted alkyl group afforded the products in moderate yields (**3k-l**).

Reactions of a variety of alkyl-substituted alkenyl iodides with 4-(4-methoxybenzyl)-3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridine (**2b**) were also examined. Alkenyl iodides with acyclic and cyclic alkyl groups were successfully converted into the corresponding products (**3m-q**). The reaction of (*Z*)-4-iodooct-4-ene (*Z*-**1g**) with **2b** afforded the tri-substituted alkene derivative (**3r**) in 30% yield.

Table 2. Reactions of alkyl-substituted alkenyl iodides (**1**) with 4-alkyl-1,4-dihydropyridines (**2**).[a]

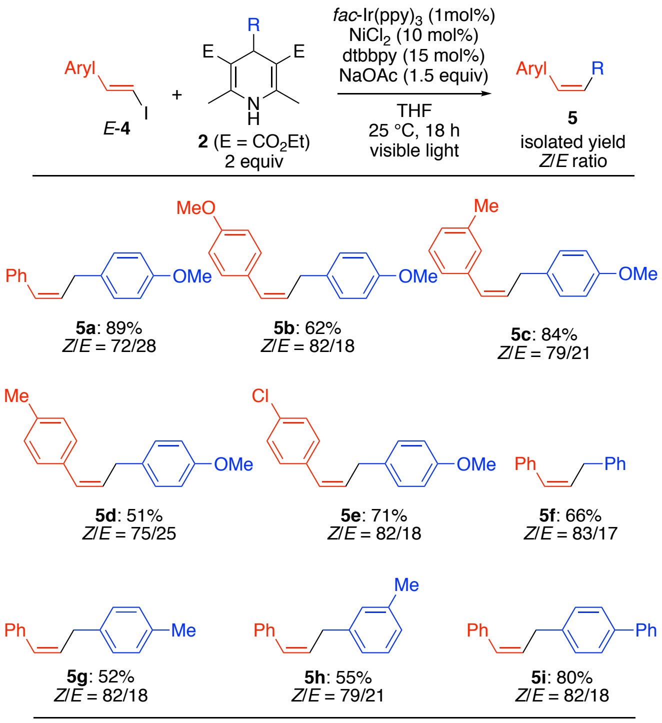


[a] All reactions of **1** (0.25 mmol) with **2** (0.50 mmol) were carried out in the presence of *fac*-Ir(ppy)$_3$ (0.0025 mmol), anhydrous $NiCl_2$ (0.025 mmol), dtbbpy (0.038 mmol) and NaOAc (0.38 mmol) in THF (2.5 mL) with 14 W white LED illumination at 25 °C for 18 h. [b] For 72 h. [c] NMR yield. [d] From (*Z*)-4-iodooct-4-ene (*Z*-**1g**).

In previously reported nickel- and photoredox-catalyzed cross-coupling reactions of alkenyl halides,[5,6] limited attention has been paid to the use of aryl-substituted alkenyl halides. Contrary to these reports, we found the present reaction system is applicable toward the transformation of alkenyl iodides bearing aromatic substituents. Furthermore, in this case, *Z*-alkenes were obtained as major products (Table 3). The reaction of (*E*)-β-iodostyrene (*E*-**4a**) with **2b** was carried out under the typical reaction conditions. The corresponding alkylated product (**5a**) was obtained in 89% yield as a mixture of *Z*- and *E*-isomers with the ratio of *Z*/*E* = 72/28. Despite the use of *E*-alkene as the starting material, the *Z*-alkene was obtained as a major isomer after the reaction.

Reactions of other alkenyl iodides with **2b** afforded the corresponding products in good yields with similar *Z*/*E* ratios (**5b-e**). Various dihydropyridines bearing a benzylic-type alkyl group were successfully transformed to give the *Z*-isomers selectively (**5f-i**).

Table 3. Reactions of alkenyl iodides bearing aromatic substituents with 4-alkyl-1,4-dihydropyridines (**2**).[a]

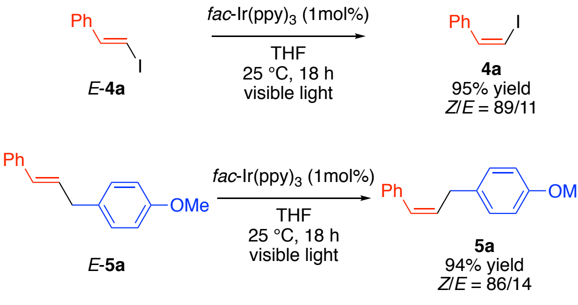


[a] All reactions of **4** (0.25 mmol) with **2** (0.50 mmol) were carried out in the presence of *fac*-Ir(ppy)$_3$ (0.0025 mmol), anhydrous $NiCl_2$ (0.025 mmol), dtbbpy (0.038 mmol) and NaOAc (0.38 mmol) in THF (2.5 mL) with 14 W white LED illumination at 25 °C for 18 h.

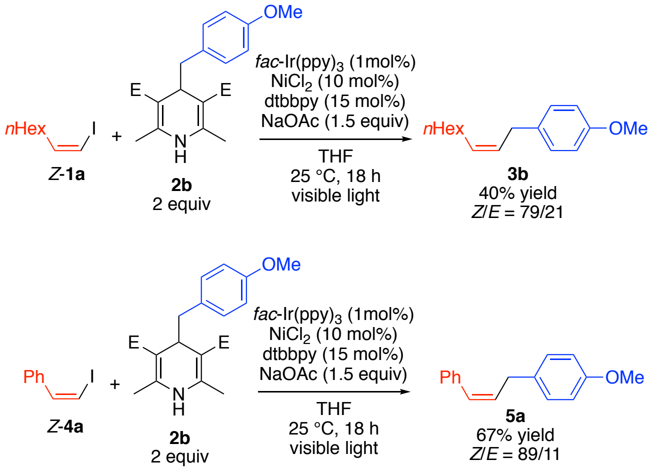
Previously, several groups reported photoredox-catalyzed *E* to *Z* isomerization of alkenes.[11] Weaver *et al.* reported *fac*-Ir(ppy)$_3$-catalyzed *E* to *Z* isomerization of styrene derivatives under visible light irradiation, where the observed *Z*/*E* ratios were similar to our present reaction system.[11b] According to these reports, the present cross-coupling reaction system is assumed to be associated with the *E* to *Z* isomerization process mediated by energy transfer from the excited Ir complex.

To obtain information on the isomerization process, we investigated photoredox-catalyzed isomerization reactions of *E*-alkenyl iodide *E*-**4a** and the cross-coupling product *E*-**5a**. As a result, we found that the isomerization was promoted only by photoredox catalyst *fac*-Ir(ppy)$_3$ and visible light irradiation. After treatment of *E*-**4a** and *E*-**5a** in the presence of *fac*-Ir(ppy)$_3$ under visible light irradiation, the *Z*-isomers of **4a** and **5a** were obtained as major isomers (Scheme 2). In the absence of *fac*-Ir(ppy)$_3$, small amounts of the *Z*-isomers were observed (>99% yield, *Z*/*E* = 11/89 for **4a**; >99% yield, *Z*/*E* = 1/>99 for **5a**). In addition, the quantum yields of the *E* to *Z* isomerization of *E*-**4a** and *E*-**5a** were determined to be Φ = 0.22 and 0.09, respectively, indicating the *E*/*Z* isomerization of the alkenyl iodide is faster than that of the cross-coupling product.

Next, we investigated reactions of *Z*-isomers of the alkyl and aryl-substituted alkenyl iodides (*Z*-**1a** and *Z*-**4a**) under the typical reaction conditions (Scheme 3). In both reactions, the corresponding *Z*-isomers were obtained as major products. It is noteworthy that the yields of the cross-coupling products were lower than those in the corresponding reactions of the *E*-isomers. This is presumably due to steric hindrance around the reaction center.



Scheme 2. Photoredox-catalyzed *E* to *Z* isomerization of *E*-**4a** and *E*-**5a**.



Scheme 3. Reactions of *Z*-alkenyl iodides (*Z*-**1a** and *Z*-**4a**) with **1b**.

To reveal the difference in reactivity of *E*- and *Z*-alkenyl iodides toward the cross-coupling process, we determined quantum yields of cross-coupling reactions of *E*- and *Z*-**1a** with **2b** under the typical reaction conditions. The quantum yields were determined to be Φ = 0.12 for *E*-**1a** and Φ = 0.05 for *Z*-**1a**. These results clearly indicate that the cross-coupling reaction of the *E*-alkenyl iodide is more rapid than that of the *Z*-alkenyl iodide.

These observations allow us to assume the following points: (1) the *E*/*Z* isomerization of the alkenyl iodide is the fastest process in the reaction system; (2) the cross-coupling process from the *E*-alkenyl iodide is faster than that from the *Z*-alkenyl iodide; (3) the *E*/*Z* isomerization of the cross-coupling product proceeds.

To confirm these assumptions, we monitored the time profile of the reaction of *E*-**4a** with **2b** to give *Z*- and *E*-**5a** (Figure 1). At early stage of the reaction, the rapid *E*- to *Z*-isomerization of the alkenyl iodide was observed. Although the *E*/*Z* isomerization process is considered to occur reversibly,[11] apparent concentration of *Z*-alkenyl iodide got higher in a short period. Then, after some induction period probably due to generation of active nickel species, formation of the cross-coupling products started. Initially the *Z*/*E* ratio of the cross-coupling product was nearly 1:1, but later the ratio of *Z*-isomer increased gradually.

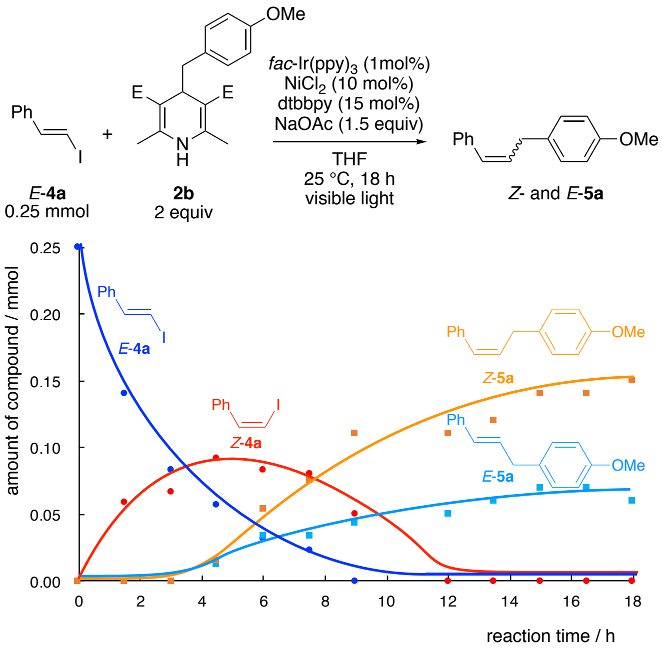
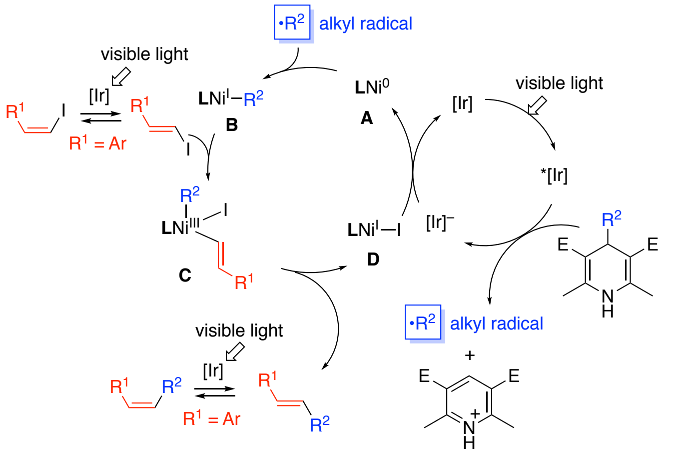


Figure 1. Time profile of reaction of *E*-**1a** with **2b** to give *Z*- and *E*-**5a**.

We consider that the present cross-coupling reaction proceeds via a similar pathway to our previous work,[7b] which was similar to the reaction pathway originally proposed by Molander and Kozlowski et al. in the nickel- and photoredox-catalyzed Suzuki-Miyaura-type cross-coupling reactions (Scheme 4).[12] In the photoredox cycle, excitation of a iridium catalyst ([Ir]) generates the excited state ([Ir]*). Then, a single electron transfer occurs to afford the reduced iridium catalyst ([Ir]$^-$) and a radical cationic dihydropyridine, which is further converted to an alkyl radical and an aromatized pyridine derivative via C–C bond cleavage.[7a] In the nickel cycle, an *in situ*-generated nickel(0) species (**A**) captures the alkyl radical to form a nickel(I)-alkyl complex (**B**). Then, oxidative addition with alkenyl iodides and reductive elimination occur to give the corresponding coupling product along with the nickel(I)-halide complex (**D**). Finally, the two catalytic cycles are completed by a single electron transfer between [Ir]$^-$ and **D**.

The cross-coupling process is assumed to proceed by a stereo-retentive manner, but in reactions of aryl-substituted alkenyl halides, *E* to *Z* isomerization via energy transfer process[11] is also included by the dual role of the photoredox catalyst. As discussed above, both the starting alkenyl iodides and the cross-coupling products undergo the *E*/*Z* isomerization. However, cross-coupling reactions of *E*-alkenyl iodides are more rapid than those of *Z*-alkenyl iodides.



Scheme 4. Plausible reaction pathway.

In summary, we have succeeded in the development of nickel- and photoredox-catalyzed cross-coupling reactions of alkenyl halides with dihydropyridines. The stereochemistry around the alkene was retained when alkyl-substituted alkenyl iodides were used. On the other hand, the use of aryl-substituted alkenyl iodides afforded the corresponding *Z*-products as major isomers. In these reactions, the *Z*-selective product formation has been achieved from the corresponding *E*-isomers of starting substrates. In general, *Z*-alkenes are thermodynamically less stable than the corresponding *E*-alkenes, and preparative methods of *Z*-alkenes have been relatively limited. The present reaction system provides a new method to synthesize *Z*-alkenyl compounds. We believe that the present findings lead to a new strategy to control the stereochemistry around alkenes.

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Keywords: dihydropyridine • nickel catalyst • photoredox catalyst • cross-coupling reaction

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Layout 2:

Cross-Coupling

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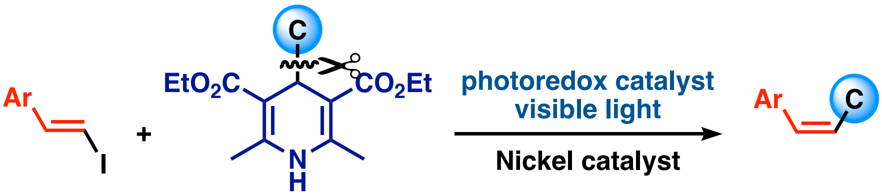
Cross-Coupling Reactions of Alkenyl Halides with 4-Benzyl-1,4-Dihydropyridines Associated with *E* to *Z* Isomerization under Nickel- and Photoredox-Catalysis



Photoredox catalyst serves dual roles. In the nickel- and photoredox-catalyzed cross-coupling reactions of alkenyl halides with dihydropyridines, the *E* to *Z* isomerization proceeds. The photoredox catalyst works not only to generate alkyl radicals but also to achieve isomerization.