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Olefin bifunctionalization: A visible-light-photoredox-catalyzed aryl alkoxylation of olefins

Eiji Yamaguchi,*[a] Wakako Tanaka,[a] and Akichika Itoh*[a]

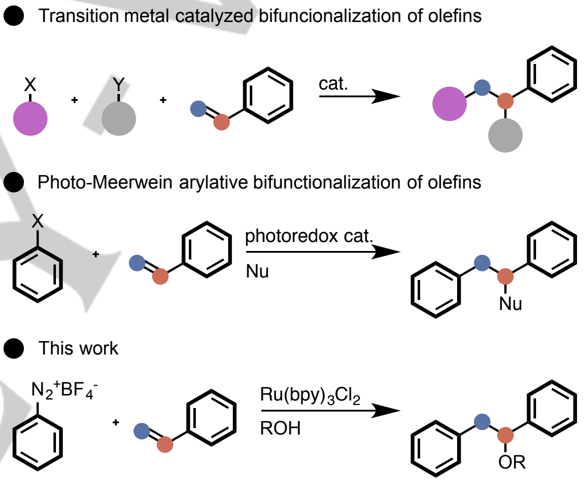
Abstract: Olefin bifunctionlization is a facile route to obtain complex molecules from abundant and commercially available olefin feedstocks. Visible light together with a catalytic amount of tris(bipyridine)ruthenium salt catalyzes the aryl alkoxylation of styrenes with aryl diazonium salts in alcohol solvents *via* a photoredox process. The scope of this proposed reaction with respect to various aryl diazonium salts and styrenes has been investigated.

Olefins are recognized as an inexpensive and ubiquitous petrochemical feedstock and are produced continuously on an industrial scale. Therefore, developing protocols that enable regioselective olefin functionalization to produce useful organic molecules is crucial in organic chemistry.[1] The vicinal bifunctionalization of olefins is a straightforward method for producing various organic molecules because two functional groups are introduced into olefins in a single operation. Thus, the catalytic bifunctionalization of C=C double bonds is a key tool in modern organic synthesis.[2] In this area, various methods have been reported based on transition-metal catalyzed olefin bifunctionalization.[3-6] However, regiospecific introduction of different functional groups into olefins remains challenging.

During the past decade, photoredox catalysis using organic dyes or metal complexes has received renewed attention as a reliable organic transformation method that does not require heat.[7] Due to remarkable recent developments in photochemistry, photocatalytic transformation *via* Meerwein-type arylation has become one of the most versatile and reliable methods of radical multi-component coupling to achieve polyfunctionalization of olefins.[8]

The photoredox-catalyzed Meerwein reaction proceeds *via* aryl-radical generation by single-electron reduction of an aryl diazonium salt. The addition of the generated radical to olefins occurs with high regioselectivity as it proceeds according to the generation of stable *C*-centered radical. The generated radical then transforms to a carbocation intermediate by single-electron oxidation from the oxidized photocatalyst, and the generated intermediate reacts with various nucleophiles to yield the olefin bifunctionalization product. Thus, olefin bifunctionalization through photoredox-catalyzed Meerwein arylation has been extensively studied. In 2014, König and co-workers reported the first photoredox-catalyzed Meerwein aryl amination of olefins (Scheme 1).[9] Encouraged by this report, various photoredox-catalyzed Meerwein-arylated bifunctionalization reactions were developed. To the best of our knowledge, photo Meerwein aryl alkoxylation has not yet been reported.[10]

At this stage, we postulated that the carbocation intermediate could be trapped by an alcoholic solvent to form the aryl-alkoxylated product. Herein, we report a facile and versatile method for olefin bifunctionalization.



Scheme 1. Previous olefin bifunctionalization methodologies and that followed in this study

Diazonium salts are labile under basic and acidic conditions. Selecting a neutral nucleophile to trap the carbocation generated by aryl-radical addition to the olefins followed by oxidation by back electron transfer to the photocatalysts would be beneficial.

Irradiation of a 4-nitrodiazonium tetrafluoroborate salt (**1a**) and styrene (**2a**) in the presence of eosin Y as photocatalyst in MeOH using a domestic 23 W compact fluorescent light (CFL) bulb afforded the corresponding olefin aryl alkoxylate (**3a**) in 12% yield (Table 1, entry 1). Solvent screening revealed that combining an alcohol solvent with Et_2O or MeCN gave better results (entries 2–3). Conducting the reaction in air affected its progress (entry 4). This indicated that the photocatalytic cycle was quenched *via* the oxidation of excited eosin Y by triplet oxygen or that the generated benzyl radical was trapped by triplet oxygen.[11] Through rapid photocatalyst screening, $Ru(bpy)_3Cl_2$ was found to be the best photocatalyst for the aryl alkoxylation (entry 5). Shortening the reaction time and lowering the catalyst loading gave a 51% product yield (entries 5–7). As the CFL bulb warmed the reaction vessel to 40 °C, we conducted the reaction using 3 W 450 nm LED to control the reaction temperature, which increased the

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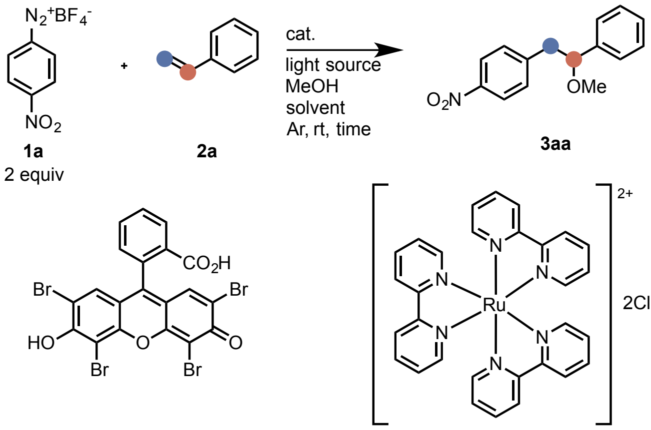
yield to 50% (entry 8). Finally, lowering the catalyst loading to 0.5 mol% and increasing the amount of styrene **2a** to two equivalents toward diazonium salt **1a** resulted in an optimal isolated yield of 55% (entry 9). Furthermore, control reaction was also carried out. Although the reaction without catalyst dropped yield of the product, reaction under dark did not proceed the desired reaction (entries 10 and 11). These results revealed that major background reaction is proceeded through direct generation of aryl radical via homolysis of **1** by irradiation from 450 nm LED (Figure S2).

Table 1. Optimization of reaction conditions



1a
2 equiv

2a

3aa

Eosin Y: **A**

Ru(bpy)$_3$Cl$_2$: **B**

entry	cat.	light source	solvent	time	yield (%)[a]
1[b]	**A** (5 mol%)	23 W CFL	MeOH	18 h	12
2[c]	**A** (5 mol%)	23 W CFL	Et$_2$O	18 h	16
3[d]	**A** (5 mol%)	23 W CFL	MeCN	18 h	22
4[d, e]	**A** (5 mol%)	23 W CFL	MeCN	18 h	4
5[d]	**B** (5 mol%)	23 W CFL	MeCN	18 h	50
6[d]	**B** (5 mol%)	23 W CFL	MeCN	4 h	48
7[d]	**B** (1 mol%)	23 W CFL	MeCN	4 h	51
8[d]	**B** (1 mol%)	3 W 450 nm LED	MeCN	4 h	50
9[d, f]	**B** (0.5 mol%)	3 W 450 nm LED	MeCN	1 h	(55)[g]
10[d, f, h]	none	3 W 450 nm LED	MeCN	1 h	28
11[d, f, h]	**B** (0.5 mol%)	dark	MeCN	1 h	0

[a] Yield were determined by ^{1}H NMR analysis of crude reaction mixture using 1,1,2,2 tetrachloroethane as an internal standard.

[b] MeOH (2 mL) was added.

[c] MeOH (1 mL), Et$_2$O (1 mL) was added.

[d] MeOH (1 mL), MeCN (1 mL) was added.

[e] Reaction performed under air.

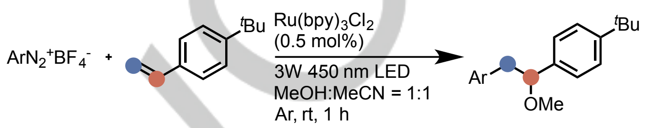
[f] Reaction performed using **1a** (0.3 mmol) with **2a** (2.0 equiv).

[g] Isolated yield.

[h] **2b** was used instead of **2a**.

With the optimized reaction conditions in hand, the scope of aryl diazonium derivatives for the olefin aryl alkoxylation reaction was examined (Table 2). Aryl diazonium salt bearing nitro group (**1a** and **1b**) were tolerated at the para and meta position (entries 1 and 2). The expected aryl alkoxylation product **3** was obtained using diazonium salts various substituents on aryl ring such as ketone (**1c**), ester (**1d**), cyano (**1e-g)** and trifluoromethyl group (**1h**) in moderate to good yield (entries 3-8). It should be noted that halogen atom such as bromo (**1i, j**), chloro (**1k**) and fluoro (**1l**) were tolerated with the present photocatalytic transformation (entries 9-12).

Table 2. Substrate scope: aryl diazonium salts (**1**)



1

2b

3

entry	Ar	Product (3)	yield (%)[a]
1	*p*-NO$_2$C$_6$H$_4$ (**1a**)	**3ab**	58
2	*m*-NO$_2$C$_6$H$_4$ (**1b**)	**3bb**	48
3	*p*-MeCOC$_6$H$_4$ (**1c**)	**3cb**	40
4	*p*-MeOCOC$_6$H$_4$ (**1d**)	**3db**	60
5	*p*-NCC$_6$H$_4$ (**1e**)	**3eb**	46
6	*m*-NCC$_6$H$_4$ (**1f**)	**3fb**	39
7	*o*-NCC$_6$H$_4$ (**1g**)	**3gb**	60
8	*p*-CF$_3$C$_6$H$_4$ (**1h**)	**3hb**	40
9	*m*-BrC$_6$H$_4$ (**1i**)	**3ib**	37
10	*o*-BrC$_6$H$_4$ (**1j**)	**3jb**	40
11	*p*-ClC$_6$H$_4$ (**1k**)	**3kb**	56
12	*p*-FC$_6$H$_4$ (**1l**)	**3lb**	26

[a] Isolated yield.

Moreover, under the developed photoredox-catalysis conditions, various aryl-alkoxylated olefins were obtained in moderate yields from a corresponding variety of substituted styrenes (Table 3).

Styrenes bearing electron-withdrawing groups acetyl and ester (**2c** and **2d**) performed well, affording 43% and 54% yields, respectively (entries 2 and 3). Halogen-containing products **3ae** and **3af** were also obtained in moderate-to-good yield (entries 4 and 5). Although this transformation proceeded smoothly with moderate yields with electron-rich styrenes having *p*-methyl (**2g**), *m*-methyl (**2h**), and *o*-methyl (**2i**) groups on the aryl ring (entries 6–8), the product yield dropped to 10% when employing *p*-MeO styrene (**2j**) as substrate (entry 9). This was probably due to the polymerization of **2j** under these conditions. The phenyl ring was replaced by 1- and 2-naphthyl groups to give moderate yields (entries 10 and 11).

Table 3. Substrate scope: styrenes (**2**)

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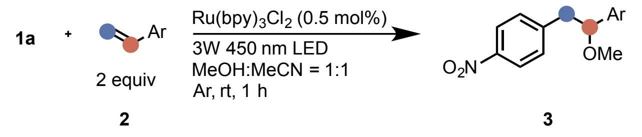


entry	Ar	product	yield (%)[a]
1	C_6H_5 (**2a**)	**3aa**	55
2	*p*-$MeCOC_6H_4$ (**2c**)	**3ac**	43
3	*p*-$MeOCOC_6H_4$ (**2d**)	**3ad**	54
4	*p*-BrC_6H_4 (**2e**)	**3ae**	54
5	*p*-ClC_6H_4 (**2f**)	**3af**	59
6	*p*-MeC_6H_4 (**2g**)	**3ag**	59
7	*m*-MeC_6H_4 (**2h**)	**3ah**	61
8	*o*-MeC_6H_4 (**2i**)	**3ai**	57
9	*p*-$MeOC_6H_4$ (**2j**)	**3aj**	10
10	1-Np (**2k**)	**3ak**	31
11	2-Np (**2l**)	**3al**	29

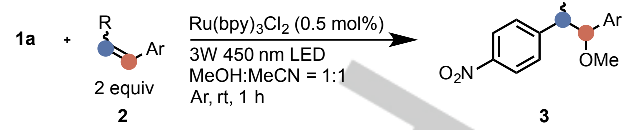
[a] Isolated yield.

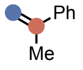
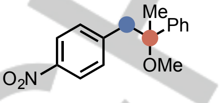
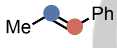
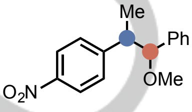
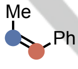
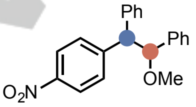
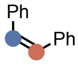
Retaining the aryl diazonium salt (**1a**) as a radical source, we varied the alkene-radical acceptor, using α- and β-substituted olefins (Table 4). Quaternary *C*-centers were formed by using α-Me styrene as a radical acceptor (entry 1). The developed aryl alkoxylation was also successful with internal alkenes. Notably, the same diastereoselectivity with complete regioselectivity was achieved when internal alkenes such as trans or cis β-methyl styrene were used as starting materials (entries 2 and 3). Similar results were obtained using trans and cis stilbene as radical acceptors (entries 4 and 5). These results indicated the reaction was initiated through aryl-radical addition to olefins to form benzyl radicals.

Control experiments were performed to determine the reaction mechanism. To explore the reaction mechanism via a radical intermediate, radical clock experiments using **4** were conducted (Eq. 1). The reaction of **1a** and **4** under optimized conditions gave the ring-opening product **5** in 56% yield. This suggested that the present photocatalysis initiated aryl-radical generation from aryldiazonium salt *via* single-electron reduction.[12, 13]

Finally, we performed “light/dark” experiments to confirm whether the reaction proceeded via chain processes in photoredox catalysis (Figure S3). When the reactions were conducted using alternating light and dark intervals, we observed that the product was only generated during periods of irradiation. These results indicated that the reaction proceeds predominantly through a photoredox process, as suggested by other “light/dark” experiments reported recently.[9, 10]

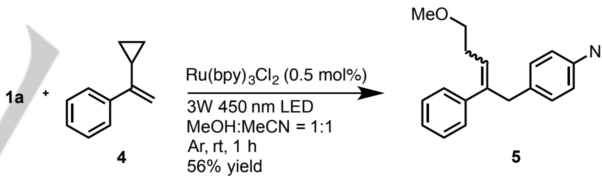
Table 4. Substrate scope: styrenes (**3**)



entry	2	product	yield (%)[a]
1	 **2m**	 **3am**	57
2	 **2n-(*Z*)**	 **3an**	33 *dr* = 56:44[b]
3	 **2n-(*E*)**	**3an**	17 *dr* = 55:45[b]
4	 **2o-(*Z*)**	 **3ao**	19 *dr* = 69:31[b]
5	 **2o-(*E*)**	**3ao**	15 *dr* = 65:35[b]

[a] Isolated yield.

[b] Diastereomeric ratio was determined by 1H NMR analysis of crude reaction mixture.



(1)

Based on the control experiments and several literature reports, a plausible reaction mechanism involving single-electron-transfer (SET) processes is shown in Scheme 3.[8a, 14] The photoredox cycle is initiated by excitation of $Ru(bpy)_3^{2+}$ to $Ru(bpy)_3^{2+*}$ by photoirradiation. Aryl radical **1’** is then formed by SET from excited $Ru(bpy)_3^{2+*}$ to diazonium salt **1**. Adding **1’** to olefin **2** generates the corresponding benzyl radical **I**, which is oxidized by Ru(III) to generate carbocation intermediate **II**, followed by solvolysis with the alcohol solvents to afford corresponding product **3**. The other plausible mechanism is chain mechanism as depicted in mechanism B. Generated benzyl radical intermediate **I** was oxidized by aryl diazonium salt **1** to form carbocation intermediate **II** and aryl radical **1’**.

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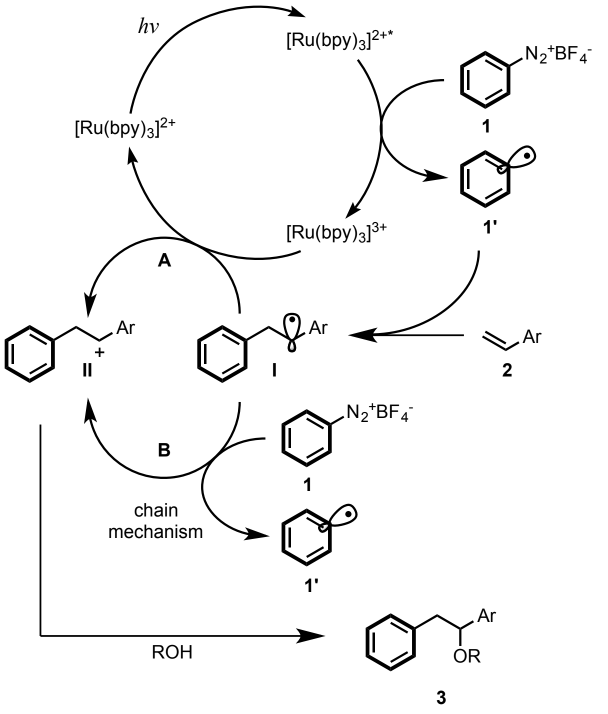

Scheme 3. Plausible reaction mechanism; (A) photo catalytic mechanism. (B) radical chain mechanism.

In conclusion, we developed a simple and versatile photoredox-catalyzed aryl alkoxylation of styrenes. Additionally, the developed method allows access to a variety of products under mild reaction conditions, with a low catalyst loading and a short reaction time. This photoredox-catalyzed aryl alkoxylation is currently being further developed in our laboratory.

Experimental Section

General Procedure for aryl alkoxylation of olefins

A Pyrex® test tube (16.5 cm × 1.5 cm) containing a mixture of diazonium salt **1** (0.3 mmol), solution of $Ru(bpy)_3Cl_2{\bullet}6H_2O$ dissolved in MeOH (0.05 equiv, 1.5×10^{-6} mmol) and styrene **2** (2.0 equiv, 0.6 mmol) in mixture of MeOH (1.0 mL) and MeCN (1.0mL) was degassed *via* FPT cycling for three times and backfilled with Ar. The tube was placed ca. 0.5 cm from 3 W LED. The resulting solution was stirred at ambient temperature for 1 h. The residue was filtrated through silica gel, washed with $CHCl_3$, concentrated *in vacuo*. The resulting mixture was purified by flash column chromatography on silica gel (*n*-hexane : EtOAc = 40 : 1) to give product **3**.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: photoredox catalyst, bifunctionalization, visible light, olefins

[1] M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem. Int. Ed.* **2004**, *43,* 3368; *Angew. Chem.* **2004**, *116*, 3448.

[2] For selected reviews of olefin bifunctionalization reaction, see: (a) J. V. obligacion, P. J. Chirik, *Nat. Rev. Chem.* **2018**, 2, 15; (b) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu, G. Dong, *Chem. Rev.* **2017**, *117*, 9333; (c) S. W. M. Crossley, C. Obradors, R. M. Martinesz, R. A. Shenvi, *Chem. Rev.* **2016**, *116*, 8912; (d) S. E. Denmark, W. E. Kuester, M. T. Burk, *Angew. Chem. Int. Ed.* **2012**, *51*, 10938; *Angew. Chem.* **2012**, *124*, 11098; (e) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981.

[3] For selected examples of Palladium catalylsis, see: (a) R. Sang, P. Kucmierczyk, K. Dong, R. Franke, H. Neumann, R. Jackstell, M. Beller, *J. Am. Chem. Soc.* **2018**, *140,* 5217; (b) Z. Kuang, K. Yang, Q. Song, *Org. Chem. Front.* **2017**, *4*, 12234; (c) W. Ren, W. Chang, J. Dai, Y. Shi, J. Li, Y. Shi, *J. Am. Chem. Soc.* **2016**, *138*, 14864; (d) V. Saini, L. Liao, Q. Wang, R. Jana, M. S. Sigman, *Org. Lett.* **2013**, *15*, 5008; (e) L. Liao, R. Jana, K. B. Urkalan, M. S. Sigman, *J. Am. Chem. Soc*. **2011**, *133*, 5784; (f) K. B. Urkalan, M. S. Sigman, *Angew. Chem. Int. Ed.* **2009**, *48*, 3146; *Angew. Chem.* **2009**, *121*, 3192.

[4] For selected examples of Rhodium catalysis, see; (a) T. J. Coxon, M. Fernandez, J. Barwick-Silk, A. I. McKay, L. E. Britton, A. S. Weller, M. C. Willis, *J. Am. Chem. Soc.* **2017**, *139*, 10142; (b) A. Ghosh, K. F. Johnson, K. L. Vivkerman, J. A. Walker Jr, L. M. Stanley, *Org. Chem. Front.* **2016**, *3*, 639; (c) Y. Bai, F. Zhang, J. Li, Y. Xu, J. Peng, W. Xiao, *J. Organomet. Che.* **2015**, *794*, 65; (d) Y. Shibata, K. Tanaka, *J. Am. Chem. Soc.* **2009**, *131*, 12552; (e) B. M. Bocknack, L.-C. Wang, M. J. Krische, *PNAS* **2004**, *101*, 5421.

[5] For selected examples of Ruthenium catalylsis, see: (a) R. Manikandan, M. Jeganmohan, *Chem. Commun.* **2017**, *53*, 8931; (b) M. Zaranek, B. Marciniec, P. Pawluć, *Org. Che. Front.* **2016**, *3*, 1337; (c) H. Konishi, T. Muto, T. Ueda, Y. Yamada, M. Yamaguchi, K. Manabe, *ChemCatChem* **2015***, 7*, 836; (d) L. Wu, Q. Liu, I. Fleischer, R. Jackstell, M. Beller, *Nture Commun.* **2014**, *5*, 3091; (e) F. Shibahara, J. Bower, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 14120.

[6] For selected examples of other metal catalylsis, see: (a) T. T. Nguyen, L. Grigorjeva, O. Daugulis, *Angew. Chem. Int. Ed.* **2018**, *57*, 1688; *Angew. Chem.* **2018**, *130*, 1704; (b) J. Yang, A. Rerat, Y. J. Lim, N. Yoshikai, *Angew. Chem. Int. Ed.* **2017**, *56*, 2449; *Angew. Chem.* **2017**, *129*, 2489; (c) L. T. Ball, G. C. Llpyd-Jones, C. A. Russell, *Chem. Eur. J.* **2012**, *18*, 2931-2937;

[7] For selected reviews of photoredox catalylsis, see: (a) L. Marzo, S. K. Pagire, O. Reiser, B. König, *Angew. Chem. Int. Ed.* **2018**, *57*, 10034; *Angew. Chem.* **2018**, *32*, 10188; (b) N. Romero, D. A. Nicewise, *Chem. Rev.* **2016**, *116*, 10075; (c) C. K. Prier, D. A. Rankic, D. W. C. Macmillan, *Chem. Rev.* **2013**, *113*, 5322.

[8] For selected reviews, see: (a) D. P. Hari and B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734; *Angew. Chem.* **2013**, *125*, 4832; (b) M. R. Heinrich, *Chem. Eur. J.* **2009**, *15*, 820.

[9] D. P. Hari, T. Hering, B. König, *Angew. Chem. Int. Ed.* **2014**, *53*, 725; *Angew. Chem.* **2014**, *126*, 743.

[10] Comprehensive reviews: (a) I. Ghosh, L. Marzo, A. Das, R. Shaikh, B. König, *Acc. Chem. Res.* **2016**, *49*, 1566; (b) M. Majek, A. J. Wangelin, *Acc. Chem. Res.* **2016**, *49*, 2316; (c) C.-J. Yao, Q. Sun, N. Rastogi, B. König, *ACS Catal.* **2015**, *5*, 2935; (d) Y.-H. Chen, M. Lee, Y.-Z. Lin, D. Leow, *Chem. Asian J.* **2015**, *10*, 1618; (e) M. Bu, T. F. Niu, C. Cai, *Catal. Sci. Technol.* **2015**, *5*, 830; (f) M. N. Hopkinson, B. Sahoo, F. Glorius, *Adv. Synth. Catal.* **2014,** *356,* 2794.

[11] (a) Y. Zhang, C. Ye, S. Li, A. Ding, G. Gu and H. Guo, *RSC Adv.* **2017**, *7*, 13240. (b) S. Maejima, E. Yamaguchi, A. Itoh, *Adv. Synth. Catal.* **2017**, 359, 3883.

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[12] (a) J. Sheng, H.-Q. Ni, H.-R. Zhang, K.-F. Zhan, Y.-N. Wang, X.-S. Wang, *Angew. Chem. Int. Ed.* **2018**, *57,* 7634; *Angew. Chem.* **2018**, *130*, 7760; (b) Y. Chen, C. Shu, F. Luo, X. Xiao, G. Zhu, *Chem. Commun.* **2018**, *54*, 5373; (c) J. Sheng, H.-Q. Ni, K.-J. Bian, Y. Li, Y.-N. Wang, X.-S. Wang, *Org. Chem. Front.* **2018**, *5*, 606.
[13] D. Griller, K. U. Ingold, *Acc. Chem. Res.* **1980**, *13*, 317.
[14] M. A. Cismesia, T. P. Yoon, *Chem. Sci.* **2015**, *6*, 5426.

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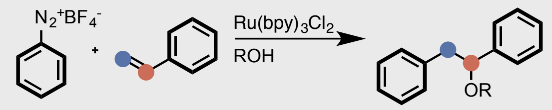

- over 20 examples
- rapid reaction
- readily available substrates

Visible light along with catalytic amount of tris(bipyridine)ruthenium salt catalyzes the aryl alkoxylation reaction of styrens with aryl diazonium salts in alcoholic solvents by a photoredox process. The scope of the reaction for various aryl diazonium salts and styrens have been investigated.

Eiji Yamaguchi, Wakako Tanaka, Akichika Itoh

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Olefin bifunctionalization: A visible-light-photoredox-catalyzed aryl alkoxylation of olefins

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