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Mizoroki–Heck-Type Reaction Mediated by Potassium *tert*-Butoxide**

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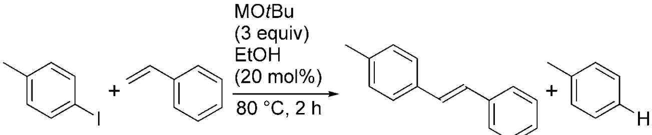
The Mizoroki–Heck reaction is a versatile method used to prepare styrene derivatives from readily available aryl halides and alkenes.[1] A major drawback of this method is the necessary use of an expensive palladium complex as a catalyst.[2] Addition of an aryl radical, which is generated from an aryl halide, to an alkene and subsequent elimination of a hydrogen radical in a similar way to homolytic aromatic substitution[3] is a possible approach for a new pathway leading to Mizoroki–Heck-type reactions. However, attack of aryl radicals to alkenes usually results in an addition reaction but not a substitution reaction.[4] Herein, we report that the substitution reaction of aryl halides with styrene derivatives takes place by just using KO*t*Bu, EtOH, and DMF, possibly through a radical mechanism.[5,6]

Treatment of 4-iodotoluene (**1a**) with styrene (**2o**: 5 equiv), KO*t*Bu[7] (3 equiv), and EtOH (20 mol%) in DMF at 80 °C for 2 hours gave 73% yield of 4-methylstilbene (**3ao**) with 17% yield of toluene (Table 1, entry 1).[8] Use of DMF as a solvent is essential: the reaction in MeCN, 1,4-dioxane, or toluene did not give **3ao** at all (Table 1, entries 2–4).[9] The reaction took place also in the absence of EtOH but the yield of **3ao** was slightly lower (Table 1, entry 5). A low conversion of **1a** was observed when either sodium or lithium *tert*-butoxide was used, both of which have lower basicity than KO*t*Bu (Table 1, entries 6 and 7). A decrease in the amount of styrene severely affected the yield (Table 1, entry 8).

Table 1: Coupling of 4-iodotoluene with styrene.[a]



1a (1 equiv) **2o** (5 equiv) **3ao** **4a**

Entry	Solvent	MO*t*Bu	Conv. of **1a** [%][b]	Yield of **3ao** [%][b]	Yield of **4a** [%][b]
1	DMF	KO*t*Bu	> 99	73	17
2	MeCN	KO*t*Bu	4	< 1	< 1
3	1,4-dioxane	KO*t*Bu	20	< 1	6
4	toluene	KO*t*Bu	6	< 1	–
5[c]	DMF	KO*t*Bu	> 99	58	15
6	DMF	NaO*t*Bu	5	< 1	4
7	DMF	LiO*t*Bu	8	< 1	< 1
8[d]	DMF	KO*t*Bu	> 99	39	32

[a] The reaction was carried out in DMF (0.50 mL) at 80 °C for 2 h under nitrogen using 4-iodotoluene (**1a**: 0.23 mmol), styrene (**2o**: 1.2 mmol), MO*t*Bu (0.69 mmol), and EtOH (0.046 mmol). [b] Determined by GC analysis. [c] In the absence of EtOH. [d] Styrene (0.28 mmol) was used. DMF = *N*,*N*-dimethylformamide.

The present *tert*-butoxide-promoted arylation of alkenes was applied to various aryl halides and styrene derivatives (Table 2).[10] Aryl and heteroaryl iodides underwent the coupling with styrene (**2o**), where substitution with a methoxy, phenyl, or methyl group on the benzene ring is compatible (Table 2, entries 1–5). In contrast, the reaction of phenyl iodides having an electron-withdrawing CF_3 group gave no coupling product with **2o** but reduction product **4g** with a high conversion (Table 2, entry 6). Almost no reaction took place with *p*-tolyl bromide or chloride (Table 2, entries 7 and 8), whereas not only iodide but also bromide and even chloride underwent coupling when the organic moiety was a 1- or 2-naphthyl group (Table 2, entries 9–13). Substitution by a conjugating group such as phenyl and alkenyl also enhanced the reactivity of aryl bromides and chlorides (Table 2, entries 14–17). Styrenes having an electron-donating or electron-withdrawing substituent were arylated in the reaction with **1a** (Table 2, entries 18 and 19). Notably, 4-chlorostyrene reacted with styrene (**2o**) at the chloroarene moiety (Table 2, entry 17) and with aryl halide **1a** at the alkene moiety (Table 2, entry 19). Almost no conversion of **1a** was observed in the reaction with a styrene having a strong electron-withdrawing CF_3 group (Table 2, entry 20). The reaction was applicable to an *ortho*-substituted styrene and to the synthesis of a polymethoxylated stilbene (Table 2, entries 21 and 22). Benzofuran accepted arylation at the 2-position under the same reaction conditions (Table 2, entry 23). Unfortunately, the reaction of alkyl-substituted alkenes, acrylic acid derivatives, or vinyl ethers did not give synthetically significant yields of products under the present conditions.

Formation of the reduction product **4** of aryl halide **1** suggests involvement of aryl radical intermediates, which are generated through single-electron transfer (SET) to Ar–X to give the radical anion $[Ar{-}X]^{\bullet-}$, and subsequent facile

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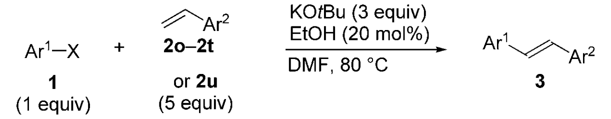
Table 2: Coupling of aryl halides with styrene derivatives mediated by KO*t*Bu.[a]



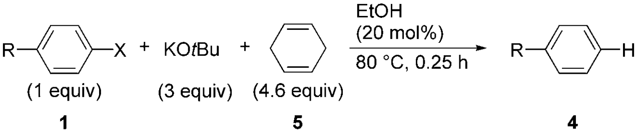
Entry	Aryl halide **1**	Ar² (**2**)	*t* [h]	Yield [%][b]
1	Ph–I (**1b**)	Ph (**2o**)	2	66
2	4-MeOC$_6$H$_4$–I (**1c**)	Ph (**2o**)	2	65
3	4-PhC$_6$H$_4$–I (**1d**)	Ph (**2o**)	2	71
4	2-MeC$_6$H$_4$–I (**1e**)	Ph (**2o**)	2.5	61
5	2-pyridyl–I (**1f**)	Ph (**2o**)	2	57
6	4-CF$_3$C$_6$H$_4$–I (**1g**)	Ph (**2o**)	2	<1
7	4-MeC$_6$H$_4$–Br (**1a′**)	Ph (**2o**)	5	2[c]
8	4-MeC$_6$H$_4$–Cl (**1a″**)	Ph (**2o**)	17	<1[d]
9	1-naphthyl–I (**1h**)	Ph (**2o**)	2	68
10	1-naphthyl–Br (**1h′**)	Ph (**2o**)	6	65
11	1-naphthyl–Cl (**1h″**)	Ph (**2o**)	6	63
12	2-naphthyl–Br (**1i′**)	Ph (**2o**)	3	76
13	2-naphthyl–Cl (**1i″**)	Ph (**2o**)	3	83
14	4-PhC$_6$H$_4$–Br (**1d′**)	Ph (**2o**)	2	62
15	4-styrylC$_6$H$_4$–Cl (**1j″**)	Ph (**2o**)	2	69
16	4-vinylC$_6$H$_4$–Br (**1k′**)	Ph (**2o**)	2	62
17	4-vinylC$_6$H$_4$–Cl (**1k″**)	Ph (**2o**)	6	61
18	4-MeC$_6$H$_4$–I (**1a**)	4-MeOC$_6$H$_4$ (**2p**)	5.5	56
19	4-MeC$_6$H$_4$–I (**1a**)	4-ClC$_6$H$_4$ (**2q**=**1k″**)	2	67
20	4-MeC$_6$H$_4$–I (**1a**)	4-CF$_3$C$_6$H$_4$ (**2r**)	2	<1[d]
21	4-MeC$_6$H$_4$–I (**1a**)	2-MeC$_6$H$_4$ (**2s**)	2	74
22	4-MeOC$_6$H$_4$–I (**1c**)	3,5-(MeO)$_2$C$_6$H$_3$ (**2t**)	3	56
23	4-MeC$_6$H$_4$–I (**1a**)	benzofuran (**2u**)	3	55[e]

[a] The reaction was carried out in DMF (0.50 mL) at 80°C under nitrogen using an aryl halide (**1**: 0.23 mmol), an alkene (**2**: 1.2 mmol), KO*t*Bu (0.69 mmol), and EtOH (0.046 mmol). [b] Yield of isolated product based on **1**. Unless otherwise noted, conversion of **1** was >99%. [c] 46% conversion of **1**, where 3- and 4-(*tert*-butoxy)toluene compounds were the main products. [d] Less than 5% conversion of **1**. [e] 2-(4-Tolyl)benzofuran was obtained in 55% yield.

elimination of X$^-$.[11] As metal alkoxides are known to act as single-electron donors towards aromatic compounds, alkyl iodides, and ketones,[12] SET from KO*t*Bu to aryl halides is possibly in operation here. Treatment of 4-iodobiphenyl (**1d**: 1 equiv) with KO*t*Bu (3 equiv) and EtOH (20 mol%) in DMF at 80°C for 0.25 hours gave reduction product **4d** in 24% yield with 79% conversion of **1d** (Table 3, entry 1).[13] The yield of **4d** was largely improved by addition of 1,4-cyclohexadiene (**5**; 4.6 equiv), which is an efficient hydrogen radical donor, thus strongly suggesting the existence of aryl radical intermediates (Table 3, entry 2). The yield was almost the same in the absence of EtOH (Table 3, entry 3). In contrast, a low yield with a low conversion was observed in the reaction of *p*-tolyl chloride (**1a″**; Table 3, entry 4), which was not consumed at all also in the reaction with styrene (**2o**; Table 1, entry 8). The correlation, which was observed also in the solvent effect (Table 3, entry 5), implies that aryl radical generation is a critical step in the coupling reaction.

Radical anions are known to be generated more easily when the starting arenes have lower absolute values of reduction potential and/or half-wave potential, which are lowered with substitution by an electron-withdrawing group including halogen (lowering effect: I > Br > Cl) and/or conjugating group such as phenyl and alkenyl as well as extended aromaticity with fused rings such as naphthalene.[14] The reactivity order of aryl halides here is consistent with aryl radical generation through radical anion intermediates, if we consider the following: 1) Aryl iodides are easily reduced to radical anions and thus fully consumed irrespective of their substituents in the reaction with styrene, though those having an electron-withdrawing group are converted exclusively into arene **4** (Table 2, entry 6), probably through further reduction of aryl radicals to aryl anions. 2) Substitution by a conjugating group or extended conjugation by introduction of a naphthalene ring makes aryl bromides and chlorides sufficiently reactive (compare Table 2, entries 7–8 vs. 10–17). 3) *p*-Tolyl iodide (**1a**) fails to react when the coupling partner is an electron-deficient styrene, which accepts an electron more easily than **1a** (Table 2, entry 20).

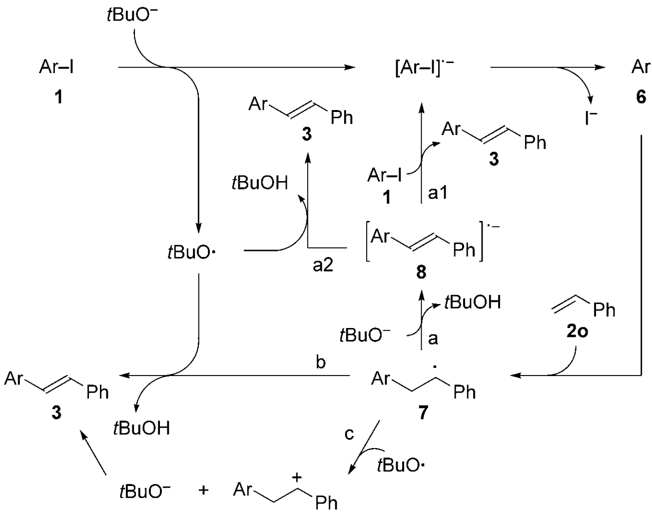
Table 3: Reaction of aryl halides with KO*t*Bu in the presence of 1,4-cyclohexadiene.[a]



Entry	R, X (**1**)	Solvent	Conv. of **1** [%][b]	Yield of **4** [%][b]
1[c]	Ph, I (**1d**)	DMF	79	24
2	Ph, I (**1d**)	DMF	>99	73
3[d]	Ph, I (**1d**)	DMF	>99	73
4	Me, Cl (**1a″**)	DMF	7	6
5	Ph, I (**1d**)	MeCN	<5	3

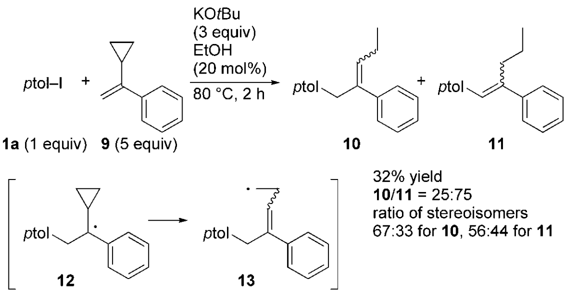
[a] The reaction was carried out in DMF (0.50 mL) at 80°C for 0.25 h under nitrogen using an aryl halide (**1**: 0.23 mmol), KO*t*Bu (0.69 mmol), 1,4-cyclohexadiene (**5**: 1.1 mmol), and EtOH (0.046 mmol). [b] Determined by GC analysis. [c] In the absence of **5**. [d] In the absence of EtOH.

Thus far, generated aryl radicals must add to styrene (**2o**), but the subsequent steps and the role of EtOH are unclear at present (Scheme 1). As adduct **7** has to lose a proton and an



Scheme 1. A plausible reaction mechanism.

electron to be converted into coupling product **3**, the subsequent pathways can be diverted into three types (a–c) according to the timing of elimination of these species. In path a, a proton is first removed to give radical anion **8**, which may give an electron to **1** to therefore give **3** and regenerate the radical anion of **1** through $S_{RN}1$ mechanism (a1)[11] or is oxidized by *t*BuO$^\bullet$ (a2). Path b includes elimination of both species at once as H$^\bullet$, whereas oxidation of **7** is followed by deprotonation in path c. Considering the high oxidation ability of *t*BuO$^\bullet$, which is generated upon SET, it can possibly act as an oxidant as in paths a2, b, or c. As shown in Scheme 2, the reaction of α-cyclopropylstyrene (**9**) with *p*-tolyl iodide (**1a**) gave a mixture of (*E*)- and (*Z*)-1-(*p*-tolyl)-2-phenyl-2-pentenes (**10**) in addition to their double bond isomers **11**, albeit in a moderate combined yield (32%). Products **10** are likely to be derived from ring-opening products **13** of addition product **12** (corresponds to **7** in Scheme 2). As cyclopropylmethyl radicals such as **12** are known to readily undergo ring opening,[15] this result supports the reaction pathway that includes addition of aryl radicals to styrenes. Base-catalyzed isomerization of **10** is likely to give **11**.



32% yield
10/**11** = 25:75
ratio of stereoisomers
67:33 for **10**, 56:44 for **11**

Scheme 2. Reaction of α-cyclopropylstyrene that gives ring-opening products.

In conclusion, we have disclosed transition-metal-free Mizoroki–Heck-type reaction, which proceeds through aryl radical intermediates and gives various stilbene derivatives by simply using KO*t*Bu, EtOH, and DMF.

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[7] For the reactions shown in Table 1–Table 3, KO*t*Bu, which was purchased from Wako Pure Chemicals Industries, Ltd. (product number 163–08425), was used as received. Its ICP-AES and ICP-MS analysis showed that the contents of Co, Ni, Ru, Rh, Pd, Ag, Ir, Pt, and Au are less than 0.05 ppm and those of Fe and Cu are 1.0 ppm and 1.1 ppm, respectively. See also Ref. [8].

[8] The reaction using a sublimed grade KO*t*Bu (99.99% purity, Aldrich Co., product number 659878) or a KO*t*Bu purified through sublimation by us gave coupling product **3ao** in a similar yield (80% or 79% yield, respectively). The contents of Fe and Cu in the sublimed KO*t*Bu are <0.2 ppm (under detection limit) and 0.25 ppm, respectively (ICP-AES analysis). These results amply indicate that the coupling is promoted by KO*t*Bu itself rather than catalyzed by contaminated transition metals. We asked Dr. Kazufumi Kohno to repeat the reaction and he confirmed that the reaction under the same conditions gave **3ao** in 71% yield.

[9] *N*,*N*-Dimethylacetamide and dimethylsulfoxide also were effective as solvents but addition of their enolates to styrene and the coupling products took place and thus the yield of **3ao** was slightly lower than that obtained when DMF was used.

[10] The products are all *E* isomers. The corresponding *Z* isomer or 1,1-disubstitued product was not observed in any reaction in Table 2.

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[13] A large amount of biphenyls having a *tert*-butoxy, dimethylamino, or hydroxy group at the 3- or 4-positions, all of which are most likely to be produced through 4-phenylbenzyne, was observed as by-products. These by-products were produced also in the coupling reaction but in lower amounts.

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