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Carbonylative Mizoroki−Heck Reaction of Alkyl Iodides with Arylalkenes Using a Pd/Photoirradiation System

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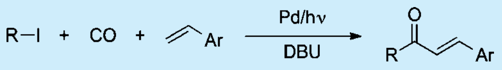
Supporting Information

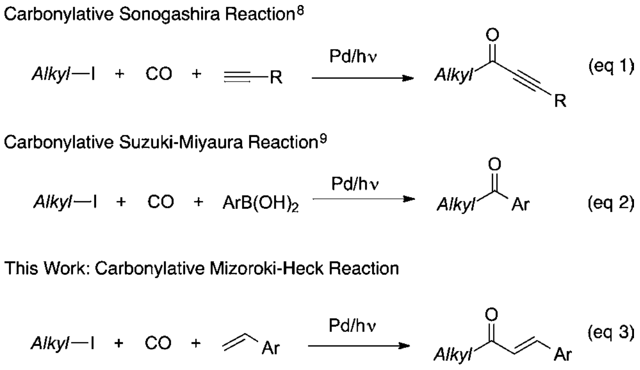
ABSTRACT: A carbonylative Mizoroki−Heck reaction using alkyl iodides was achieved with a Pd/photoirradiation system using DBU as a base. In this reaction, alkyl radicals were formed from alkyl iodides via single-electron transfer (SET) and then underwent a sequential addition to CO and alkenes to give *β*-keto radicals. It is proposed that DBU would abstract a proton *α* to carbonyl to form radical anions, giving *α*,*β*-unsaturated ketones via SET.



Carbonylative cross-coupling reactions of organic halides have found wide applications in organic synthesis since they provide straightforward access to a variety of carbonyl compounds.[1] In the carbonylative Mizoroki-Heck reaction that leads to a,b-unsaturated ketones,[2] aryl and vinyl halides are the most suitable substrates, but the reaction limits the use of alkyl halides[3] due to the instability of key alkyl Pd species, which allow isomerization via facile *β*-Pd−H elimination.[4,5]

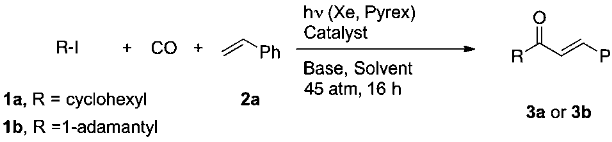
In contrast to the alkyl Pd species, alkyl radicals are sufficiently stable to isomerization. Thus, we were interested in developing a cooperative reaction system wherein both radical species and organometallic species could work cooperatively so as to clear the substrate limitations.[6] Consequently, we developed a series of Pd/light-induced cascade carbonylation reactions wherein alkyl radicals would act as transient radicals and in the end carbonylation would give acyl radicals, which could be transformed to acylpalladium species.[7] The Pd/light system has been effective for carbonylative Sonogashira reaction[8] and carbonylative Suzuki−Miyaura reaction[9] of alkyl iodides (Scheme 1, eqs 1 and 2). We report herein that the carbonylative Mizoroki−Heck reaction of alkyl iodides with arylalkenes proceeded well using a Pd/light system with DBU as a base (Scheme 1, eq 3). Alexanian and co-workers recently reported an intramolecular carbonylative Mizoroki−Heck reaction using a Pd catalyst under thermal conditions.[10] To the best of our knowledge, however, the present study is the first report on the intermolecular processing of alkyl halides.

Scheme 1. Carbonylative Cross-Coupling Reactions of Alkyl Iodides using a Pd/Light System



We first attempted the reaction of iodocyclohexane **1a** or 1-iodoadamantane **1b** and styrene **2a** as a model reaction (Table 1). When a mixture of **1a** or **1b**, **2a**, K_2CO_3, and a catalytic amount of $Pd(PPh_3)_4$ was irradiated using a xenon lamp (500 W)

Table 1. Optimization of the Reaction Conditions[a]



entry	1	Catalyst	Base[b]	Solvent[c]	3	yield (%) (*E*/*Z*)[d]
1	**1a**	$Pd(PPh_3)_4$	K_2CO_3	toluene	**3a**	0
2	**1b**	$Pd(PPh_3)_4$	K_2CO_3	toluene	**3b**	0
3	**1b**	$Pd(PPh_3)_4$	Et_3N	toluene	**3b**	0
4	**1b**	$Pd(PPh_3)_4$	DABCO	toluene	**3b**	9 (44/56)
5	**1b**	$Pd(PPh_3)_4$	TMG	toluene	**3b**	34 (56/44)
6	**1b**	$Pd(PPh_3)_4$	MTBD	toluene	**3b**	48 (51/49)
7	**1b**	$Pd(PPh_3)_4$	DBU	toluene	**3b**	60 (50/50)
8	**1a**	$Pd(PPh_3)_4$	DBU	toluene	**3a**	41 (63/37)
9	**1a**	$Pd(PPh_3)_4$	DBU	BTF	**3a**	58 (57/43)
10	**1b**	$Pd(PPh_3)_4$	DBU	BTF	**3b**	67 (54/46)
11[e]	**1a**	$Pd(PPh_3)_4$	DBU	BTF	**3a**	0
12	**1a**	none	DBU	BTF	**3a**	10 (90/10)
13	**1a**	$Mn_2(CO)_{10}$	DBU	BTF	**3a**	33 (63/37)
14	**1a**	$PtCl_2(PPh_3)_2$	DBU	BTF	**3a**	59 (58/42)
15	**1a**	$Fe_3(CO)_{12}$	DBU	BTF	**3a**	0
16	**1a**	$NiCl_2(PPh_3)_2$	DBU	BTF	**3a**	0

[a] Reaction conditions: **1a** or **1b** (0.3 mmol), $Pd(PPh_3)_4$ (5 mol %), base (2 equiv), styrene [2 equiv (For entries 8 and 10 are 10 equiv)], solvent (8 mL), CO (45 atm), 16 h. [b] DABCO: 1,4-diazabicyclo[2.2.2]octane. TMG: 1,1,3,3-tetramethylguanidine. MTBD: 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene. [c] BTF: benzotrifluoride. [d] GC yields. [e] Conducted under thermal conditions (120 °C).

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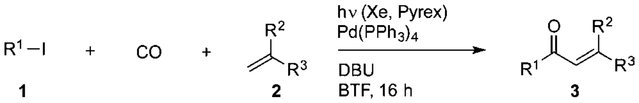
through a Pyrex filter under 45 atm of CO, no carbonylative Mizoroki–Heck reaction took place (Table 1, entries 1 and 2). Then, after amine bases were screened for the reaction of **1b** (Table 1, entries 3–7), we were pleased to find that the addition of DBU gave 60% yield of the desired product **3b** (Table 1, entry 7). Changing toluene to the more-polar BTF (benzotrifluoride)[11] improved the yield of **3b** to 67% (Table 1, entry 10). A similar tendency of this solvent effect was observed in the conversion of **1a** to **3a** (Table 1, entries 8 and 9). The reaction of **1a** with **2a** under thermal conditions (120 °C) did not give **3a** (Table 1, entry 11). Interestingly, however, a photoirradiation reaction in the absence of palladium catalyst but with DBU gave **3a**, albeit in a low yield (Table 1, entry 12). The reaction in the presence of $Mn_2(CO)_{10}$[12] instead of $Pd(PPh_3)_4$ gave **3a**, but the efficiency was inferior to using the Pd catalyst (Table 1, entry 13). $PtCl_2(PPh_3)_2$ gave a result comparable to that for palladium catalyst (Table 1, entry 14). On the other hand, $Fe_3(CO)_{12}$ and $NiCl_2(PPh_3)_2$ did not work in this reaction system (Table 1, entries 15 and 16). In all cases examined, noncarbonylative Mizoroki–Heck reaction products were not observed, whereas byproducts via the second addition to the product enones are often formed.

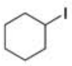
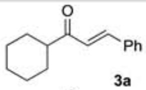
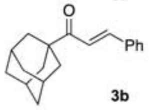
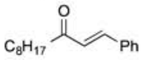
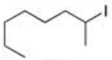
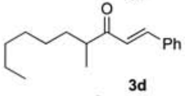
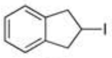
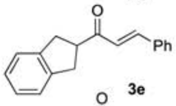
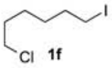
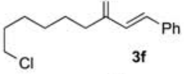
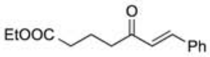
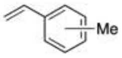
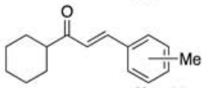
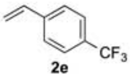
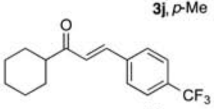
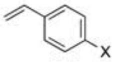
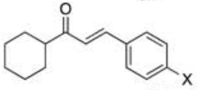
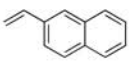
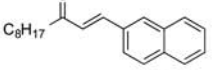
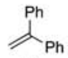
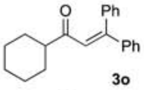
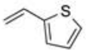
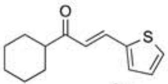
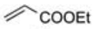
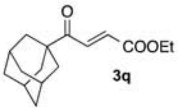
Using the conditions of entry 9 or 10 in Table 1, we then examined the generality of the carbonylative Mizoroki–Heck reaction for a variety of alkyl iodides and alkenes, and the results are summarized in Table 2. The reactions of primary and secondary alkyl iodides **1c** and **1d** with **2a** gave the corresponding *α*,*β*-unsaturated ketones **3c** and **3d** in moderate to good yields (Table 2, entries 3 and 4). The reaction of 2-iodoindane **1e** with **2a** gave an enone **3e** in 40% yield (Table 2, entry 5). Functionalized Iodoalkanes with chlorine or ester moieties, **1f** and **1g**, also proceeded to give the corresponding enones **3f** and **3g** (Table 2, entries 6 and 7). A variety of arylalkenes also participated in the present reaction (Table 2, entries 8–16). For example, **1a** reacted with *o*-, *m*-, and *p*-methylstyrene (**2b**, **2c**, and **2d**) to give the corresponding *α*,*β*-unsaturated ketones **3h**, **3i**, and **3j**, respectively (Table 2, entries 8–10). Styrenes with an electron-withdrawing group also participated in the present reaction. Thus, the reaction of **1a** with *p*-CF_3-substituted styrene **2e** gave **3k** in 59% yield (Table 2, entry 11). The reaction of **1a** with *p*-fluoro-substituted styrene **2f** gave **3l** in 54% yield (Table 2, entry 12). In the case of *p*-bromo-substituted styrene **2g**, the reaction gave the corresponding enone **3m**, with the carbon–bromine bond remaining intact (Table 2, entry 13). 2-Vinylnaphthalene **2h** and 1,1-diphenylethylene **2i** were also acceptable and gave the corresponding products **3n** and **3o** (Table 2, entries 14 and 15). On the other hand, the reaction of **1a** with 2-vinylthiophene **2j** gave enone **3p** in a low yield (Table 2, entry 16). We also examined the reaction of **1b** with ethyl acrylate **2k**, and it gave the product **3q** in a low yield (Table 2, entry 17).

To understand the role of radical species in this carbonylative Mizoroki–Heck reaction, we examined the reaction of (iodomethyl)cyclopropane **1h**, CO, and **2a** (Scheme 2). The reaction gave 3-butenyl styryl ketone **3r** in 53% yield with no trace of cyclopropylcarbinyl ketone **3s**. This suggests that in this system a cyclopropylcarbinyl radical forms and undergoes quick isomerization to a homoallyl radical.[13]

We checked into whether the *E*/*Z* geometry of the enones changes under photoirradiation. When the isolated *E*-**3a** or *Z*-**3a** was irradiated with no reagents, both *E* and *Z* forms of **3a** were isomerized to another isomer, giving the same *E*/*Z* ratio (Scheme 3). Upon further heating of the *E*/*Z* mixture of **3a** under dark conditions at 80 °C for 16 h, only *E*-**3a** was obtained.

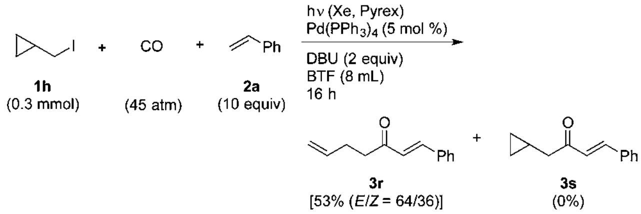
Table 2. Carbonylative Mizoroki–Heck Reaction Using Alkyl Iodides 1 and Alkenes 2[a]



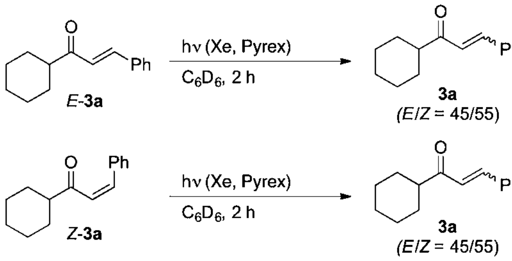
entry	R^1–I	alkene 2	product	yield (%) (*E*/*Z*)
1	 **1a**	 **2a**	 **3a**	58 (57/43)
2	 **1b**	**2a**	 **3b**	67 (54/46)
3	C_8H_{17}–I **1c**	**2a**	 **3c**	47 (50/50)
4	 **1d**	**2a**	 **3d**	57 (56/44)
5	 **1e**	**2a**	 **3e**	40 (48/52)
6	 **1f**	**2a**	 **3f**	54 (58/42)
7	 **1g**	**2a**	 **3g**	46 (57/43)
8	**1a**	 **2b**, *o*-Me	 **3h**, *o*-Me	50 (47/53)
9		**2c**, *m*-Me	**3i**, *m*-Me	60 (67/33)
10		**2d**, *p*-Me	**3j**, *p*-Me	44 (47/53)
11	**1a**	 **2e**	 **3k**	59 (83/17)
12	**1a**	 **2f**, X = F	 **3l**, X = F	54 (60/40)
13		**2g**, X = Br	**3m**, X = Br	65 (68/32)
14	**1c**	 **2h**	 **3n**	41 (78/22)
15	**1a**	 **2i**	 **3o**	42
16	**1a**	 **2j**	 **3p**	12 (54/46)
17[b]	**1b**	 **2k**	 **3q**	23 (61/39)

[a] Reaction conditions: **1** (0.3 mmol), CO (45 atm), **2** (3 mmol), $Pd(PPh_3)_4$ (5 mol %), DBU (2 equiv), BTF (benzotrifluoride) (8 mL), *hν* (xenon lamp, Pyrex), 16 h. [b] **2k** (2 equiv).

Scheme 2. Carbonylative Mizoroki–Heck Reaction Using (Iodomethyl)cyclopropane 1h

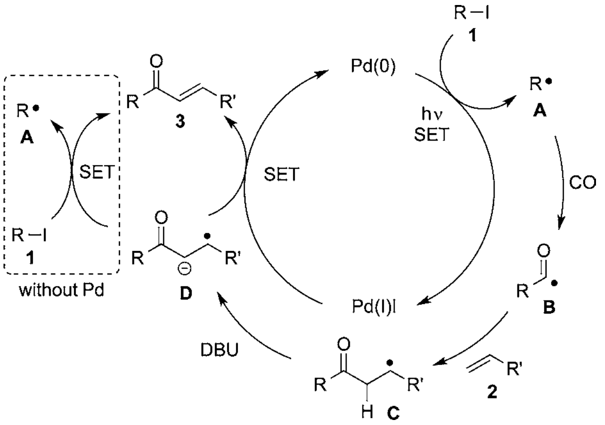


Scheme 3. Isomerization of 3a under Photoirradiation Conditions



A proposed reaction mechanism for the present carbonylative Mizoroki–Heck reaction is shown in Scheme 4. Initially, alkyl radical **A** and Pd^{I}I are generated from **1** and Pd^0 via photoinduced single-electron transfer (SET).[6,14,15] Alkyl radical **A** would be quickly converted to acyl radical **B** under the employed pressurized CO conditions.[16] β-Keto radical **C** was formed by the addition of acyl radical **B** to alkene **2**.[17] DBU would then abstract hydrogen from the α-position of carbonyl of **C** to form radical anion **D**.[18] This is followed by SET from **D** to Pd^{I}I species, which would give product enone **3** and Pd^0. In the case of without the Pd catalyst, we believe the reaction would also include a SET process with **D** and **1** to give enone **3** and alkyl radical **A** for the formation of a chain-reaction system.[19]

Scheme 4. Proposed Reaction Mechanism



In summary, we have demonstrated that an intermolecular carbonylative Mizoroki–Heck reaction using alkyl iodides is possible via a combined Pd/photoirradiation system using DBU as a base. In this reaction, we propose a radical-SET combined mechanism involving the addition of acyl radicals to alkenes and a consecutive generation of radical anions from the deprotonation caused by DBU. Additional mechanistic investigations as well as synthetic applications of the carbonylative cross-coupling reactions of alkyl substrates are now underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02302.

Detailed experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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