<u>Organic</u> LETTERS

Carbonylative Mizoroki–Heck Reaction of Alkyl lodides with Arylalkenes Using a Pd/Photoirradiation System

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(5) 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 $R = 1 + CO + Ar \xrightarrow{Pd/hv}_{DBU} \xrightarrow{O}_{R}$

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 $\alpha_{,\beta}$ -unsaturated ketones via SET.

C arbonylative 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 halides³ 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 reaction⁸ and carbonylative Suzuki-Miyaura reaction⁹ 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

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

Carbonylative Sonogashira Reaction⁸

 $Alkyl-I + CO + = R \xrightarrow{Pd/hv} Alkyl \xrightarrow{V} (eq 1)$

Carbonylative Suzuki-Miyaura Reaction9

 $A/ky/-1 + CO + ArB(OH)_2 \xrightarrow{Pd/hv} A/ky/Ar$ (eq 2)

This Work: Carbonylative Mizoroki-Heck Reaction

 $A/ky/-I + CO + Ar \xrightarrow{Pd/hv} A/ky/Ar \xrightarrow{O} Ar$ (eq 3)

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.

We first attempted the reaction of iodocyclohexane 1a or 1iodoadamantane 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(PPh₃)₄ was irradiated using a xenon lamp (500 W)

Table 1. Optimization of the Reaction Conditions^a

1a 1b	R-I I, R = cy I, R =1-a	+ clohe: idama	- CO + 🥢 kyl 2a	h C Ph B 4	v (Xe, Pyrex) aatalyst ase, Solvent 5 atm, 16 h		→ R 3a o	Ph r 3b
	entry	1	Catalyst	Base ^b	Solvent ^c	3	yield (%) (<i>E</i>	/Z) ^d
1	1	1a	Pd(PPh ₃) ₄	K ₂ CO	3 toluene	3a	0	
	2	1b	Pd(PPh ₃) ₄	K ₂ CO	3 toluene	3b	0	
	3	1b	Pd(PPh ₃) ₄	Et ₃ N	toluene	3b	0	
	4	1b	Pd(PPh ₃) ₄	DABC	O 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(PPh₃)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: 1,4diazabicyclo[2.2.2]octane. TMG: 1,1,3,3-tetramethylguanidine. MTBD: 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene. DBU: 1,8diazabicyclo[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(PPh₃)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 2iodoindane 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 pmethylstyrene (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-CF₃-substituted styrene 2e gave 3k in 59% yield (Table 2, entry 11). The reaction of 1a with *p*-fluoro-substituted styrene 2f gave 31 in 54% yield (Table 2, entry 12). In the case of *p*-bromosubstituted 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



Table 2. Carbonylative Mizoroki-Heck Reaction Using Alkyl

^aReaction conditions: 1 (0.3 mmol), CO (45 atm), 2 (3 mmol), Pd(PPh₃)₄ (5 mol %), DBU (2 equiv), BTF (benzotrifluoride) (8 mL), $h\nu$ (xenon lamp, Pyrex), 16 h. ^b2k (2 equiv).

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.

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

Scheme 4. Proposed Reaction Mechanism



radical **A** and Pd^II are generated from **1** and Pd⁰ 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^II species, which would give product enone **3** and Pd⁰. 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

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

S 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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