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A transition-metal-free Heck-type reaction between alkenes and alkyl iodides enabled by light in water[†]

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A transition-metal-free coupling protocol between various alkenes and non-activated alkyl iodides has been developed by using photoenergy in water for the first time. Under UV irradiation and basic aqueous conditions, various alkenes efficiently couple with a wide range of non-activated alkyl iodides. A tentative mechanism, which involves an atom transfer radical addition process, for the coupling is proposed.

Concern over synthetic efficiency and the increased recognition on sustainable green chemistry have provoked chemists to seek novel approaches for producing chemicals more efficiently, cleanly, under milder conditions, and in an environmentally favourable fashion.¹ Although applications of transition-metal-catalysis have generally been considered the most salient breakthrough in modern synthetic chemistry in the 20^{th} century, the issues related to removal of metal residues and consumption of non-renewable expensive metals have aroused misgivings in pharmaceutical and electronics industries. Transition-metal (depleting and precarious)^{2,3} free couplings in water (a greener solvent)⁴ promoted by photons (a cleaner energy input)⁵ provide tremendous opportunities towards more sustainable synthetic chemistry.

The palladium-catalyzed Heck reaction is an important organic synthetic tool to couple alkenes with aryl/vinyl halides (or sulfonates), and plays an essential role in constructing C–C bonds in modern organic chemistry. However, the seminal Heck protocol is not applicable for the alkyl halides mainly due to two reasons: the difficult oxidative addition and the facile β -H elimination.⁶ Therefore, early Heck-type couplings related to alkyl halides were focused on the alkyl halides without β -H, such as benzyl halides.⁷ Despite these intrinsic challenges, the last decade has witnessed the progress in coup-

ling of the substrates bearing β -H by employing diverse metals including Pd, ⁸ Ni, ⁹ Co, ¹⁰ Zr¹¹ and Cu.¹²

Pioneered by Fu's group, the palladium-catalyzed Heck-type couplings involving alkyl halides were initially only successful for the intramolecular reactions, in which alkene insertion was expected to be faster than β -H elimination.^{8a} In 2014, Alexanian's group^{8c} and Zhou's group^{8d} both developed a general protocol to conduct the Heck coupling related to alkyl halides through a palladium catalyst at the same time. However, in their protocols, a special solvent (PhCF₃) and a high temperature were required (>100 °C), which could limit the application of these methods. Besides palladium, nickel was also employed to mediate the Heck-type reaction related to alkyl halides. In 2011, Jamison's group^{9c} reported a method to directly couple benzyl chloride with simple olefins. The reaction conditions were mild (room temperature) but the scope of this reaction was restricted to benzyl chloride and required a stoichiometric amount of a Lewis acid. In 2013, Lei's group¹³ reported a nickel-catalyzed Heck-type reaction related to alkyl halides, in which only activated secondary and tertiary bromides (α -carbonyl bromide type compounds) could be successfully coupled. In 2006, Oshima's group^{10d} reported a cobaltcatalyzed trimethylsilylmethylmagnesium-promoted radical alkenylation of alkyl halides, one drawback of which was that a stoichiometric amount of Grignard's reagent was required to activate the cobalt catalyst. In 2011, Carreira's group¹⁴ reported a cobalt-mediated protocol to couple alkenes with alkyl halides without Grignard's reagent, which was only applicable to intramolecular coupling. Besides transition metal catalysts, the photo-redox catalysts were also brought into this area by Lei's group.¹⁵ Although this visible light-initiated investigation contributed a new pathway to the Heck chemistry, the photo-redox strategy was only capable of coupling alkenes with activated halides such as benzyl bromide and α -carbonyl bromides, which would pose some limitation expanding this protocol to non-activated halides. Therefore, a more general, green, and economical protocol to couple alkenes with alkyl halides would be highly desirable.

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Previous work:



Scheme 1 (1) Classical Heck reaction involving aryl halides; (2) Heck reaction involving alkyl halides catalyzed by various metals; (3) our work on the coupling of alkenes and alkyl iodides without any transition metals in water promoted by ultraviolet light.

Recently, we have reported a transition-metal-free protocol to couple terminal alkynes with non-activated alkyl iodides in water promoted by using UV light.¹⁶ Inspired by this work, herein, we wish to report a transition-metal-free protocol to couple alkenes with various non-activated alkyl iodides in water promoted by UV under mild conditions. Our protocol was greener (water was the sole solvent), efficient (most of the substrates were consumed over 1 h) and mild (temperature was <50 °C). More importantly, our protocol is transition-metal-free, which not only avoids the consumption of expensive palladium, toxic nickel or other transition metals, but also eliminates the transition metal residue problem (Scheme 1).³

To commence our investigation, we selected 4-methoxystyrene and cyclohexyl iodide for the model reaction. All the parameters that have an impact on the reaction are listed in Table 1. Entries 2 and 3 showed the indispensability of UV. No product could be detected in the absence of UV even at a higher temperature (100 °C). Use of various optical filters (entries 23-25) further validated that UV was crucial for this reaction and that the effective wavelength should be <320 nm. A commercial photoreactor¹⁷ was not efficient enough to promote this reaction (entry 4). Screening of different inorganic bases demonstrated that NaO^tBu was the optimum one¹⁸ (entries 5–8). Use of an organic base could also produce the desired coupling product although the yield was lower (entry 13). The addition of inorganic salt was not helpful to increase the reaction yield (entry 9). Concerning the solvent effect, aprotic polar and protic organic solvents were all less effective than H₂O (entries 14-19). The amounts of cyclohexyl iodide and base were crucial to guarantee a good yield since the elimination reaction of alkyl iodides in water could be tremendously accelerated by UV light,19 which would consume

Table 1 Optimization of the model reaction

	•	
	+ $(V) light, V light$	
0.077mmol	40 min	3b
Entry	Variation from standard conditions	Yield ^a
1	No change	99% (84%)
2	No UV at 50 °C	0%
3	No UV at 100 °C	0%
4^b	Commercial photoreactor	<5%
5	NaOH instead of NaO ^t Bu	74%
6	NaHCO ₃ instead of NaO ^t Bu	26%
7	K_3PO_4 instead of NaO ^t Bu	57%
8	K_2CO_3 instead of NaO ^t Bu	18%
9 ^c	LiClO ₄ instead of water	17%
10	8 equiv. cyclohexyl iodide	90%
11	Distilled cyclohexyl iodide	98%
12	60 mg (8 equiv.) NaO ^t Bu	77%
13	Triethylamine	23%
14^d	TFE instead of H ₂ O	0%
15	CH ₃ CN instead of H ₂ O	40%
16	MeOH instead of H_2O	10%
17	^t BuOH instead of H ₂ O	<5%
18	DMF instead of H ₂ O	<5%
19	DMSO instead of H ₂ O	0%
20	0.5 mL H ₂ O	40%
21	2.5 mL H ₂ O	86%
22	1 equiv. CuI	8%
23	280 nm Optical filter	39%
24	320 nm Optical filter	<5%
25	360 nm Optical filter	0%
26	Under O ₂ atmosphere	0%

^{*a*} The reaction yield (combined yield of E/Z isomers) was determined through GC analysis by using dodecane as an internal standard; the isolated yield is in parentheses. ^{*b*} See the ESI for the details of this photoreactor and the setup of the apparatus. ^{*c*} 1.3 mL saturated LiClO₄ solution and 0.2 mL distilled water. LiClO₄ was added to increase the polarity of the solvent, which might affect the reaction. ^{*d*} TFE: trifluoroethanol.

the base and the iodide. Therefore, to obtain a decent yield, we decided to use 10 equivalents of bases and iodides in the current study²⁰ (entries 10 and 12). The concentration, as a key factor for a photochemical reaction, affected this reaction dramatically. Either a very high concentration or very low concentration was detrimental to the yield (entries 20 and 21). To further exclude the potential influence of transition metals, distilled cyclohexyl iodide²¹ was subjected to the standard conditions, which did not bring any discrepancy in the reaction yield (entry 11). Furthermore, when 1 equivalent of CuI was added, the reaction yield decreased distinctively probably because the formed precipitate, *i.e.* Cu(OH), would disturb the absorption of UV by the reactants. Finally, we found that O₂ was pernicious to this reaction (entry 26), perhaps because O_2 can initiate the styrene polymerization especially in the presence of UV light.

With the optimized conditions in hand, the scope of various alkenes and non-activated alkyl iodides was investigated. Regarding the alkenes, various types of styrene derivatives could be coupled successfully, including styrene derivatives with strong electron donating groups (**3c**, **3d**, EDG,

such as -OMe), strong electron withdrawing groups (3e, 3k, 3q, EWGs, such as $-CF_3$ and -F) as well as electron neutral groups (3a, 3l, 3m). The styrene derivatives with EDGs (3c, 3d) produced better yields than those with EWGs (3e, 3k) due to the fact that some reduction products could be formed for the EWG bearing substrates (15-25%, please see the ESI[†]) besides the desired Heck coupling products. Diverse functional groups including -OMe (3a), -Cl (3o), -F (3q), -CF₃ (3k) and -CN (3p) on the styrene rings could be tolerated but aldehyde, ketone, ester and -NO2 were not compatible with our current conditions (not shown here) probably because of the interference of UV as well as the strong basicity of the reaction conditions. It was worthwhile to note that a non-styrene type conjugated linear alkene (3g) could result in the desired product albeit with a lower yield. Internal alkenes rather than terminal alkenes show a more complex reactivity depending on the steric hindrance of the substituents on the double bond. More sterically hindered internal alkenes (please see ESI Fig. S5[†]) could not give the desired products, while the less sterically hindered internal alkenes (3n) could produce the desired coupling products in a low yield under the standard conditions. Moreover, 1-vinyl naphthalene (3i) could also work efficiently. For the heterocyclic styrene type alkenes, although 4-vinylpyridine (3f) could result in a 10% yield, 2-vinylpyridine and 1-vinylimidazole failed to couple with the iodides (please see the ESI Fig. S5[†]). As to the scope of the alkyl halides, our current protocol was only applicable to alkyl iodides instead of alkyl chlorides and bromides. Among diverse alkyl iodides,

Table 2 Scope of the various alkenes



Table 3 Scope of the various alkyl iodides



both primary alkyl iodides and secondary alkyl iodides could be coupled successfully while tertiary alkyl iodides failed. Generally speaking, secondary alkyl iodides behaved better than primary iodides and cyclic secondary alkyl iodides produced the best yields among all the alkyl iodides (Tables 2 and 3).

To gain more insight into the reaction mechanism, we conducted further mechanistic investigations. When cyclopropylmethyl iodide was subjected to the standard conditions, only the cyclopropyl ring opening product (2a in Scheme 2a) could be isolated, while the direct coupling product (2e in Scheme 2a) could not be detected at all. This radical clock control experiment clearly confirmed the existence of a radical intermediate. Besides the radical clock investigation, we also attempted to use (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) to trap the radial intermediates. After carefully scrutinizing the GC trace, we were able to detect the signal of the trapped radical intermediate (2b in Scheme 2b). Besides these, the formation of the reduced byproduct 2d along with the desired coupling product could shed more light on the mechanism (vide infra).

Combining all the observations mentioned above, we proposed the following mechanism in Scheme 3 to rationalize this reaction. The C–I bond underwent homolytic cleavage under the irradiation of UV, resulting in a radical pair of carbon and iodine.²² Addition of the carbon radical (**4b**) to the



Scheme 2 Some control experiments conducted to probe the mechanism.



Scheme 3 Our proposed mechanism.

styrene (4c) would produce a stabilized benzyl radical (4d), which would trap another iodide atom to produce the radical addition product 4e. Followed by a base induced elimination, the desired alkene coupling product 4f could be formed, which could isomerize into 4g under the irradiation of UV. Based on this proposed mechanism, the formation of the reduced byproduct 4h could also be explained from intermediate 4d.²³ So far, we have not obtained any evidence to support the photosensitizing role of the styrenes in this reaction.

Conclusions

In summary, we have developed a transition-metal-free methodology to couple alkenes with non-activated alkyl iodides (the Heck-type reaction) in water induced by UV for the first time, although there are still some limitations in our protocol such as the requirement of a large amount of base and alkyl iodides as well as the narrow scope of alkenes (mainly suitable for styrene derivatives). Further efforts will be devoted to reduce the amount of base and alkyl iodides, and to expand the substrate scope.

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