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Photocatalytic acylarylation of unactivated alkenes with diaryliodonium salts toward indanones and related compounds

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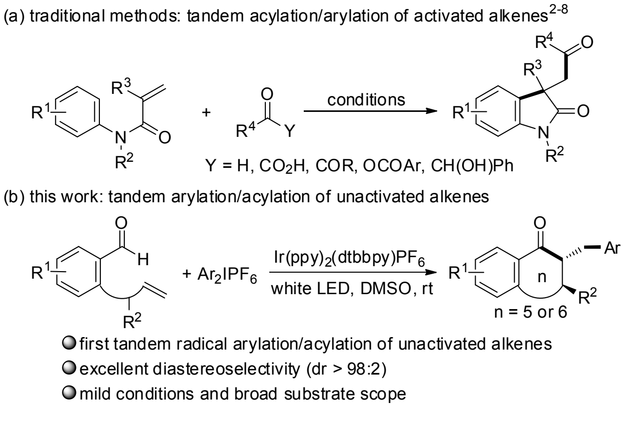
Yongtao Chen, Chenyun Shu, Fang Luo, Xiaohui Xiao,* and Gangguo Zhu*

A novel photocatalytic acylarylation of unactivated alkenes using diaryliodonium salts as the arylation reagent is described. The reaction produces a variety of 2-benzyl indanones, 3,4-dihydronaphthalen-1(2*H*)-ones, and 2,3-dihydroquinolin-4(1*H*)-ones in promising yields with excellent diastereoselectivity under very mild conditions, which may be appealing for the synthesis of biologically active molecules.

Difunctionalization of alkenes has emerged as a very powerful tool for the rapid assembly of important building blocks of natural products and pharmaceutical compounds because of its high reaction efficiency and molecule diversity.[1] In particular, the radical acylarylation of alkenes attracts more and more attention in the past few years.[2-9] For example, Li and co-workers reported a TBHP-promoted dehydrogenative coupling of aldehydes with *N*-arylacrylamides, giving a direct access to 3-(2-oxoethyl)indolin-2-ones in moderate to high yields (Scheme 1a).[2] Later, a variety of alkene acylarylation has developed by using α-oxocarboxylic acids,[4] carboxylic acids,[5] benzoins,[6] aromatic carboxylic anhydrides,[7] or α-diketones[8] as the acylation reagent. It should be noted that the previous methods are mainly restricted to the utilization of activated alkenes, while the more common, unactivated alkenes still remain challenging partners for this transformation.[9] Moreover, the traditional methods[2-8] involve the addition of acyl radicals to alkenes, followed by a subsequent intramolecular arylation. In contrast, the reaction triggered by radical arylation of alkenes has not been achieved yet. Therefore, the exploration of a novel, mild, and general protocol that enables the acylarylation of simple alkenes is highly demanded.[10]

Recently, we started a project on the development of catalytic radical transformation of aldehydes.[11] As an example, an oxidative radical addition strategy has been developed for the rapid synthesis of ketones featuring the attack of carbon radicals to aldehydes.[11] Following this concept, we reasoned that the radical arylation of alkenes and a subsequent dehydrogenative addition to aldehydes might offer an alternative pathway for the alkene acylarylation. On the other hand, diaryliodonium salts are widely used as the aryl radical source in organic synthesis.[12,13] Particularly, enabled by the rapid development of photoredox catalysis,[14] the alkene arylfunctionalization, such as oxyarylation,[13a-c] aminoarylation,[13a] and desulfonylative arylation,[13d] has been realized with diaryliodonium salts under very mild reaction conditions. Inspired by these promising results, we present here a novel photocatalytic acylarylation of simple alkenes using readily accessible diaryliodonium hexafluorophosphates as the arylation reagent, which produces a series of cyclic ketones such as 2-benzyl indanones, 3,4-dihydronaphthalen-1(2*H*)-ones, and 2,3-dihydroquinolin-4(1*H*)-ones at room temperature (Scheme 1b). Notably, *trans*-2,3-disubstituted indanones can be exclusively assembled via this method. The mild reaction conditions, high efficiency, broad substrate scope, and excellent diastereoselectivity render it an attractive method for the fast construction of biologically active molecules like indanones. As compared to the traditional methods depending on sequential acylation/arylation, this reaction proceeds via the tandem radical arylation/acylation pathway, thus offering a new possibility for the acylarylation of alkenes, especially the unactivated ones.



Scheme 1 Summary of radical acylarylation of alkenes.

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[a] Key Laboratory of the Ministry of Education for Advanced Catalysis Materials, Department of Chemistry, Zhejiang Normal University, 688 Yingbin Road, Jinhua 321004, P. R. China. E-mail: xxh@zjnu.cn, gangguo@zjnu.cn

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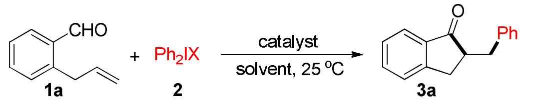
At the outset, we screened the photoredox catalyst by examining the reaction between 2-allyl benzaldehyde (**1a**) and diphenyliodonium hexafluorophosphate (**2a**) in DMSO using a 8 W white LED at room temperature (25 °C). When 2 mol% of $Ru(bpy)_3Cl_2$ was employed as the catalyst, the 2-benzyl indanone **3a** was obtained in 16% yield (Table 1, entry 1). To our delight, the yield was increased to 70% by switching the photoredox catalyst from $Ru(bpy)_3Cl_2$ to $Ir(ppy)_2(dtbbpy)PF_6$ (entries 2-4). Meanwhile, we tested other diphenyliodonium salts including the tetrafluoroborate (**2b**) and triflate (**2c**); however, reduced yields were observed in these cases (entries 5 and 6). The choice of solvent turned out to be crucial for this reaction, as replacing DMSO by other solvents, such as MeOH, EtOH, $ClCH_2CH_2Cl$, DMF, and MeCN, resulted in inferior results (entries 7-11). Lastly, the control experiment showed that the photoredox catalyst $Ir(ppy)_2(dtbbpy)PF_6$ is essential for the acylarylation reaction (entry 12).

Table 1. Evaluation of reaction conditions[a]

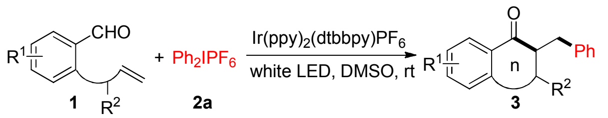


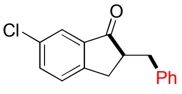
Entry	Catalyst	2	Solvent	Yield (%)
1	$Ru(bpy)_3Cl_2$	Ph_2IPF_6/**2a**	DMSO	16
2	$Ir(ppy)_3$	Ph_2IPF_6/**2a**	DMSO	23
3	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	Ph_2IPF_6/**2a**	DMSO	52
4	$Ir(ppy)_2(dtbbpy)PF_6$	Ph_2IPF_6/**2a**	DMSO	70
5	$Ir(ppy)_2(dtbbpy)PF_6$	Ph_2IBF_4/**2b**	DMSO	55
6	$Ir(ppy)_2(dtbbpy)PF_6$	Ph_2IOTf/**2c**	DMSO	40
7	$Ir(ppy)_2(dtbbpy)PF_6$	Ph_2IPF_6/**2a**	MeOH	62
8	$Ir(ppy)_2(dtbbpy)PF_6$	Ph_2IPF_6/**2a**	EtOH	19
9	$Ir(ppy)_2(dtbbpy)PF_6$	Ph_2IPF_6/**2a**	$ClCH_2CH_2Cl$	Trace
10	$Ir(ppy)_2(dtbbpy)PF_6$	Ph_2IPF_6/**2a**	DMF	7
11	$Ir(ppy)_2(dtbbpy)PF_6$	Ph_2IPF_6/**2a**	MeCN	Trace
12	/	Ph_2IPF_6/**2a**	DMSO	0

[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.75 mmol), catalyst (2 mol%), solvent (2 mL), white LED, 25 °C, 36 h. Yields of the isolated products are given.

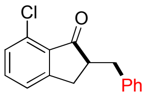
With the optimized reaction conditions in hand, we examined the structural diversity of substrates **1** by assessing the substitution effect on them, and the results are summarized in Table 2. Chlorinated aldehydes **1b**, **1c**, and **1d** afforded the corresponding 2-benzyl indanones **3b**, **3c**, and **3d** in respective yields of 76%, 72%, and 68%, suggesting that the substitution pattern has no significant impact on the reaction. Remarkably, the substrate **1g**, with a strong electron-withdrawing group (CO_2Et) on the benzene ring, was smoothly converted into the desired indanone **3g** in 82% yield. Since electron-deficient benzenes are poor substrates for the Friedel-Crafts acylation, our method provides a good alternative protocol for the access of this type of compounds. In contrast to our previous report that was enabled by the base-promoted epimerization,[11e] this reaction displayed excellent *trans*-diastereoselectivity (dr > 98:2) under the base-free conditions. Specifically, the reaction of **1k**-**1m** exclusively afforded *trans*-2,3-disubstituted indanones **3k**-**3m** in good yields, which were determined by the NOE measurements. Furthermore, the substitution of the C-C double bond of **1** with substituents like methyl group led to a decline in the yield (**3o** and **3p**), presumably due to the increased steric hindrance of alkene. In addition to the generation of indanone derivatives, this reaction can be applicable for the construction of other cyclic ketones. For instance, the coupling of **1q** with **2a** occurred efficiently to deliver the 3,4-dihydronaphthalen-1(2*H*)-one **3q** in 66% yield. Facile conversion of **1s** into the 2,3-dihydroquinolin-4(1*H*)-one derivative **3s** was also feasible. In contrast, substrates **1t** and **1u**, possessing an activated alkene, were not engaged in this reaction (**3t** and **3u**).

Table 2. Scope of alkenyl aldehydes[a]

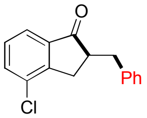




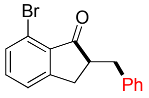
3b, 76%



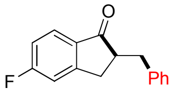
3c, 72%



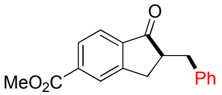
3d, 68%



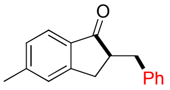
3e, 83%



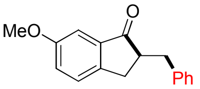
3f, 76%



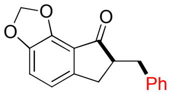
3g, 82%



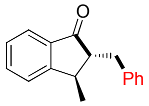
3h, 74%



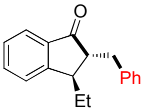
3i, 67%



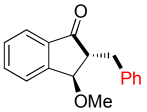
3j, 50%



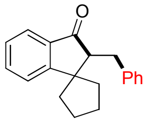
3k, 74%[b]



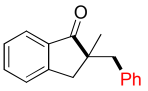
3l, 80%[b]



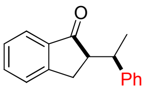
3m, 64%[b]



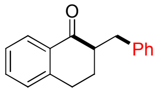
3n, 82%



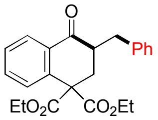
3o, 36%



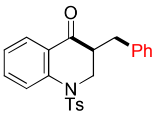
3p, trace



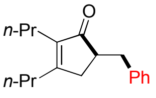
3q, 66%



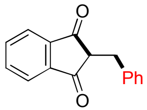
3r, 63%



3s, 60%



3t, trace



3u, trace

[a] Reaction conditions: **1** (0.25 mmol), **2a** (0.75 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (2 mol%), DMSO (2 mL), white LED, 25 °C, 36 h. Yields of the isolated products are given. [b] dr > 98:2.

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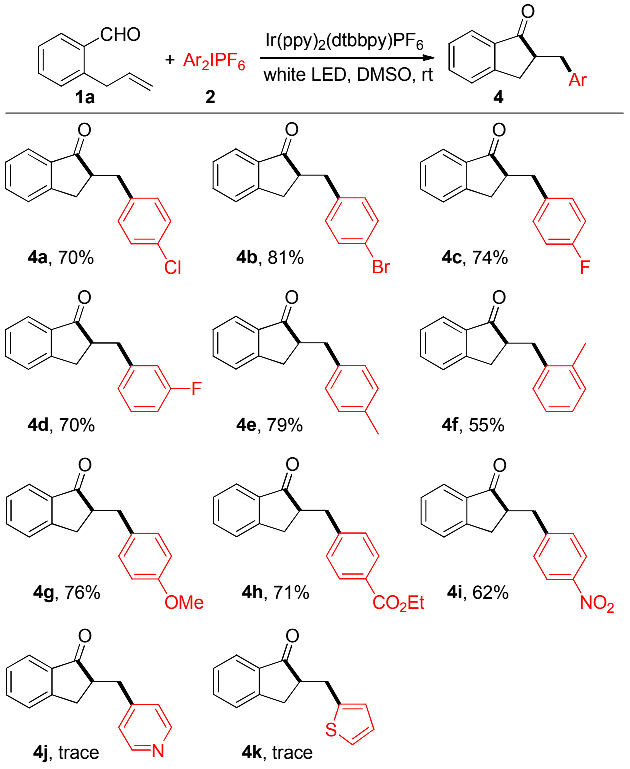
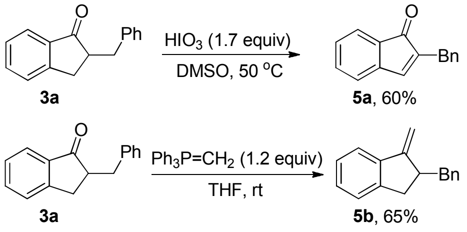
Subsequently, various diaryliodonium hexafluorophosphates were tested under the optimal reaction conditions. As shown in Table 3, diaryliodonium salts bearing different halogen atoms such as Cl, Br, and F were viable substrates for this reaction (**4a**-**4d**), which may be used for further synthetic elaborations through transition-metal-catalyzed cross-coupling reactions. The reaction of electron-rich substrate **2j** and electron-poor one **2k** afforded the desired products **4g** and **4h** in 76% and 71% yield, respectively, implying that the electronic effect of diaryliodonium hexafluorophosphates has little influence on the reaction. Gratifyingly, the substrate **2l**, possessing a NO_2 group on the benzene ring, was also effective for the indanone formation (**4i**). Unfortunately, diheteroaryliodoniums were incompatible for this reaction (**4j** and **4k**).

Table 3. Scope of diaryliodonium hexafluorophosphates[a]



[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.75 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (2 mol%), DMSO (2 mL), white LED, 25 °C, 36 h. Yields of the isolated products are given.

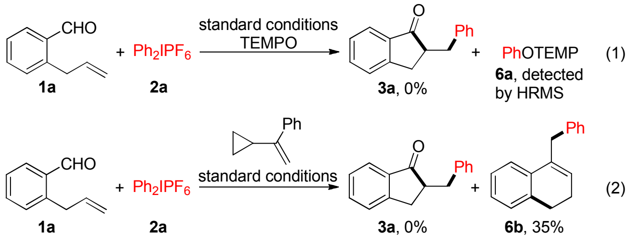


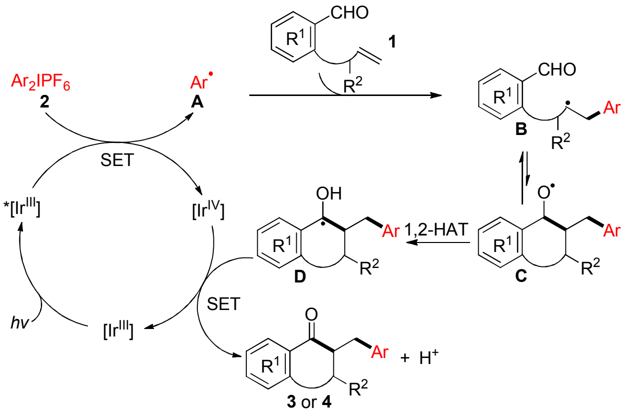
Scheme 2 Transformation of **3a**.

The resultant product **3a** was subjected to further modification (Scheme 2). Using 1.7 equiv of HIO_3 as the oxidant,[15] it was smoothly converted into 2-benzyl-1*H*-inden-1-one (**5a**) in 60% yield. Additionally, the ketone olefination was also feasible, as demonstrated by the facile synthesis of compound **5b** via the Wittig reaction.

To gain some insights into the reaction pathway, we conducted a few control experiments. In the presence of 3 equiv of the radical scavenger 2,2,6,6-tetramethylpiperidinooxy (TEMPO), the formation of **3a** was completely inhibited, and instead, the TEMPO-adduct **6a** could be detected by HRMS analysis (eq 1). Additionally, the radical clock experiment with (1-cyclopropylvinyl)benzene as the radical probe led to a ring-expanded product **6b** in 35% yield (eq 2). These results indicated that the formation of phenyl radical may be involved in the catalytic cycle.

As such, a possible mechanism has been proposed in Scheme 3 for this photocatalytic acylarylation of unactivated alkenes. Initially, the reduction of diaryliodonium salts **2** with a photoexcited Ir(III)* species produces the aryl radical **A**, accompanied by the generation of an Ir(IV) intermediate. Trapping the aryl radical **A** with the C-C double bond of **1** followed by an intramolecular addition to aldehyde delivers an alkoxy radical **C**, which can be transformed to an α-hydroxy carbon radical **D** via a formal 1,2-hydrogen atom transfer (1,2-HAT).[16] Afterward, the SET oxidation of **D** by Ir(IV) furnishes the corresponding products **3** or **4** with concurrent formation the Ir(III) catalyst, a precursor for the photoexcited Ir(III)* species.





Scheme 3 Possible mechanism.

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In conclusion, we have developed a novel photocatalytic acylarylation of unactivated alkenes using diaryliodonium hexafluorophosphates as the arylation reagent, thus generating a variety of 2-benzyl indanones, 3,4-dihydronaphthalen-1(2*H*)-ones, and 2,3-dihydroquinolin-4(1*H*)-ones in promising yields at room temperature. *trans*-2,3-Disubstituted indanones can be exclusively synthesized via this protocol. The mild reaction conditions, high efficiency, broad substrate scope, and excellent diastereoselectivity enable it a very attractive method for the fast construction of biologically active molecules including indanones. This reaction represents a new type of alkene acylarylation featuring the tandem radical arylation/acylation. It permits the successful transformation of unactivated alkenes, thus providing a good complementary protocol to the existing methods.

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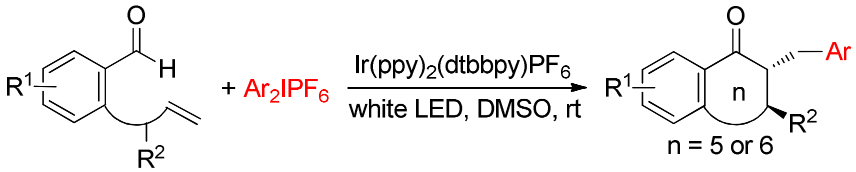
A photocatalytic acylarylation of unactivated alkenes using diaryliodonium salts is described, giving 2-benzyl indanones and related compounds in promising yields with excellent diastereoselectivity.



- first tandem radical arylation/acylation of unactivated alkenes
- excellent diastereoselectivity (dr > 98:2)
- mild conditions and broad substrate scope