### Visible-Light Photocatalytic Radical Alkenylation of α-Carbonyl Alkyl Bromides and Benzyl Bromides

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Abstract: Through the use of [Ru- $(bpy)_3Cl_2$ ] (bpy=2,2'-bipyridine) and (ppy = phenylpyridine) $[Ir(ppy)_3]$ as photocatalysts, we have achieved the first example of visible-light photocatalytic radical alkenylation of various acarbonyl alkyl bromides and benzyl bromides to furnish a-vinyl carbonyls and allylbenzene derivatives, prominent structural elements of many bioactive molecules. Specifically, this transformation is regiospecific and can tolerate primary, secondary, and even tertiary alkyl halides that bear  $\beta$ -hydrides, which can be challenging with traditional palladium-catalyzed approaches. The key initiation step of this transformation is visible-light-induced single-electron reduction of C–Br bonds to generate alkyl radical species promoted by photocatalysts. The following carbon–carbon bond-forming step involves a radical addition step rather than a metal-mediated process, thereby avoiding the undesired  $\beta$ -hy-

**Keywords:** alkenylation • halides • photocatalysis • radical reactions • transition metals

dride elimination side reaction. Moreover, we propose that the Ru and Ir photocatalysts play a dual role in the catalytic system: they absorb energy from the visible light to facilitate the reaction process and act as a medium of electron transfer to activate the alkyl halides more effectively. Overall, this photoredox catalysis method opens new synthetic opportunities for the efficient alkenylation of alkyl halides that contain  $\beta$ -hydrides under mild conditions.

Theoretically, in addition to the oxidative addition pathway, alkyl halides can also be activated by means of single-

electron reduction process to generate the key intermediate alkyl radical species.<sup>[6]</sup> The following carbon–carbon bond-

forming step involves a radical addition step rather than a

metal-mediated process, thereby avoiding the undesired  $\beta$ -

hydride elimination side reaction.<sup>[7]</sup> However, only a very

### Introduction

The palladium-catalyzed Heck reaction of alkenes with aryl or vinyl halides (or sulfonates) has been widely applied in organic synthesis and related disciplines.<sup>[1]</sup> Although considerable efforts have been made towards expanding the synthetic applications of this reaction, alkyl halides still pose a major challenge,<sup>[2]</sup> especially for secondary and tertiary alkyl halides.<sup>[3]</sup> The difficulty is mainly attributed to two problems: sp<sup>3</sup>-hybridized alkyl halides are generally reluctant to undergo oxidative addition processes with low-valent palladium catalyst,<sup>[4]</sup> and the alkyl-palladium intermediates normally undergo  $\beta$ -hydride elimination more facilely than olefin insertion.<sup>[5]</sup> Both of them are inherent conundrums for palladium-catalyzed Heck reaction of alkyl halides.

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suggested to have the capability of photocatalytic generation of electron-deficient alkyl radicals from activated alkyl halides irradiated with visible light.<sup>[11]</sup> In addition, photocatalytic alkenylation of aryl diozanium salts has been reported

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few radical alkenylation reactions catalyzed by transition metals other than palladium by means of the single-electron transfer (SET) process have been reported.<sup>[8]</sup> These kinds of radical alkenylation reactions promoted by titanocene and cobalt catalysts are normally stoichiometric in highly reactive alkylmagnesium reagents, thus limiting their potential applications.<sup>[8a-c,9]</sup> In addition, nickel-catalyzed alkenylation of benzyl chlorides and  $\alpha$ -carbonyl alkyl bromides has also been developed.<sup>[8e,f]</sup> In spite of the significant progress offered by this method, issues of substrate scope limitation,<sup>[10]</sup> high catalyst loading, the use of air-sensitive Ni<sup>0</sup> catalyst, and high temperature still remain concerns. To achieve the radical alkenylation reaction of these activated alkyl halides in a more facile manner, we sought to identify other easyto-handle reagents that could accomplish catalytic formation of electron-deficient alkyl radicals by the single-electron reductive cleavage of C-X bonds under mild conditions. As we know, Ru<sup>2+</sup>- or Ir<sup>3+</sup>-polypyridyl complexes are

very recently.<sup>[12]</sup> Accordingly, we envisioned that alkenylation of activated alkyl halides could be realized by means of the photoredox catalysis process that takes visible light as the terminal energy source. With this idea in mind, we developed a novel method to accomplish the alkenylation of various  $\alpha$ -carbonyl alkyl bromides and benzyl bromides under mild conditions through visible-light photoredox catalysis (Scheme 1a and b), which is emerging as a promising



Scheme 1. Visible-light photocatalytic alkenylation of a)  $\alpha$ -carbonyl alkyl halides and b) benzyl halides.

tool for bond breaking and bond making in organic synthesis. Moreover, the recent developments in photoredox catalysis further demonstrate the broad potential of these methods to promote various useful chemical transformations by irradiation with visible light.<sup>[13]</sup>

### **Results and Discussion**

As shown in Table 1, our initial studies confirmed the feasibility of the proposed alkenylation process when 1,1-diphenylethene (**2a**) was exposed to ethyl  $\alpha$ -bromopropionoate

Table 1. Optimization studies of the alkenylation of 1a with 2a.<sup>[a]</sup>

Br ⊥		x mol % organocatalyst		OFt	
1a	Ph 0 2a	20 mol % Et <sub>3</sub> solven	N, 1 equiv base t, <i>hv</i> , 36 h <b>3a</b>		
Entry	Base	Solvent	Additive ([mol%])	Yield [%] <sup>[b]</sup>	
1	Na <sub>2</sub> CO <sub>3</sub>	DMF	none	42	
2	NaHCO <sub>3</sub>	DMF	none	46	
3	NaOAc	DMF	none	9	
4	NaOH	DMF	none	0	
5	$K_3PO_4$	DMF	none	0	
6	NaHCO <sub>3</sub>	MeCN	none	19	
7	NaHCO <sub>3</sub>	MeOH	none	0	
8	NaHCO <sub>3</sub>	$CH_2Cl_2$	none	0	
9	NaHCO <sub>3</sub>	$PhNO_2$	none	0	
10	NaHCO <sub>3</sub>	DMA	none	33	
11	NaHCO <sub>3</sub>	DMF	4-methoxypyridine (40)	64	
12 <sup>[c]</sup>	NaHCO <sub>3</sub>	DMF	4-methoxypyridine (40)	78	
13 <sup>[d]</sup>	NaHCO <sub>3</sub>	DMF	4-methoxypyridine (40)	73	
14 <sup>[c,e]</sup>	NaHCO <sub>3</sub>	DMF	4-methoxypyridine (40)	90	
15 <sup>[c,e]</sup>	NaHCO <sub>3</sub>	DMF	pyridine (40)	84	
16 <sup>[c,e]</sup>	NaHCO <sub>3</sub>	DMF	DMAP (40)	59	

[a] Conditions: **1a** (0.5 mmol), **2a** (0.25 mmol),  $[RuCl_2(bpy)_3]$  (0.005 mmol), additive, Et<sub>3</sub>N (0.05 mmol), base (0.25 mmol), solvent (2 mL), irradiation with 25 W household light bulb, 36 h. [b] GC yields. [c] Et<sub>3</sub>N (0.1 mmol). [d] Et<sub>3</sub>N (0.15 mmol). [e] DMF (1 mL).

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(1a),  $[RuCl_2(bpy)_3]$  (2 mol%; bpy=2,2'-bipyridine), Et<sub>3</sub>N (20 mol%), and a 25 W household fluorescent lamp in the presence of Na<sub>2</sub>CO<sub>3</sub> (1 equiv) in DMF (Table 1, entry 1; 42% yield). Importantly, no alkenylation product was observed only with either [RuCl<sub>2</sub>(bpy)<sub>3</sub>] catalyst or light, which indicated that the photoredox catalysis is essential to this process. A brief screen of bases revealed that NaHCO<sub>3</sub> afforded the best yield of the alkenylation product (Table 1, entries 1-5). Subsequent investigations uncovered the importance of solvent (Table 1, entries 3 and 6-10). Other tested solvents were less effective than DMF for this transformation. However, at this stage, the reaction was still inefficient with less than 50% conversion. To further increase the reaction conversion, pyridine derivatives were employed as the additives to improve the reactivity, which made the substrate more electron-deficient and introduced a better leaving group (Table 1, entries 14–16).<sup>[14]</sup> To our delight, 4methoxypyridine clearly increased the reaction yield (Table 1, entries 11-14). Actually, the combination of photocatalysis and organocatalysis has been exploited since 2008, and it will substantially broaden the booming field of visible-light photocatalytic synthesis.<sup>[11a,c,14,15]</sup> Finally, the optimized result was obtained by raising both the amount of sacrificial reductant Et<sub>3</sub>N and the reaction concentration (Table 1, entry 14; 90% yield).

With the optimal reaction conditions established, we then examined the scope of this reaction by coupling a variety of alkenes 2 with 1a (Scheme 2). Alkenylation of 1a with varied electronically diverse 1,1-diarylethenes proceeded under mild conditions to give modest to excellent yields (Scheme 2, 3a-g). Both electron-donating and electronwithdrawing substituents on 1,1-diarylethenes were satisfactorily tolerated. In particular, the transformation is compatible with aryl bromide and aryl chloride functional groups,



Scheme 2. Scope of alkenes  ${\bf 2}$  for visible-light photocatalytic radical alkenylation reaction with  ${\bf 1a}$ .

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which are normally reactive in the Pd- or Ni-catalyzed coupling reactions (Scheme 2, 3f and 3g). However, it was difficult to control the stereoselectivity for the reactions of unsymmetrical 1,1-disubstituted ethylenes. Mixed E/Z isomers were obtained from these substrates (Scheme 2, 3d-g). Styrenes substituted with electron-donating groups were also suitable substrates (Scheme 2, 3h and 3i). Moreover, the stereoselectivity for alkylation of substituted styrenes was selective to be trans. The isolated trans products were stable under the standard reaction conditions for 5 h without cistrans isomerization (Scheme S1 in the Supporting Information). The electron-deficient alkyl radical intermediate generated from 1a is more readily trapped by electron-rich olefins.<sup>[16]</sup> As a result, styrenes with electron-withdrawing substituents did not work in the visible-light-induced radical alkenylation reaction.

We next extended this alkenylation reaction to other  $\alpha$ carbonyl alkyl bromides as well (Schemes 3 and 4). Under the optimized reaction conditions described above, secondary  $\alpha$ -carbonyl alkyl bromides bearing ester and cyano groups were shown to react with *p*-methoxystyrene **2h** and 1,1-diphenylethene **2a** in 63–92% yield (Scheme 3, **3h–k**). In addition, tertiary  $\alpha$ -carbonyl alkyl bromides underwent the alkenylation transformation with **2a** and **2h** smoothly as well (Scheme 3, **3l–n**).



Scheme 3. Scope of secondary and tertiary  $\alpha$ -carbonyl alkyl bromides 2 for visible-light photocatalytic radical alkenylation reaction with 1.

It is known that primary  $\alpha$ -carbonyl alkyl bromides are less likely to undergo single-electron reduction of C–Br bonds than secondary and tertiary ones. This is due to the relatively unstable primary alkyl radicals produced.<sup>[17]</sup> Hence, the previous Ni-catalyzed approach could not afford the corresponding alkenylation products of primary  $\alpha$ -carbonyl alkyl bromides.<sup>[8f]</sup> To our delight, this photocatalytic reaction system could solve this problem and furnish the desired Heck-type products of primary alkyl bromides in good yields (Scheme 4), although the reaction conditions are different from the optimized conditions with the change of photocatalyst from [RuCl<sub>2</sub>(bpy)<sub>3</sub>] to *fac*-[Ir(ppy)<sub>3</sub>] (ppy = phenylpyridine). Excitation of *fac*-[Ir(ppy)<sub>3</sub>] (Ir<sup>4+</sup>/Ir<sup>3+\*</sup> = -1.73 V versus SCE in CH<sub>3</sub>CN), which is a stronger reduc-



Scheme 4. Scope of primary  $\alpha$ -carbonyl alkyl bromides **2** for visible-light photocatalytic radical alkenylation reaction with **1**.

ing agent than  $[Ru(bpy)_3]^+$   $(Ru^{2+}/Ru^{1+} = -1.33 \text{ V}$  versus SCE in CH<sub>3</sub>CN).<sup>[18]</sup> It could therefore perform the reductive cleavage of C–Br bonds of less-reactive primary alkyl halides without the assistance of organocatalyst.

We proposed a plausible mechanism for the radical alkenylation reaction of  $\alpha$ -carbonyl alkyl bromides (Scheme 5). Irradiation of  $[Ru(bpy)_3]^{2+}$  with visible light engenders its



Scheme 5. Proposed mechanism of  $[Ru(bpy)_3Cl_2]\mbox{-}catalyzed$  alkenylation reaction of 1.

excited  $[Ru(bpy)_3]^{2+*}$  through metal-to-ligand charge transfer (MLCT),<sup>[19]</sup> which will be initially quenched by sacrificial reductant Et<sub>3</sub>N to form [Ru(bpy)<sub>3</sub>]<sup>+</sup>. 4-Methoxypyridine can react with **1a** to afford the corresponding electron-poor pyridinium salt.<sup>[20]</sup> Single-electron transfer from [Ru(bpy)<sub>3</sub>]<sup>+</sup> to pyridinium salt furnishes the electron-deficient radical I and regenerates  $[Ru(bpy)_3]^{2+}$ .<sup>[14,21]</sup> Since electron-deficient radicals are known to react with electron-rich olefins to form C-C bonds,<sup>[16a]</sup> the key bond-formation step through rapid addition of radical I to the electron-rich olefin 2 forms the  $\gamma$ -carbonyl radical II. It then undergoes single-electron transfer (SET) with  $[Ru(bpy)_3]^{2+*}$  to deliver cation intermediate 4 and  $[Ru(bpy)_3]^+$ , which finally fulfils the photocatalytic cycle. The desired alkenylation product 3 was acquired by means of the deprotonation of 4 with NaHCO<sub>3</sub>.  $Et_3N$  displayed luminescence quenching of the  $[Ru(bpy)_3]^{2+}$ \* excited state, whereas no emission quenching was observed in the presence of substrates 1, thus illustrating that this reaction was achieved through the reductive quenching of the photocatalyst (Figure S1 in the Supporting Information). Furthermore, this alkenylation process is completely shut down in the presence of radical inhibitor (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), which indicates that the single-electron transfer process exists within the catalytic cycle (see Scheme S2 in the Supporting Information).

Meanwhile, we cannot rule out the radical-chain propagation mechanism, but this Ru-catalyzed transformation has been proven to require continuous irradiation of visible light (Figure 1), which indicates that chain propagation is



Figure 1. Time profile of photocatalytic radical alkenylation reaction of **2a** and **1a**.

not the major reaction pathway. Atom-transfer radical addition (ATRA) followed by the elimination of HBr with the assistance of base could be another possible reaction pathway as well. Although we cannot completely exclude this possibility, an ATRA-type product is not observed during this radical alkenylation reaction process (Figure S2 in the Supporting Information). Additionally, under the standard conditions in the absence of base, there was no ATRA-type product formed either (see Scheme S3 in the Supporting Information). As a result, the ATRA reaction pathway is not favored.<sup>[22]</sup>

Encouraged by the positive results of  $\alpha$ -carbonyl alkyl bromides, we turned our attention to the investigation of the photocatalytic radical alkenylation reaction of less-reactive substrates, benzyl bromide derivatives. 1-Bromo-2-(bromomethyl) benzene **5a** and **2h** were chosen as model substrates to determine the optimum reaction conditions. However, there was no reaction in the presence of  $[RuCl_2(bpy)_3]$  as the photocatalyst [Eq. (1)].



As mentioned above, fac-[Ir(ppy)<sub>3</sub>] could generate a stronger reducing agent to perform the reductive cleavage of the C-Br bond more efficiently. Therefore, we started to investigate the impact of different parameters on the efficiency of this reaction by using fac-[Ir(ppy)<sub>3</sub>] as the photocatalyst (Table 2), and we ultimately found that the combination of

Table 2. Optimization studies of the alkenylation of 5a with 2h.<sup>[a]</sup>

Br	Br + MeO	1 mol% [Ir(ppy) <sub>3</sub> ] x mol % Et <sub>3</sub> N, 1 equiv base solvent, $h_V$ , 36 h		Br
∑ 5a	2h		6a	Ţ
Entry	Solvent	Base	Et <sub>3</sub> N [mol%]	Yield [%] <sup>[b]</sup>
1	DMSO	NaHCO <sub>3</sub>	10	trace
2	MeCN	NaHCO <sub>3</sub>	10	60
3	MeOH	NaHCO <sub>3</sub>	10	46
4	DCE	NaHCO <sub>3</sub>	10	45
5	DMF	NaHCO <sub>3</sub>	10	66
6	DMF	KHCO <sub>3</sub>	10	60
7	DMF	$K_2CO_3$	10	64
8	DMF	$Cs_2CO_3$	10	56
9	DMF	Li <sub>2</sub> CO <sub>3</sub>	10	65
10	DMF	lutidine	10	41
11	DMF	Na <sub>2</sub> CO <sub>3</sub>	10	76
12	DMF	Na <sub>2</sub> CO <sub>3</sub>	0	60
13	DMF	Na <sub>2</sub> CO <sub>3</sub>	20	70
14 <sup>[c]</sup>	DMF	Na <sub>2</sub> CO <sub>3</sub>	10	80
15 <sup>[d]</sup>	DMF	Na <sub>2</sub> CO <sub>3</sub>	10	70

[a] Conditions: **5a** (0.5 mmol), **2h** (0.25 mmol),  $[Ir(ppy)_3]$  (0.0025 mmol), Et<sub>3</sub>N, base (0.25 mmol), solvent (2 mL), irradiation with 25 W household light bulb, 36 h. [b] GC yields. [c] DMF (1 mL). [d] DMF (3 mL).

[Ir(ppy)<sub>3</sub>] (1 mol%)/Na<sub>2</sub>CO<sub>3</sub> (1 equiv)/Et<sub>3</sub>N (10 mol%) in DMF yielded most of the alkenylation product **6a** (Table 2, entry 14). DMF and Na<sub>2</sub>CO<sub>3</sub> revealed superior performances among all the solvents and bases examined (Table 2, entries 1–11). In the absence of Et<sub>3</sub>N, the reaction yield was reduced from 76 to 60% (Table 2, entry 12). Increasing the amount of Et<sub>3</sub>N to 20 mol% afforded lower yield as well (Table 2, entry 13)

After the successful photocatalytic radical alkenylation of **5a** with **2h**, the reaction scope toward structurally diverse primary substituted benzyl bromides **5** was examined (Scheme 6). Under the standard conditions, Ir-catalyzed alkenylation of electron-deficient substrates could generate the desired allylbenzene derivatives smoothly, and moderate to high yields were obtained for various substrates. A wide range of functional groups, including C–Br, C–Cl, C–F, C–I, nitro groups, cyano groups, and so forth, were compatible with this method. In addition, the method is regiospecific as well, with only *trans*-linear alkenylation products generated in most cases (with the exception of fluoro-substituted products **6c** and **6i**).

Secondary benzyl bromides were also suitable substrates for this photocatalytic radical alkenylation reaction. This Ircatalyzed radical alkenylation reaction could provide the corresponding alkenylation products in moderate to good

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Scheme 6. Scope of substituted benzyl bromides **5** for visible-light photocatalytic radical alkenylation reaction.

yields (Scheme 6, **6k–l**). To the best of our knowledge, this is the first example of the intermolecular alkenylation reaction of secondary benzyl halides that bear  $\beta$ -hydrides.

As revealed in Scheme 7, this photocatalytic alkenylation technology tolerated a wide range of olefins 2 as well, including various substituted styrene derivatives (40 to 83% yield; Scheme 7, 6n-q) and 1,1-diarylalkenes (58 to 80% yield; Scheme 7, 6r-v). As was the case for benzyl coupling partner, this transformation also proceeded with perfect regioselectivity in the presence of a variety of olefin substrates except unsymmetrical 1,1-diarylalkenes (Scheme 7, 6u and 6v).

The proposed mechanistic explanation for the Ir-catalyzed radical alkenylation reactions is described in Scheme 8. *fac*-[Ir(ppy)<sub>3</sub>] could readily accept a photon from a visible-light source (a household fluorescent bulb) to populate the \**fac*-[Ir(ppy)<sub>3</sub>] excited state,<sup>[18b]</sup> which underwent an SET process with benzyl bromides **5** to render the electrophilic radical **III** and Ir<sup>IV</sup> metal complex. As shown in Figure 2, various substrates **5** displayed luminescence quenching of the \**fac*-[Ir(ppy)<sub>3</sub>] excited state, thereby supporting the SET process between \**fac*-[Ir(ppy)<sub>3</sub>] and **5** (for luminescence quenching of more substrates, see the Supporting Information for details). The key C–C bond-formation step occurred through rapid addition of radical **III** to the  $\pi$ -rich olefin **2**, thus forming the radical **IV**. Given that radical **IV** should have a



Scheme 7. Scope of alkenes 2 for visible-light photocatalytic radical alkenylation reaction with 5.



Scheme 8. Proposed mechanism of fac-[Ir(ppy)<sub>3</sub>]-catalyzed radical alkenylation reaction of **5**.



Figure 2. Luminescence quenching by substrates 5 and Et<sub>3</sub>N.

lower barrier of oxidization due to the existence of the electron-rich substituted groups Ar' and R', a second electrontransfer event with  $fac-[Ir(ppy)_3]$  would generate the cation intermediate 7 and finally close the photoredox catalytic cycle. The desired Heck-type product 6 would be produced through the deprotonation of cation 7 with Na<sub>2</sub>CO<sub>3</sub>.

In addition, the radical chain propagation mechanism could be another possible reaction pathway as a substoichiometric amount of  $Et_3N$  benefits this transformation. In this case,  $Et_3N$  is proposed to donate one single electron to  $Ir^{IV}$  species, thus regenerating the *fac*-[Ir(ppy)<sub>3</sub>] catalyst. Even so, this transformation still requires continuous irradiation with visible light (see Figure S3 in the Supporting Information), thereby revealing that radical chain propagation is not the major reaction route. Moreover,  $Et_3N$  could react with substrate **5** to produce quaternary ammonium salts **5'** [Eqs. (2) and (3)]. Hence,  $Et_3N$  is also capable of acting as an additive like 4-methoxypyridine to promote the reductive cleavage of C–Br bonds.



#### Conclusion

We have developed a mechanistically novel radical alkenylation reaction of various  $\alpha$ -carbonyl alkyl bromides and benzyl bromides under mild conditions, which is the first example of visible-light photocatalytic radical alkenylation reaction of alkyl halides. The key initiation step of this transformation is visible-light-induced single-electron reduction of the C–Br bond promoted by the photocatalysts. In particular, primary, secondary, and tertiary alkyl bromides are all suitable substrates for this photocatalytic transformation, which is a beneficial supplement to the previous Ni-catalyzed protocols from a synthetic point of view.<sup>[8e,f]</sup> The application of this powerful strategy to the synthesis of natural products and further development of other related synthetically valuable reactions are continuing efforts in our laboratory.

#### **Experimental Section**

General procedure for the photocatalytic radical alkenylation of  $\alpha$ -carbonyl alkyl bromides: A dried Schlenk tube equipped with a stirrer bar was loaded with  $\alpha$ -carbonyl alkyl bromide (0.5 mmol), sodium bicarbonate (0.25 mmol), and [Ru(bpy)<sub>3</sub>Cl<sub>2</sub>] (0.005 mmol, 2 mol%). The tube was evacuated and backfilled with nitrogen before alkene (0.25 mmol), Et<sub>3</sub>N (0.1 mmol), and 4-methoxypyridine (0.1 mmol) were added. Then DMF

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(1 mL) was added into the reaction tube with a syringe. The reaction mixture was degassed by the freeze-pump-thaw method and then irradiated with a 25 W fluorescent household light bulb (distance approximately 10 cm) for 36 h. After completion of the reaction, it was quenched with a diluted HCl solution and extracted with ethyl acetate ( $3 \times 10$  mL). The organic layers were combined and the pure product was obtained by flash column chromatography on silica gel.

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