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Silver-Catalyzed Decarboxylative Acylarylation of Acrylamides with α-Oxocarboxylic Acids in Aqueous Media

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Abstract: A mild and efficient silver-catalyzed acylarylation of activated alkenes with easily available α-oxocarboxylic acids has been developed. The reactions provide a rapid access to a variety of functionalized oxindoles *via* a tandem decarboxylative radical cyclization strategy. This transformation proceeds well under mild reaction conditions and exhibits excellent functional group tolerance, affording the desired oxindoles in good to excellent yields.

Keywords: acylarylation; decarboxylation; oxindoles; radicals; silver catalysts

The transition metal-catalyzed oxidative vicinal difunctionalization of alkenes has attracted great interest in recent years and has been applied successfully for the synthesis of various valuable organic compounds.[1] Over the last several years, Pd-catalyzed aminohalogenation,[2] aminooxygenation,[3] diamination,[4] and dioxygenation[5] reactions of alkenes have been a major focus of research in this field. Among these methods, the intramolecular difunctionalization of alkenes has emerged as a new and efficient tool for the synthesis of biologically active heterocyclic compounds.[6] For example, Zhu and co-workers have developed the palladium-catalyzed carbo-heterofunctionalization of alkenes for the synthesis of oxindoles and spirooxindoles.[7] Other important examples include the intramolecular oxidative arylalkylation and aryltrifluoromethylation of activated alkenes, leading to functionalized oxindoles.[8] Although remarkable results have been achieved, the metal-catalyzed intramolecular oxidative difunctionalization of alkenes *via* C–H bond cleavage remains underdeveloped. In view of the importance of economy and environment for chemical synthesis, it is still highly desirable to develop new strategies to prepare functionalized oxindoles that are environmentally friendly, utilizing inexpensive substrates and proceeding under mild conditions.

Carboxylic acids are usually environmentally benign and readily available reagents. Decarboxylation of carboxylic acids by loss of CO_2, then coupling with another reagent, is currently one of the most powerful methods to construct C–C and C–heteroatom bonds.[9] In this context, α-oxocarboxylic acids are usually utilized as acyl sources because of of their stability and easily preparation. Pioneering work by Kochi in the 1970s demonstrated the oxidative decarboxylation of carboxylic acids *via* a radical mechanism.[10a,b] Minisci reported that the Ag-catalyzed decarboxylation of α-oxocarboxylic acids leads to acyl radicals, then homolytic acylation of heteroarenes.[10c–e] A significant breakthrough was recently made by Gooßen, who developed a palladium-catalyzed decarboxylative cross-coupling of α-oxocarboxylic acid salts with organic halides to afford the corresponding diaryl ketones.[11] Later on, the palladium-catalyzed oxidative acylation of unactivated C(sp^2)–H bonds through decarboxylative coupling of α-oxocarboxylic acids was also reported.[12] We have been interested in transition metal-catalyzed decarboxylative cross-coupling reactions, and we recently reported the decarboxylative dehydrogenative of α-oxocarboxylic acids with enamides.[12c] We postulated that arylacylation of activated alkenes would be achieved *via* the Pd(II) intermediates **I**, which are formed by an oxidative intramolecular arylation of alkenes,[7,8] then anion exchange with α-oxocarboxylic acids[12] (Scheme 1a). Alternatively, the highly desired arylacylation of alkenes might also be realized *via* an intramolecular radical substitution reaction[13] under silver catalysis (Scheme 1b). Herein, we report a novel Ag-catalyzed decarboxylative acylarylation of acrylamides with easily available α-oxocarboxylic acids in aqueous solution. To the best of our knowledge, no examples of

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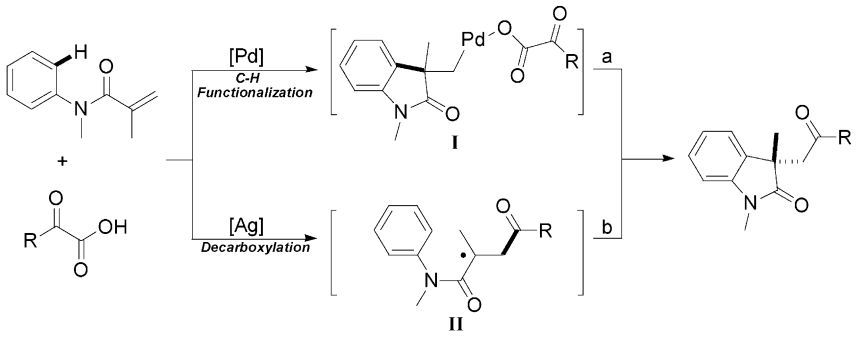


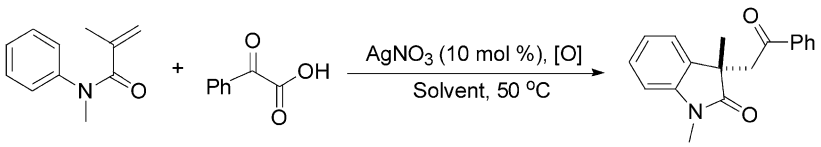
Scheme 1. Transition metal-catalyzed decarboxylative acylarylation of activated alkenes.

catalytic decarboxylative difunctionalization of alkenes to functionalized oxindoles have been reported.

Our investigation commenced with the silver-catalyzed decarboxylative difunctionalization of *N*-methyl-*N*-phenylmethacrylamide (**1a**) with phenylglyoxylic acid (**2a**).[14] Treatment of **1a** with **2a** in the presence of 10 mol% of $AgNO_3$ and 1 equiv. of $K_2S_2O_8$ as oxidant in DCM/H_2O (1:1) at 50 °C for 24 h under nitrogen, led to a complex mixture (Table 1, entry 1). We envisioned that this two-phase system disfavored the decarboxylative reaction, and that a homogeneous phase system might be required to promote this reaction. To our delight, using CH_3CN/H_2O as a solvent gave the clean formation of the expected product **3a** in 75% isolated yield (entry 2). Further optimization showed that acetone/H_2O gave the best yield (entry 5). Notably, a high yield was also obtained even when applying water alone as the solvent, a major advantage of this new protocol from an ecological perspective (entry 7). Among the oxidants tested, $K_2S_2O_8$ was the most efficient oxidant for this reaction (entries 7–9). Ag_2CO_3 was also effective (entry 11). It should be noted that the yield of **3a** was moderate when the reaction was carried out under air (entry 12).

With the optimal conditions in hand, we next explored the scope of the decarboxylative acylarylation reaction (Table 2). Both electron-rich and electron-poor *p*-substituents on the phenylglyoxylic acids led to the desired oxindoles in good to excellent yields

Table 1. Optimization of the reaction conditions.[a]



Entry	Oxidant (equiv.)	Solvent	Yield [%][b]
1	$K_2S_2O_8$ (1)	DCM/H_2O (1:1)	mixture
2	$K_2S_2O_8$ (1)	CH_3CN/H_2O (1:1)	75
3	$K_2S_2O_8$ (1)	DMF/H_2O (1:1)	32
4	$K_2S_2O_8$ (1)	dioxane/H_2O (1:1)	54
5	$K_2S_2O_8$ (1)	acetone/H_2O (1:1)	90
6	$K_2S_2O_8$ (1)	acetone	trace
7	$K_2S_2O_8$ (1)	H_2O	90
8	$(NH_4)_2S_2O_8$ (1)	H_2O	82
9	Oxone (1)	H_2O	n.r.
10[c]	$K_2S_2O_8$ (1)	H_2O	n.r.
11[d]	$K_2S_2O_8$ (1)	H_2O	86
12[e]	$K_2S_2O_8$ (1)	H_2O	58

[a] *Reaction conditions:* 10 mol% of $AgNO_3$, **1a** (0.2 mmol, 1 equiv.), **2a** (0.4 mmol, 2 equiv.), solvent (2 mL), oxidant (1 equiv.), 50 °C, 24 h, under nitrogen, unless otherwise noted. n.r. = no reaction.
[b] Yield of isolated product.
[c] Ag_2O was used as a catalyst.
[d] Ag_2CO_3 was used as a catalyst.
[e] Under air.

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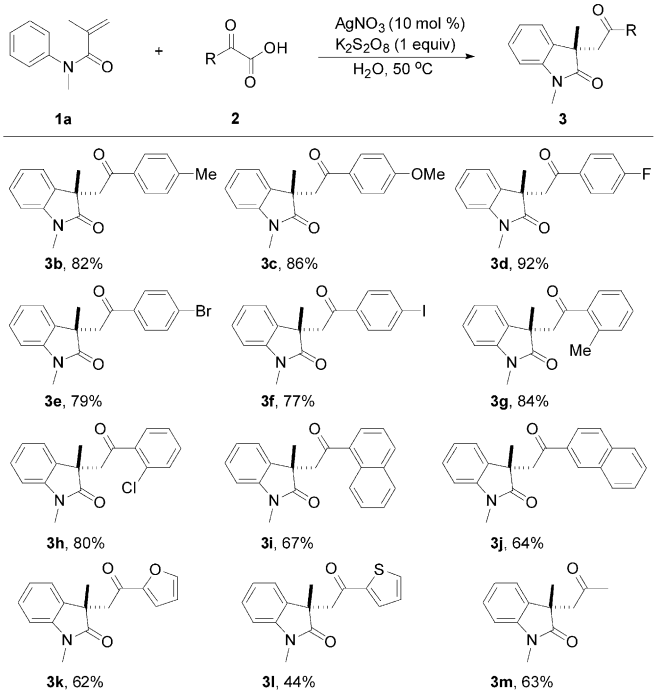
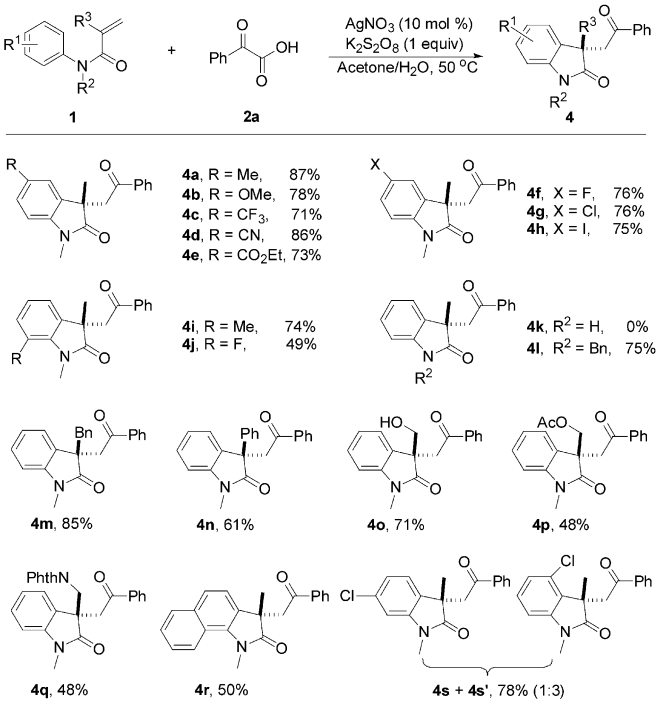
Table 2. Decarboxylative acylarylation of acrylamide **1a** with various phenylglyoxylic acids **2**.[a]



[a] *Reaction conditions:* 10 mol% of $AgNO_3$, **1a** (0.2 mmol, 1 equiv.), **2** (0.4 mmol, 2 equiv.), H_2O (2 mL), $K_2S_2O_8$ (1 equiv.), 50 °C, 24 h, under nitrogen.

Table 3. Decarboxylative acylarylation of various acrylamides **1** with phenylglyoxylic acid **2a**.[a]



[a] *Reaction conditions:* 10 mol% of $AgNO_3$, **1** (0.2 mmol, 1 equiv.), **2a** (0.4 mmol, 2 equiv.), acetone/H_2O (1:1, 2 mL), $K_2S_2O_8$ (1 equiv.), 50 °C, 24 h, under nitrogen.

(**3b**–**3f**). It is noteworthy that halo-substituted phenylglyoxylic acids survived well and gave the corresponding halo-substituted oxindoles (**3d**–**3f**), which could be used for further transformation under transition metal catalytic systems. *o*-Substituted phenylglyoxylic acids **2g** and **2h** also reacted smoothly with **1a** to furnish **3g** and **3h** in 84% and 80% yields, respectively. In addition to the substituted phenylglyoxylic acids, α- and β-naphthyloxoacetic acid could also be applied to give the corresponding functionalized oxindoles (**3i** and **3j**). Furthermore, furoylformic acid and 2-thienylglyoxylic acid resulted in somewhat lower yields under the optimal conditions (**3k** and **3l**). The reaction is not limited to aromatic α-oxocarboxylic acids; aliphatic α-oxocarboxylic acids such as pyruvic acid also underwent the decarboxylation reaction in moderate yield (**3m**).

Subsequently, other substituted *N*-arylacrylamides **1** were examined. As shown in Table 3, substrates derived from various substituted anilines all reacted smoothly under the optimized conditions,[15] and the corresponding oxindoles were obtained in moderate to high yields. A variety of electron-donating, electron-withdrawing, and even potentially sensitive functional groups such as ester and cyano on the aniline moieties survived well in this transformation (**4a**–**4e**). Particularly noteworthy was that the halo-substituted acrylamides were also well tolerated, leading to the desired products **4f**–**4h** in good yields. The sterically congested *o*-substituted substrates were also effectively coupled with phenylglyoxylic acids in moderate yields (**4i** and **4j**). However, unprotected *N*-arylacrylamide was inefficient for this transformation (**4k**). *N*-Arylacrylamide **1l** bearing a benzyl protecting group on the nitrogen also proceeded smoothly to give the desired product **4l** in 75% yield. Satisfactorily, acrylamides bearing different functional groups at the α-position also worked well with **2a**, affording the products **4m**–**4q** in reasonable to high yields. Treatment of *N*-methyl-*N*-naphthylacrylamide **1r** with **2a** resulted in the desired oxindole in 50% isolated yield. *N-meta*-Chloromethacrylamide provided a mixture of **4s** and **4s′** with moderate regioselectivity (1:3 ratio).

It is well known that α-keto acids are easily transformed to acyl radicals in the presence of Ag(I)/$K_2S_2O_8$, which implies that the reaction should proceed through a free-radical mechanism.[10] In order to gain a better insight into the mechanism, further investigations were performed. Some intramolecular and intermolecular kinetic isotope effect (KIE) experiments were carried out under the standard reaction conditions. Neither an intra- nor an intermolecular KIE was observed [$k_H/k_D = 1.0$ and 1.0, Eqs. (1) and (2)]. These results indicate that the reaction in-

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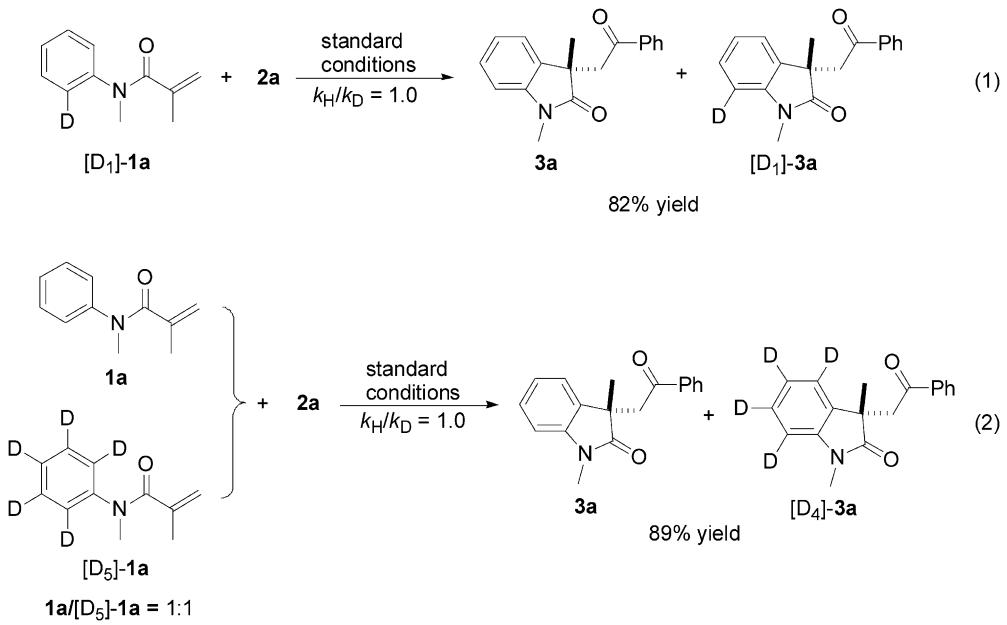
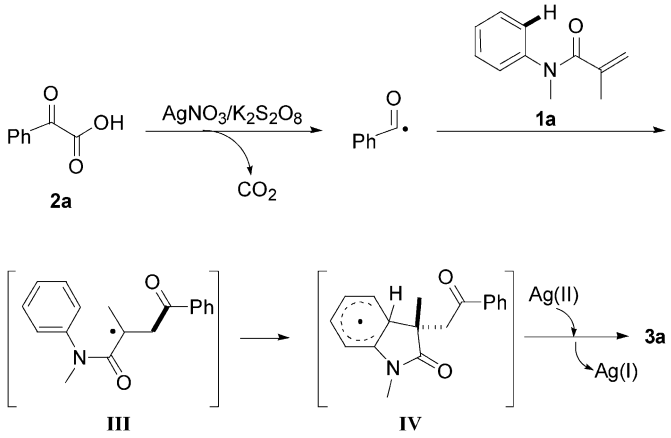


volves either electrophilic aromatic substitution or free-radical substitution.[13,16] Furthermore, the reaction was also suppressed by addition of a radical scavenger, such as TEMPO. Thus, we propose that the reaction proceeds *via* a radical process (Scheme 2). Firstly, phenylglyoxylic acid is converted into the corresponding nucleophilic acyl radical in the presence of Ag(I)/$K_2S_2O_8$,[10] and then attack of the acyl radical onto the C=C bond of *N*-arylacrylamides **1a** would give radical intermediate **III**. Secondly, the radical **III** undergoes an intramolecular cyclization to generate radical intermediate **IV**. Finally, an Ag(II)-mediated oxidation of intermediate **IV** into the corresponding carbocation followed by the loss of H^+ affords the annulated oxindole **3a**.

In summary, we have described a new and efficient silver-catalyzed tandem radical cyclization reaction to furnish a large variety of functionalized oxindoles. This method involves a first decarboxylative acylarylation of acrylamides with readily available α-oxocarboxylic acids. The method shows some advantages such as mild conditions, good to excellent yields and tolerance of a broad range of functional groups. Further investigations on the detailed mechanisms, and expanding the reaction scope to other types of carboxylic acids, are currently underway in this group.



Scheme 2. Proposed mechanism for the decarboxylative acylarylation of acrylamides.

Experimental Section

General Procedure for the Decarboxylative Acylarylation of Acrylamide with α-Oxocarboxylic Acids

A 10-mL oven-dried Schlenk-tube was charged with $AgNO_3$ (3.4 mg, 10 mol%), acrylamide (**1**, 0.2 mmol, 1.0 equiv.) and $K_2S_2O_8$ (54 mg, 0.2 mmol, 1.0 equiv.). The tube was evacuated and backfilled with nitrogen (three times). α-Oxocarboxylic acids (**2**, 0.4 mmol, 2.0 equiv.) in H_2O or acetone/H_2O (1:1) 2 mL were added by syringe under nitrogen. The tube was then sealed and the mixture was stirred for 24 h at 50 °C. The resulting mixture was then extracted with EtOAc. The combined organic phase was dried over anhydrous Na_2SO_4 and the solvent was then removed under vacuum. The residue was purified by chromatography column on silica gel (gradient eluent of EtOAc/petroleum ether: 1/15 to 1/5) to give the corresponding products **3** or **4** in the yields listed in Table 2 and Table 3.

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[14] Initially, on treatment of **1a** with **2a**, in the presence of Pd(II) catalysts and various oxidants, such as hypervalent iodines, persulfates and silver(I) salts, only very small amounts of the desired product **3a** ($<5\%$) were detected in some cases.

[15] When substituted *N*-arylacrylamides were used as substrates, we found that acetone/H_2O was much more effective than H_2O as the sole solvent.

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