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Ir-Photoredox-Catalyzed Decarboxylative Michael Addition of Glyoxylic Acid Acetal as Formyl Equivalent

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We reported herein an iridium-photoredox-catalyzed decarboxylative conjugated addition of glyoxylic acid acetals with various Michael acceptors, including unsaturated amide, ester, aldehyde, ketone, and nitrile under irradiation. Vinyl pyridine and α -aryl styrene are also suitable substrates. The reaction offers various types of acetal products, which are of synthetic significance as protected aldehydes.

Introducion of a formyl group into an organic molecule via formal addition of formyl anion equivalent onto an unsaturated carbon-carbon bond is a very useful transformation in organic synthesis.¹ Because of the versatile transformations of aldehyde functionality in organic synthesis, ² extensive efforts have been devoted to synthesize aldehydes from olefins via hydroformylation.³ These transformations transition-metal-catalyzed been achieved via have hydroformylation of styrenes and simple alkenes using syngas, while for an electron-deficient alkene, conjugated addition of an formyl anion equivalent with Michael acceptor is method of choice.⁴⁻⁶ Literatures reported 4-isopropyl-2-oxazoli-5-one⁴ and formaldehyde N,N-dialkylhydrazone⁵ as convenient formyl anion equivalents for conjugated additions with Michael acceptors (Figure 1a and 1b). Chi et al. also revealed using carbohydrates as formaldehyde equivalent for formyl 1,4additions by using N-heterocyclic carbene catalyst (Figure 1c).⁶ Recently, Wang and Mariano successfully applied glyoxylic acid acetal as formyl anion equivalent to couple with aryl and alkenyl electrophiles by applying organophotoredox/nickel dual catalytic system⁷ and very recently they reported organophotoredox catalyst, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6dicvanobenzene (4CzIPN) can catalyze formal hydroformylation of styrenes with glyoxylic acid acetal with high chemoselectivity and regioselectivity.⁸ We reported in this work that an iridium photoredox catalyst⁹ is efficient to

catalyze decarboxylative Michael addition of glyoxylic acid acetal with a broad scope of Michael acceptors including α , β unsaturated amide, ester, aldehyde, ketone, and nitrile at room temperature (Figure 1d). These Michael acceptors generally are less effective substrates for transition-metalcatalyzed hydroformylation using CO and H₂ as syngas.¹⁰ Interestingly, vinyl pyridine and α -aryl styrene are also suitable substrates for this transformation. The reaction directly delivers acetals as protected aldehyde, which is more synthetically useful because generally aldehyde is a reactive functionality always needing protection against oxidation or reduction in synthesis. The reaction described herein offers a new pathway to synthesize functionalized acetals under mild reaction conditions and also expands the synthetic power of iridium photoredox catalysis in decarboxylative reactions.^{11,12}

Figure 1 Formyl anion equivalent for conjugated additions



We commenced our experimentation by testing the decarboxylative addition of diethoxyacetic acid with *N*-methyl-*N*-phenylacrylamide using a photoredox catalyst with stoichiometric amount of base, because we believe that a suitable photoredox catalyst may oxidize diethoxyacetate to induce radical decarboxylation to deliver diethoxymethyl radical that can be intercepted by the Michael acceptor. The optimized reaction condition is shown in Table 1, equation 1. Mixing diethoxyacetic acid (0.3 mmol), *N*-methyl-*N*-phenylacrylamide (0.2 mmol), and K₂HPO₄ (0.24 mmol) with an

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iridium photoredox catalyst, $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (Ircat.) in N,N-dimethylformamide (DMF) under irradiation at room temperature afforded the desired conjugated addition product in 92% yield. The optimal iridium photoredox catalyst (Ir-cat.) is known for its long excitation life-time and high oxidative potential of excitation state (E $_{1/2}$ *111/11 = +1.21 V vs SCE)¹³ to oxidize carboxylate anion (E^{ox} = +0.95 V vs SCE)⁷. Other metallaphotoredox catalysts, such as Ir(bpy)3, $Ru(bpy)_3Cl_2 \bullet 6H_2O$, and $Ru(bpy)_3$ (PF₆)₂, were screened and were proved to be ineffective due to the short excitation lifetime and low oxidative potential of excitation state (entries 1-3). 4CzIPN is an effective catalyst while the yield is comparably lower than using the iridium catalyst (Ir-cat.) (entry 4). $Ir(ppy)_2(dtbbpy)PF_6$, a catalyst with lower excitationstate oxidative ability is much less effective compared with Ircat. (entry 5). The base also affects the reaction outcome, as among all the inorganic bases tested, K₂HPO₄ appeared to be optimal, while KOAc gave comparable yield (entries 6-8). Interestingly, though a base is required for this reaction to deprotonate diethoxyacetic acid, direct use of sodium diethoxyacetate or lithium diethoxyacetate as reactant gave inferior results (entries 9 and 10). The salts have relatively poor solubility compared with acid in DMF and solubility issue may accounts for the reduced yield.

Table 1 Studies of optimal reaction conditions^a

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O O O H O O B M O H O B M O H O C H O H O C H O C H O C H O H O C B O H O C B O H O C B O H O S mmol	Ir-cat. (2 mo/%) MF (2 equiv.), DMF (2 o ml), blue LEDs, r.t., Ar, 12 h 92%	$(dtbbpy)PF_{6} (ir-cat.)$
entry	changes from standard condition	yields(%)
1	Ir(ppy) ₃ used instead of Ir-cat.	trace
2	Ru(bpy) ₃ Cl ₂ -6H ₂ O used instead of Ir-cat.	trace
3	Ru(bpy) ₃ (PF ₆) ₂ used instead of Ir-cat.	trace
4	4CzIPN used instead of Ir-cat.	71
5	$\ensuremath{\text{Ir}}\xspace[(\ensuremath{\text{ppy}}\xspace)_2(\ensuremath{\text{dtb}}\xspace{\text{byp}}\xspace)]\ensuremath{PF}\xspace_6$ used instead of $\ensuremath{\text{Ir-cat.}}\xspace$	47
6	$\rm Cs_2CO_3$ used instead of $\rm K_2HPO_4$	23
7	Na_2CO_3 used instead of K_2HPO_4	83
8	KOAc used instead of K_2HPO_4	87
9	using sodium 2,2-diethoxyacetate without base	40
10	using lithium 2,2-diethoxyacetate without base	66

^aReaction conditions: diethoxyacetic acid (0.3 mmol), *N*-methyl-*N*-phenylacrylamide (0.2 mmol), **Ir-cat.** (0.004 mmol) and K₂HPO₄ (0.24 mmol) in solvent (2 mL) irradiated by 36 W blue LEDs for 12 h under Ar. Isolated yields.

The reaction scope with respect to the Michael acceptors were studied and demonstrated in Scheme 1. α , β -Unsaturated amides including secondary and tertiary amides are amenable substrates (1, 2). *N*,*N*-diphenyl acrylamide works well to give addition product 3 in 78% yield. For acrylate esters, the

reactions give desired products in moderate to good yields (4-10). The reaction is very efficient for diethyl 2ethylidenemalonate (11) and diethyl 2-benzylidenemalonate (13). Diethyl maleate as substrate gave the product 12 in high yield. For α , β -unsaturated esters, substituent at both α - and β-positions are tolerable (13, 14, 15). Unsaturated ketone (16), aldehyde (17), and nitrile (18) are all amenable substrates showing broad substrate scope. The reaction can tolerate a series of functional groups such as aryl chloride, aryl fluoride, boronate, and N-heteroarenes. Ethyl 3aldehvde. coumarincarboxylate, a natural product derived substrates also works well giving desired product 19 in 54% yield. Besides 2,2-diethoxyacetic acid, other glyoxylic acid acetals such as 4,4,5,5-tetramethyl-1,3-dioxolane-2-carboxylic acid and 5,5dimethyl-1,3-dioxane-2-carboxylic acid also reacted well (20, 21, 22).

Scheme 1 Reaction scope regarding to Michael acceptors and different glyoxylic acid acetals $^{\rm a}$



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^aReaction conditions: acid (0.3 mmol), Michael acceptor (0.2 mmol), **Ir-cat.** (0.004 mmol) and K₂HPO₄ (0.24 mmol) in DMF (2 mL) irradiated by 36 W blue LEDs for 12 h under Ar. Isolated yields. ^bNaOAc (0.3 mmol) was used as the base.

Although the reaction does not work with simple styrene (23) or styrenes possessing electron-withdrawing substituents (see SI for more information), we were delighted to find besides Michael acceptors, 2-vinylpyridine and 4-vinylpyridine were all reactive to give desired products in moderate to good yields (Scheme 2, 24-26). Compared with the recent report by Wang and Mariano where styrene can be used as amenable substrate when 4CzIPN as photoredox catalyst was applied⁸, the redox potential of the radical anion of 4CzIPN (- 1.21 V vs SCE) is higher than the potential of Ir-cat. ($E_{1/2}^{\parallel \parallel / \parallel} = -1.37$ V vs SCE). Thus, from thermodynamic aspect we cannot explain why styrene did not work using the iridium photoredox catalyst. The failure may come from other side effects such as energy transfer between iridium photoredox catalyst and styrene or side reaction of oligomerization of styrene. α -Aryl styrenes are suitable substrates (27, 28).

Scheme 2 Reaction scope regarding to styrene derivatives^a



^aReaction conditions: acid (0.3 mmol), Michael acceptor (0.2 mmol), **Ir-cat.** (0.004 mmol) and K₂HPO₄ (0.24 mmol) in DMF (2 mL) irradiated by 36 W blue LEDs for 12 h under Ar. Isolated yields. ^bNaOAc (0.3 mmol) was used as the base.

We observed an interesting intramolecular selectivity when *N*-methyl-*N*-(4-vinylphenyl)acrylamide was used as substrate. The decarboxylative addition selectively takes place at the electron-deficient acrylamide moiety in 77% yield while leaving the styrene moiety intact. Product of preferential reaction at the styrene moiety of this substrate was not observed. (Figure 2).

Figure 2 Selectivity between electron-deficient olefin and electron-rich olefin



We further demonstrated the synthetic utility of this method by conducting two gram-scale reactions. The yield of gram scale reaction is comparable with small scale reaction. By direct hydrolysis without isolating the acetal product, the desired aldehyde product can be obtained in one pot. (Figure 3).

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Figure 3 Gram scale synthetic application and one-pot aldehyde synthesis



The reaction mechanism should be similar with recently reported various photoredox catalyzed conjugated addition reactions (Figure 4).¹⁴ First, the excited iridium photoredox catalyst can oxidize 2,2-diethoxyacetate anion to induce radical decarboxylation to generate diethoxymethyl radical. The existence of radical intermediate in the reaction was corroborated by a radial-trapping experiment using (2,2,6,6-Tetramethylpiperidin-1-yl)oxy (TEMPO), which showed complete suppression effect (see SI for more information). The diethoxymethyl radical is intercepted by Michael acceptor to generate a more stable radical with stronger oxidative ability to reoxidize the reduced iridium photoredox catalyst back to Ir(III). We cannot entirely exclude a pathway that diethoxymethyl radical competes to oxidize Ir(II) catalyst to generate diethoxymethyl anion to attack Michael acceptor.

Figure 4 Discussion of reaction mechanism



In summary, we have developed an iridium-photoredox catalyst catalyzed decarboxylative conjugated addition of glyoxylic acid acetals with various Michael acceptors, including unsaturated amide, ester, aldehyde, ketone, and nitrile at room temperature under LED irradiation. Vinyl pyridine and α -aryl styrene are also suitable substrates. The reaction offers a new method to access various functionalized acetal products that are of synthetic significance as protected aldehydes.

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