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A Unique 1,2-Acyl Migration for the Construction of Quaternary Carbon by Visible Light Irradiation of Platinum(II) Polypyridyl Complex and Molecular Oxygen

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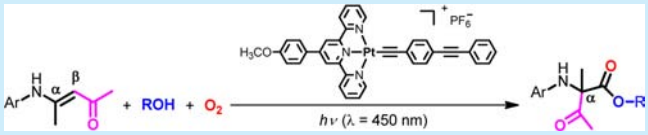
Supporting Information

ABSTRACT: A unique 1,2-acyl migration for the construction of quaternary carbon in a one-pot reaction under visible light is described. By irradiating a platinum(II) polypyridyl complex with visible light, enamine **1** is able to react with alcohol **2** to yield compound **3** featuring a quaternary carbon via 1,2-acyl migration and concurrent esterification. Studies on the mechanism reveal that the platinum(II) complex is able to generate singlet oxygen ($^1O_2$) that is responsible for this unprecedented intramolecular 1,2-acyl migration transformation.



Developing an efficient, atom- and step-economic approach for C−C bond formation is always an important concern for synthetic chemistry. Acyl migration reactions have become a recognized tool for the rapid and concise construction of complex molecules,[1] some of which have been embodied in classical named reactions, for example, the Baker−Venkataraman reaction.[2] Of particular significance is that acyl migration has recently shown promise in the functionalization of carbon or heterocyclic compounds. For instance, Romo et al. reported dyotropic rearrangements involving 1,2-acyl migration to produce spirocyclic, bridged γ-lactones.[3] Fensterbank et al. described a gold-catalyzed transformation of hepta-1,6-diyn-3-yl esters involving a 1,5-acyl shift.[4] Wang et al. employed intermolecular acyl transfer to synthesize diversely substituted pyridines.[5] These achievements demonstrate that the acyl migration reaction is an intriguing subject even though the use of acyl migration to realize the construction of quaternary carbon from acyclic compounds remains challenging.

Here, an unprecedented acyclic 1,2-acyl migration for the efficient construction of a quaternary carbon in a one-pot reaction is reported. Owing to the inherent *green* and *mild* character of light, visible light catalysis[6] has recently appeared at the forefront of organic synthesis. By using Ru(II), Ir(III), Pt(II) complexes and organic dyes eosin Y as photosensitizers, a variety of organic transformations including the aza-Henry reaction,[7] oxidative addition,[8] and cross-coupling reaction[9] have been accomplished in good to excellent yields under ambient conditions. Herein, a platinum(II) polypyridyl complex[10] was used as a photosensitizer to initiate a cross-coupling reaction of enamine **1a** and nucleophiles under visible light irradiation, which is an extension of our previous work on the functionalization of the α-position of nitrogen atom compounds.[11] To our surprise, none of cross-coupling products could be achieved; instead a new product formed exclusively when methanol served as the nucleophile. Close examination of the product skeleton revealed that the migration of the acetyl from the β- to α-position of the nitrogen atom in enamine **1a** takes place accompanied by the ester group formation. Independently, Li et al. reported that visible-light-mediated aerobic oxidation of secondary enaminones by singlet oxygen could afford quaternary amino acid derivatives through the process of 1,2-acyl migration.[12]

The photochemical reaction was carried out at room temperature. As enamine **1a** and methanol **2a** were irradiated in acetonitrile by LEDs (λ = 450 nm) under ambient conditions for 20 h, the acetyl migration product **3a** was obtained in 8% yield (Table 1, entry 1). Solvent screening indicated that chloroform was a more effective reaction medium than tetrahydrofuran, trifluorotoluene, and dichloromethane for the transformation (Table 1, entries 2−5). Direct use of methanol to replace chloroform enhanced the yield of **3a** greatly (Table 1, entry 6). More excitingly, the reaction was accelerated from 20 to 1.5 h of irradiation when molecular oxygen was employed instead of air (Table 1, entry 7). It is clear that molecular oxygen plays a crucial role in this unique 1,2-acyl migration transformation.

Compared with famous ruthenium(II) complex $Ru(bpy)_3^{2+}$ that is widely applied in visible light catalysis,[6,8,9,12] the platinum(II) polypyridyl complex has shown superior reaction activity; i.e., 0.5 mol % of the platinum(II) complex enables generation of 1,2-acyl migration product **3a** in 66% yield, while, under the same conditions, $Ru(bpy)_3^{2+}$ is less effective and affords **3a** in a 50% yield (Table 1, entries 11 and 12). Additionally, other photosensitizers were employed for this transformation, yet inferior results were obtained (Figure S1).

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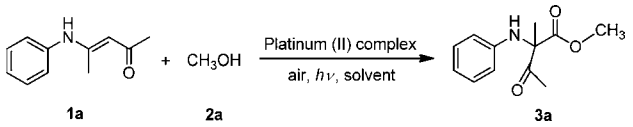
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	solvent	conditions	yield (%)[b]
1	CH_3CN	air, $h\nu$	8
2	THF	air, $h\nu$	0
3	Ph−CF_3	air, $h\nu$	30
4	CH_2Cl_2	air, $h\nu$	33
5	$CHCl_3$	air, $h\nu$	38
6	CH_3OH	air, $h\nu$	60
7	CH_3OH	O_2, $h\nu$	66
8[c]	CH_3OH	O_2, $h\nu$	0
9[d]	CH_3OH	O_2	0
10	CH_3OH	N_2, $h\nu$	0
11[e]	CH_3OH	O_2, $h\nu$	66
12[f]	CH_3OH	O_2, $h\nu$	50
13[g]	CH_3OH	O_2, $h\nu$	52

[a]Unless otherwise specified, 0.1 mmol of **1a**, 2 mmol of **2a**, and 0.001 mmol of platinum(II) complex in 2 mL of the solvent under corresponding conditions; irradiation of LEDs (blue light) at rt. [b]Isolated yields. [c]In the absence of platinum(II) complex. [d]The reaction was carried out in the dark. [e]0.0005 mmol of platinum(II) complex was used. [f]$Ru(bpy)_3(PF_6)_2$ was used instead of platinum(II) complex as the photosensitizer. [g]0.0001 mmol of Pt(II) complex was used.

Further decreasing the amount of the platinum(II) complex to 0.1 mol % could also promote the process, albeit in low efficiency (Table 1, entries 13). More importantly, the reaction can smoothly proceed at gram scale with reasonable yield with visible light irradiation of 0.5 mol % of platinum(II) polypyridyl complex in an oxygen atmosphere (Scheme S1).

Such an effective transformation might not be a free radical mechanism because no alternation could be observed in the reactivity when radical-trapping reagent 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added into the solution under the same conditions (Scheme S2). To understand the primary process of the reaction, control experiments were carried out and results indicated that each component, the platinum(II) complex, molecular oxygen, and light, was essential for the 1,2-acyl migration reaction of enamine **1a** and methanol **2a**. The absence of the platinum(II) complex resulted in no conversion of **1a** under the same conditions (Table 1, entry 8), and no reaction could be detected when the reaction was conducted in the dark (Table 1, entry 9). Obviously, the 1,2-acyl migration is achieved by an aerobic photochemical reaction.

It is established that the photoexcited platinum(II) complex can react with molecular oxygen to generate singlet oxygen ($^1O_2$)[10] or the superoxide radical anion ($O_2^{\bullet-}$)[11a] to facilitate organic transformations. In order to determine the active species of oxygen involved in the present work, we employed 2,2,6,6-tetramethylpiperidine (TEMP) and 5,5-dimethyl-pyrroline-*N*-oxide (DMPO) to capture $^1O_2$ and $O_2^{\bullet-}$, respectively.[13] Irradiation of the methanol solution of TEMP and the platinum(II) complex in air by blue LEDs resulted in the formation of the characteristic signal of the $^1O_2$ adduct with TEMP (Figure 1a and 1b), similar to our previous observation.[10b,c] When enamine **1a** was added into the solution, the TEMPO signal disappeared immediately, suggesting that enamine **1a** reacted with $^1O_2$ efficiently to consume it completely

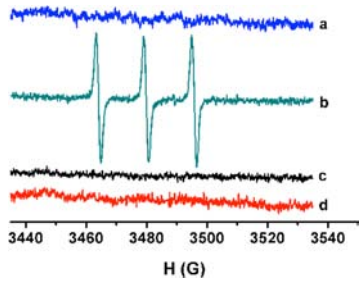
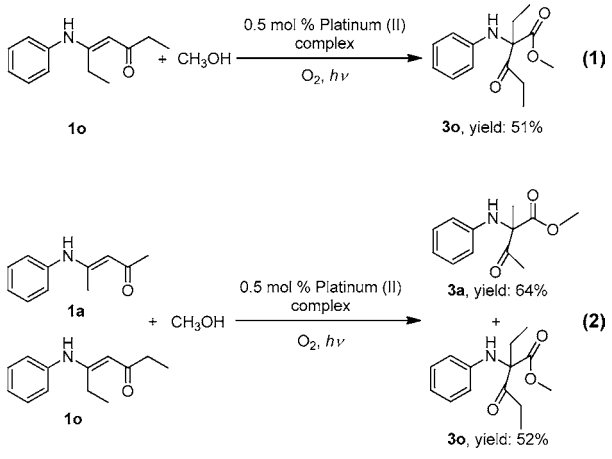


Figure 1. Electron spin resonance (ESR) spectrum: (a) a solution of TEMP (0.12 M), platinum(II) complex (2.5×10^{-4} M) in air-saturated CH_3OH without irradiation; (b) a solution of TEMP (0.12 M), platinum(II) complex (2.5×10^{-4} M) in air-saturated CH_3OH upon irradiation with LEDs (blue light) for 30 s; (c) **1a** (5.0×10^{-2} M) was added into the above solution (b) quickly; (d) a solution of **1a** (5.0×10^{-2} M), DMPO (2.0×10^{-2} M), and platinum(II) complex (2.5×10^{-4} M) in air-saturated CH_3OH upon irradiation with LEDs (blue light) for 30 s.

once generated in the reaction system (Figure 1c). On the other hand, when DMPO, an $O_2^{\bullet-}$ scavenger, was used instead of TEMP in the same air-saturated solution, the $O_2^{\bullet-}$ adduct with DMPO was hardly detected in the presence of **1a** (Figure 1d). From these results, we believe that the active species of oxygen responsible for the reaction is $^1O_2$ rather than $O_2^{\bullet-}$.

To shed more light on the mechanistic pathway for the 1,2-acyl migration process, a crossover experiment was conducted. Irradiation of **1o** and methanol **2a** under aerobic visible light (λ = 450 nm) resulted in the propionyl migration from the β- to α-position of the nitrogen atom, giving rise to the desired product **3o** in 51% yield (Scheme 1, eq 1). Treatment of

Scheme 1. Crossover Experiments



equimolar amounts of enamines **1a** and **1o** with methanol **2a** under the same conditions produced 1,2-acyl migration product **3a** and **3o** in a yield of 64% and 52%, respectively (Scheme 1, eq 2). No crossover product could be detected by ^1H NMR and ESI-HRMS analysis throughout irradiation, indicating that the 1,2-acyl migration occurs in an intramolecular fashion.

Next, we designed a set of experiments with an ^{18}O labeled substrate to identify the source of oxygen in the reaction. To exclude that the oxygen in product **3** may be from H_2O in the system, equimolar amounts of H_2O^{18} was first introduced into the reaction system. The product obtained is the same as the 1,2-acyl migration product **3a** with m/z = 221 (Scheme S3, eq 1).

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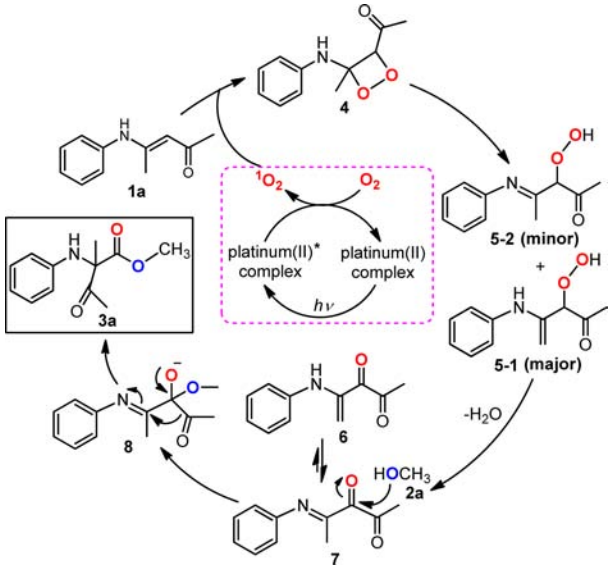
However, when $^{18}O_2$ was used to replace $^{16}O_2$, the 1,2-acyl migration product **3p** showed the m/z peak at 223 evidenced by HR-MS analysis (Scheme S3, eq 2). Furthermore, when deuterated CD_3OD was selected to react with enamine **1a**, the methyl adjacent to the quaternary carbon was partially deuterated in addition to the totally deuterated methyl of the ester group, and the ratio of **3r** and **3s** was noted as 1:1.8, which indicated that hydrogen abstraction from the methyl evolved primarily over other approaches (Scheme S3, eq 3). From these observations together with the fact that the ester group depends on the alcohol used, it is reasonable to consider that the oxygen of carbonyl in the newly formed ester group is from molecular oxygen.

On the basis of above results, we proposed a general mechanism for the 1,2-acyl migration reaction (Scheme 2).

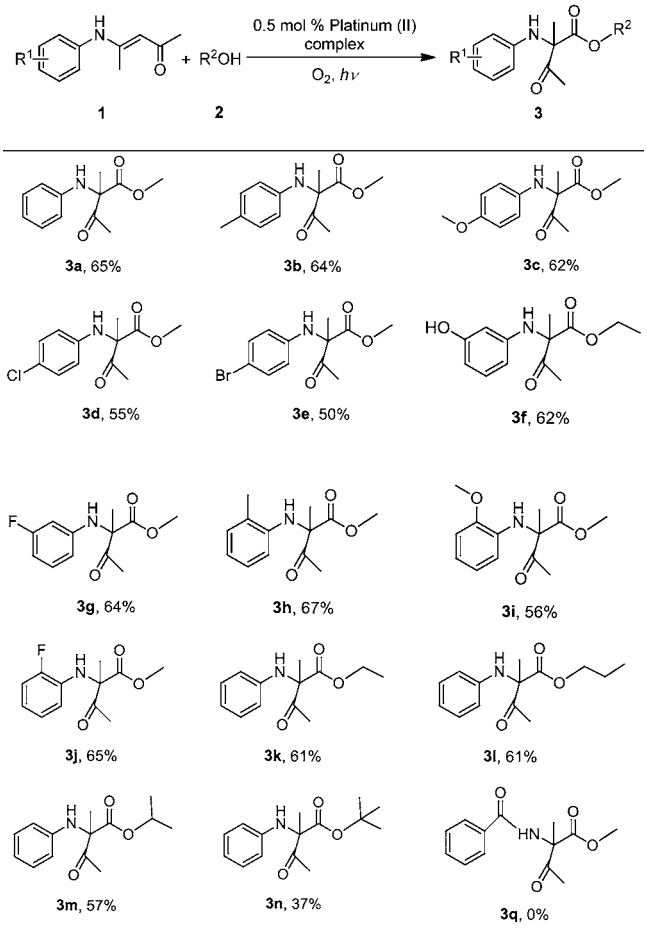
Scheme 2. Proposed Mechanism



Upon visible light irradiation, the platinum(II) complex is pumped to its excited state of ^{3}[MLCT] (metal-to-ligand-charge-transfer state),[10] which is able to interact with molecular oxygen to generate singlet oxygen $^1O_2$, and at the same time to restore the platinum(II) complex to its ground state by an energy transfer pathway.[14] The generated $^1O_2$ is reacted with the electron-rich double bond[14] of enamine **1a** leading to the formation of dioxetane intermediate **4** (Scheme 2). As shown in the deuterium experiment, the hydrogen abstraction by dioxetane intermediate **4** from the allylic hydrogen at the methyl adjacent to the nitrogen atom occurs to give rise to hydroperoxide **5-1**. Subsequent elimination of one molecular H_2O from **5-1** produces dicarbonyl intermediate **6**, which further tautomerizes into more stable imine **7**. Alternatively, the hydrogen abstraction by dioxetane intermediate **4** directly from the nitrogen can give hydroperoxide **5-2**, which would be also transformed into imine **7**. The formed imine **7** is further attacked by methanol **2a** to yield intermediate **8**, which undergoes intramolecular 1,2-acyl migration from the β- to α-position of the nitrogen atom to consequently deliver the target quaternary carbon product **3a**.

With an understanding of the reaction mechanism, we explored the generality of the 1,2-acyl migration reaction on the scope of enamines **1**. When electron-donating and -withdrawing groups were introduced at different positions of the phenyl in enamines **1**, the desired 1,2-acyl migration product could be obtained smoothly (Scheme 3). In particular, the

Scheme 3. Substrate Scope of 1,2-Acyl Migration Reactions[a,b]



[a]General conditions: 0.1 mmol of **1** and 0.0005 mmol of platinum(II) complex in 2 mL of the corresponding solvent **2** saturated with molecular oxygen under the irradiation of LEDs (blue light) at rt. [b] Isolated yields.

products containing chloro-, bromo-, fluoro-, or hydroxy functionalities can serve as potential intermediates for further modification of the quaternary carbon. Note that the substrate **1** with a methyl or methoxy group at the ortho-position showed decreased efficiency, probably due to the steric hindrance. When alcohols, i.e. ethanol, *n*-propanol, or even isopropanol, were examined, on the other hand, both 1,2-acyl migration and esterification proceeded efficiently (Scheme 3, **3k**, **3l**, and **3m**). Due to steric hindrance, *tert*-butanol also displayed a relatively low reactivity (Scheme 3, **3n**). Meanwhile, the lower electron density of the double bond C═C of the benzoyl enamine renders the addition of $^1O_2$ inefficiently, thereby leading to no reaction at all (Scheme 3, **3q**).

In summary, we have developed an unprecedented approach for the synthesis of a quaternary carbon through the process of intramolecular 1,2-acyl migration. The mild and simple reaction is accomplished under an aerobic atmosphere at room temperature. Upon visible light irradiation (λ = 450 nm) of the platinum(II) polypyridyl complex and molecular oxygen, enamine **1** is able to react with alcohol **2** to yield compound **3** featuring a quaternary carbon via 1,2-acyl migration and

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concurrent esterification. ESR measurement, crossover, and isotope experiments demonstrate that singlet oxygen ($^1O_2$) is responsible for the unique intramolecular 1,2-acyl migration and the oxygen of the carbonyl in the newly formed ester is from molecular oxygen. Exploration of this unique acyl migration as a key step for the construction of quaternary carbons occurring in natural bioactive molecules is actively being carried out in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, methods, and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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