Acyl Oxime Ester

Subjects: Chemistry, Organic

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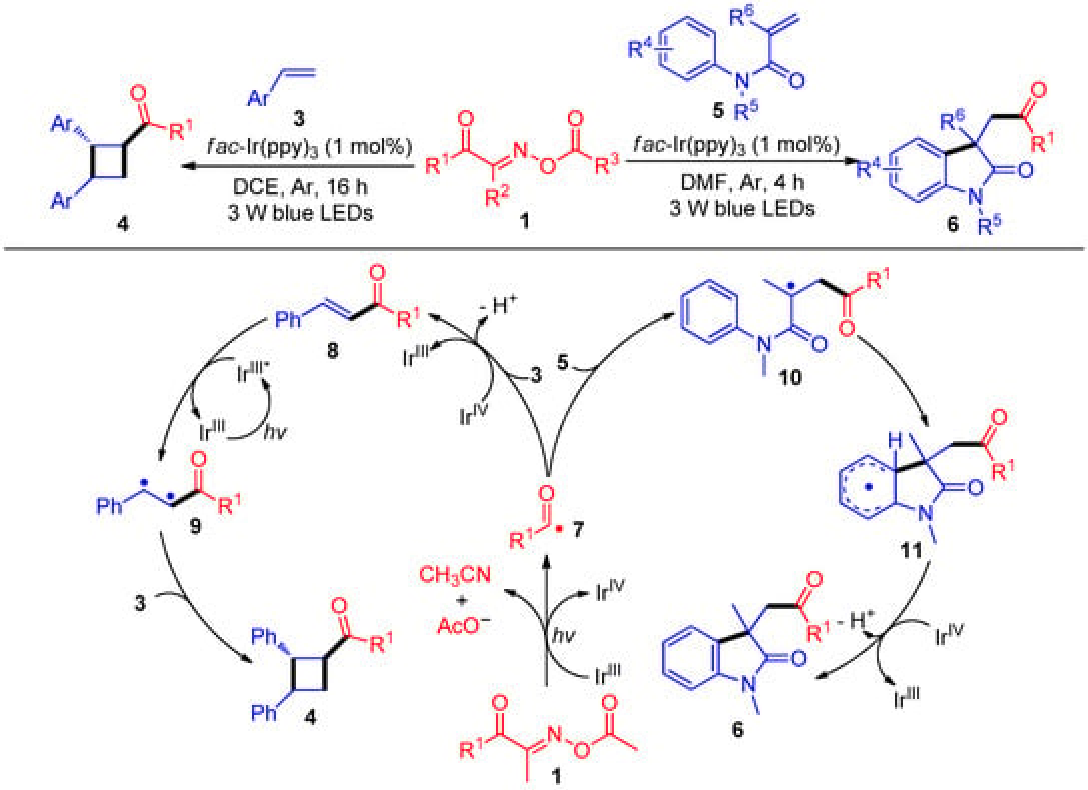
The synthetic strategies of oxime derivatives participating in radical-type reactions have been rapidly developed in the last few decades. Among them, the N–O bond cleavage of oxime esters leading to formation of nitrogen-centered radicals triggers adjacent C–C bond cleavage to produce carbon-centered free radicals, which has been virtually used in organic synthesis in recent years.

radical reactions oxime ester C-C bond cleavage

1. Radical Addition

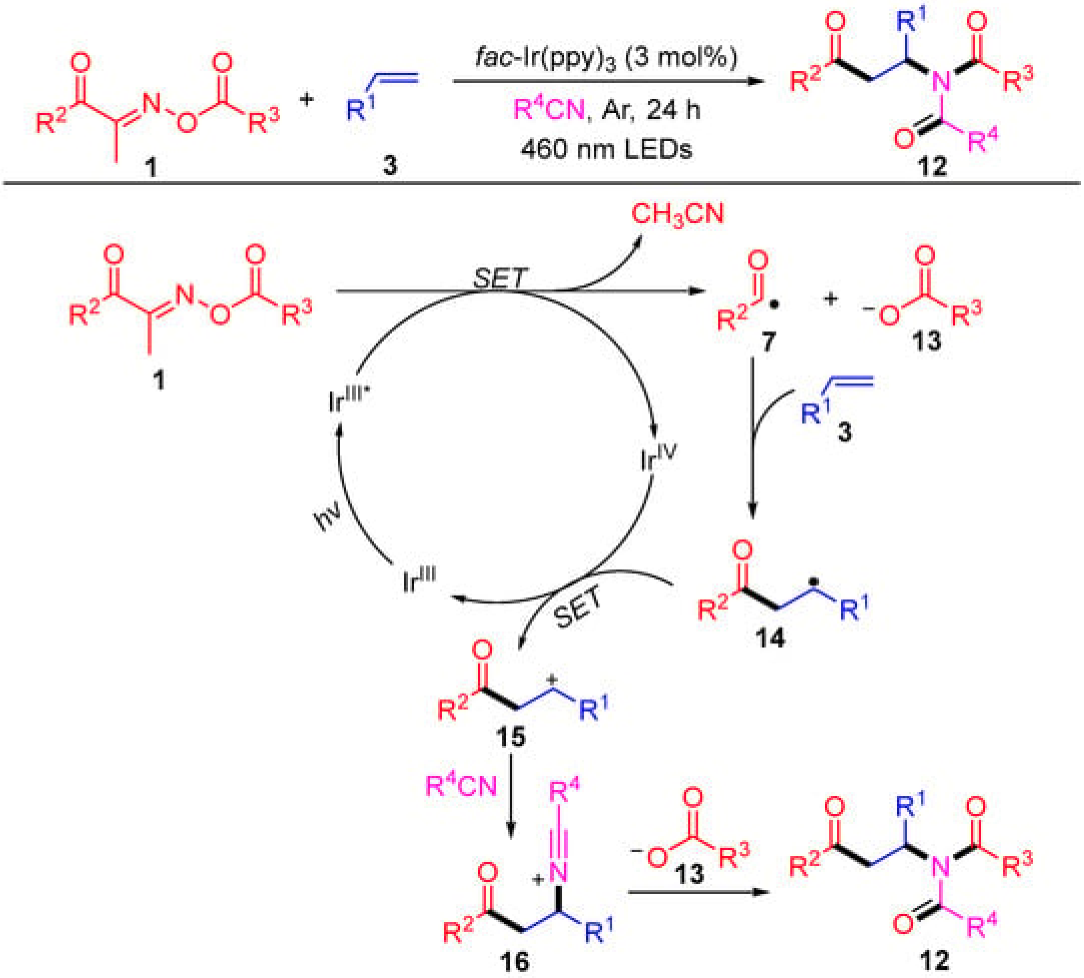
1.1. Acyl Addition to Alkenes

In 2019, the Wu and Tung group demonstrated a groundbreaking example of acylation/cyclization of Michael acceptors with acyl radicals derived from acyl oxime esters **1** with C–C bond cleavage. Hence, cyclobutyl ketone derivatives **4** and acylated oxindoles **6** were obtained using *fac*-Ir(ppy)$_3$ as a photosensitizer at room temperature (Scheme 1) [1]. The mechanism studies show that the acyl oxime esters **1** are first reduced by a Ir^{III} catalyst under 3 W blue-light conditions, and then the acyl radicals **7** are produced by C–C bond cleavage. On the one hand, the acyl radical **7** is captured by styrene **3** and oxidized by Ir^{IV} to remove a proton to produce enone **8**, which is sensitized by Ir^{III*} to further react with another styrene **3** to lead to cross [2 + 2] cyclization and obtain acylated cyclobutanones derivatives **4**. Alternatively, acyl radicals **7** could also add to the C–C double bond of the acrylamides **5** to afford structurally useful acylation oxindole skeletons **6**.



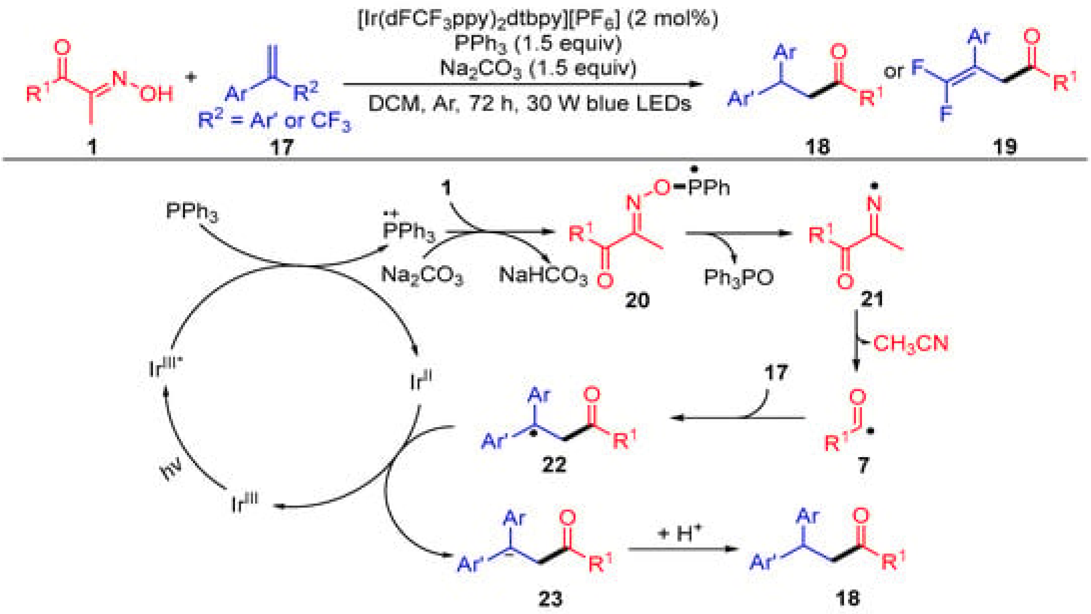
Scheme 1. Visible-light-induced radical acylation/cyclization of acyl oxime esters with olefins.

In the same year, this group reported a novel three-component difunctionalization reaction of acyl oxime esters, olefins and alkane nitriles, which generated a series of β-carbonyl imides **12** with excellent yields (Scheme 2) [2]. The isotope tracking experiment and control experiments revealed the efficient intermolecular reorganization of oxime esters into styrene with the aid of solvent exchange. A possible reaction mechanism is shown in Scheme 2. First, the acyloxime esters **1** are cleaved to nitrile, carboxylate anions **13** and acyl radicals **7** by a single electron transfer (SET) process with the excited state Ir^{III*}, which is generated from Ir^{III} under blue-light irradiation. Then, a SET occurs between intermediate **14**, which is produced by the addition of an acyl radical **7** to the olefin **3** and Ir^{IV} to complete the cycle of catalyst Ir and produce the carbocation **15**. The intermediate **16**, produced by the nucleophilic attack of nitrile to cation **15**, undergoes a Mumm rearrangement with carboxylate anions **13** to obtain the amide products **12**.



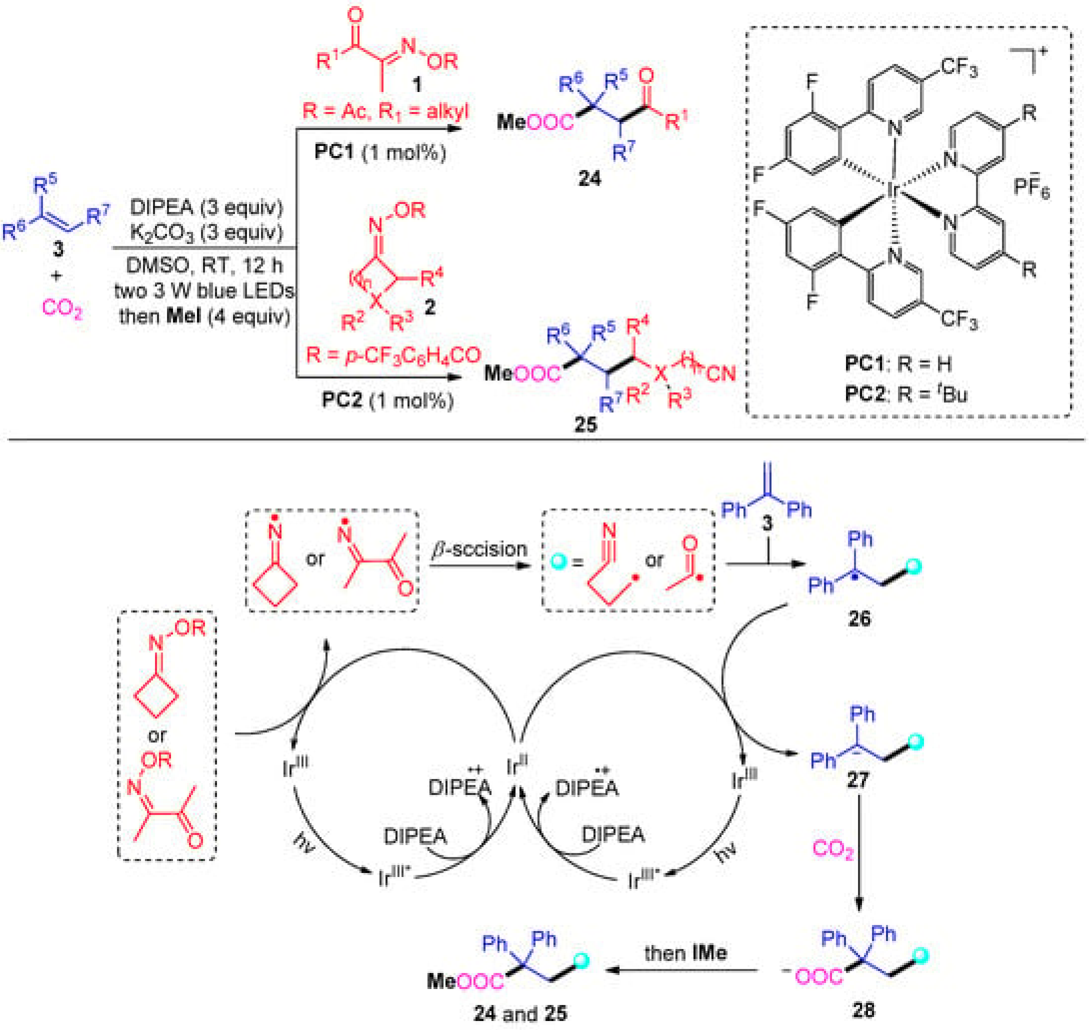
Scheme 2. Visible-light-induced radical difunctionalization of acyl oxime esters with styrenes and nitriles.

A photocatalytic hydroacylation of alkenes with acyl oximes for the synthesis of valuable ketones was developed by Yang et al. (Scheme 3) [3]. When CF_3-attached styrenes were used, a E1cB-type fluoride elimination pathway was proposed for the obtainment of the 1,1-difluoroolefin products **19**. In this difunctionalization reaction, the triphenylphosphine radical cation generated by the reaction of the excited catalyst Ir^{III*} with triphenyl phosphine combines with the nucleophile acyl oximes **1** to obtain the phosphorus radical intermediate **20**. The N–O bond cleavage of the intermediate **20** gives the iminyl radical **21** via β-scission. The imino radical **21** undergoes C–C bond scission to give acyl radical **7** and a molecule of acetonitrile. The acyl radical is added to alkene **17** and reduced by Ir^{II} to get the carbanion intermediate **23**, with the following protonation to generate the desired product **18**.



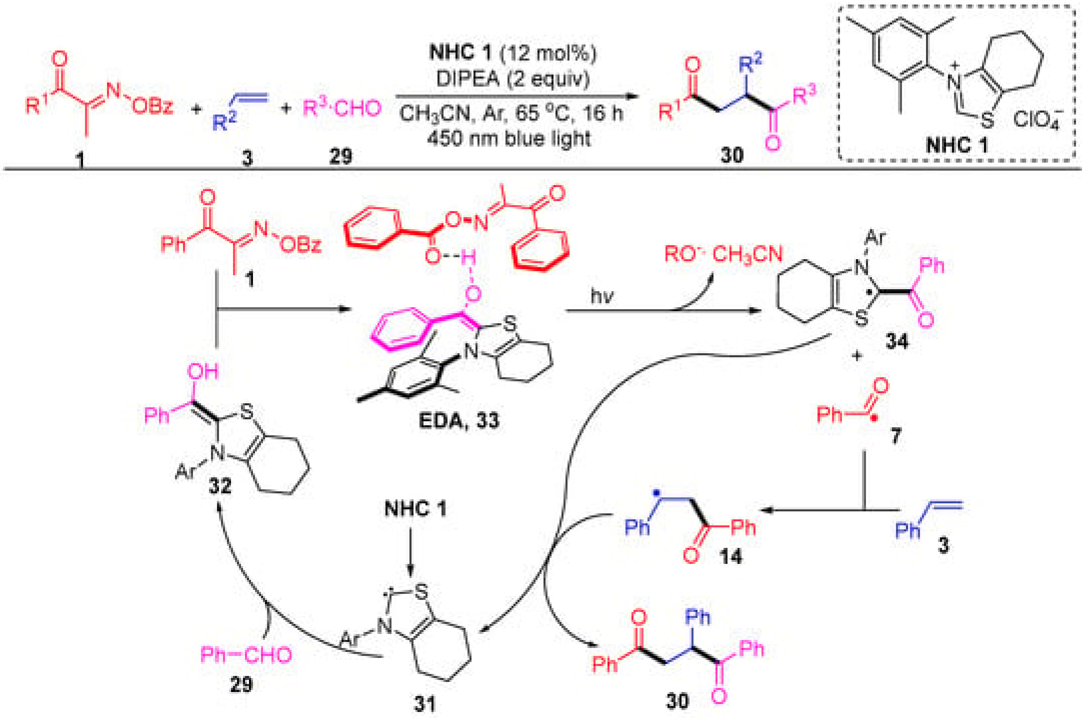
Scheme 3. Visible-light-induced hydroacylation of acyl oximes with alkenes.

In 2021, Sun and co-workers developed a distinctive carbonylation approach using Ir and DIPEA to access γ-keto acids **24** and cyanocarboxylic acids **25** (Scheme 4) [4]. Mechanistically, this reaction involves the photocatalytic radical addition of acyl radicals and cyanoalkyl radicals to aromatic olefins and then carbon dioxide capture. The valuable dicarbofunctionalization tolerates a wide range of cyclic ketoxime substrates; however, only aliphatic acyl oxime esters proceed smoothly to afford corresponding γ-keto ester products.



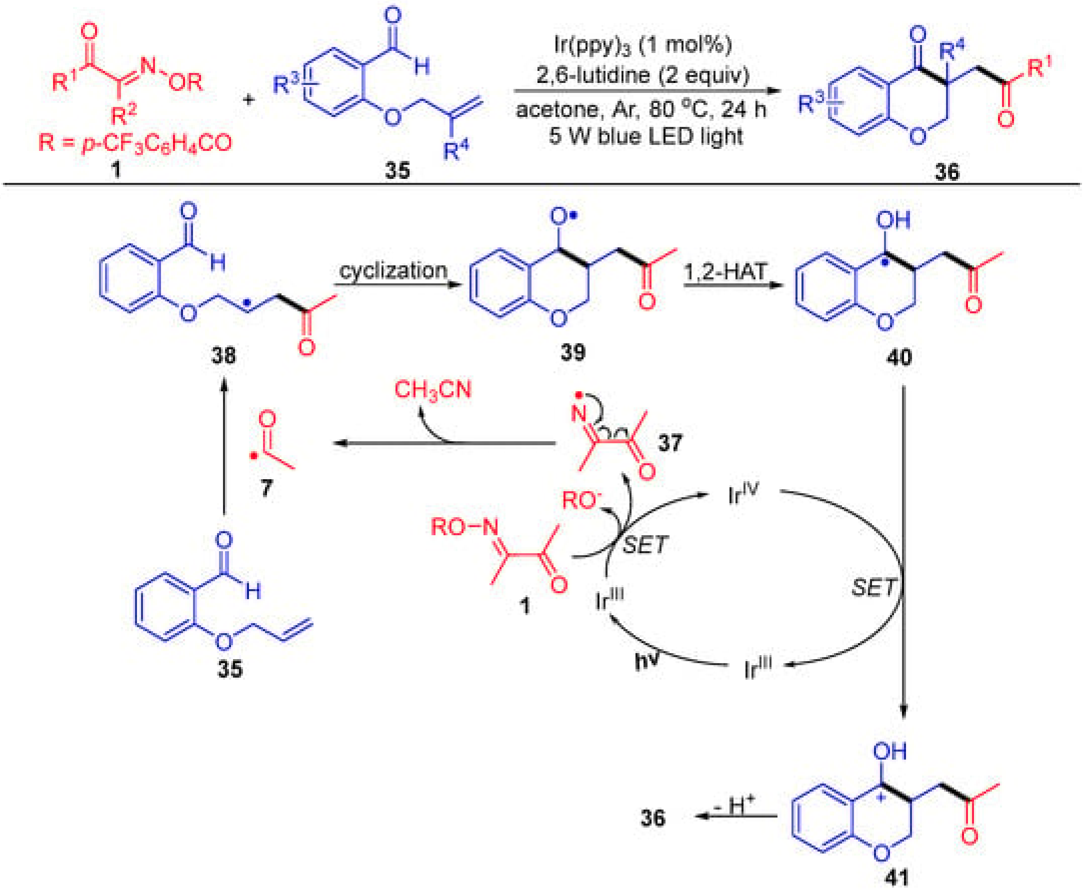
Scheme 4. Visible-light photoredox-catalyzed dicarbofunctionalization of styrenes with oxime esters and CO_2.

Larionov's group described a *N*-heterocyclic, carbene-photocatalyzed, three-component regioselective 1,2-diacylation of alkenes, using acyl oxime esters and aldehydes as two different acylating agents (Scheme 5) [5]. In particular, the authors demonstrated the mechanism by density functional theory (DFT) and time-dependent-DFT (TD-DFT), where an EDA intermediate is probably formed in the diacylation, which initiates photoexcitation to mediate charge transfer. The EDA intermediate **33**, formed by the complexation of the Breslow intermediate **32** with the acyl oxime ester **1**, is excited under light conditions and subsequently cleaved to remove BzO^- and acetonitrile to give the intermediate **34** and acyl radical **7**. The intermediate **14** produced by the addition of the acyl radical **7** to the olefin **3** couples with the intermediate **34** and then decomposes to a diketone product **30** and carbene **31**.



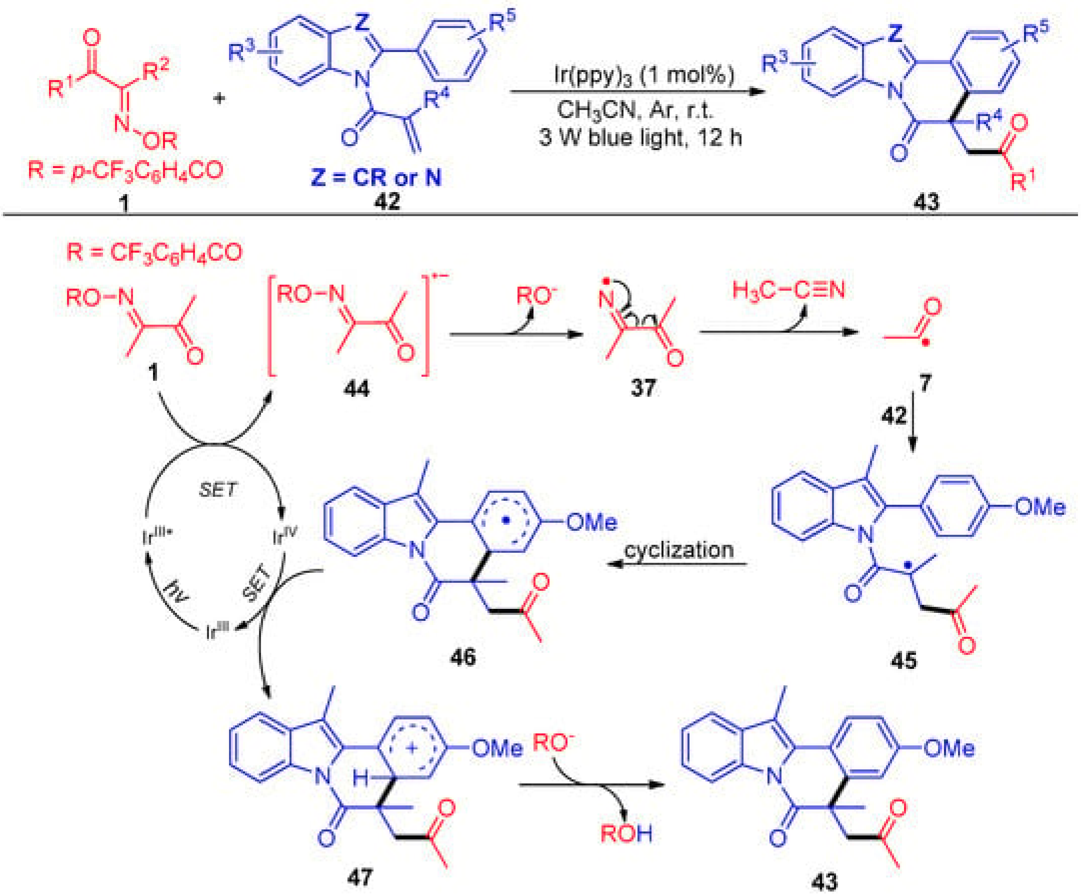
Scheme 5. *N*-heterocyclic carbene-photocatalyzed 1,2-diacylation of alkenes with acyl oxime esters and aldehydes.

Liu and Huang's group reported an intriguing route to 3-acyl-substituted chroman-4-one derivatives **36**, which involves SET reduction of acyl oxime esters **1** by *fac*-Ir(ppy)$_3$ under thermal and light conditions (Scheme 6) [6]. In this functionalization reaction, the acyl radical generated from the acyl oxime ester first adds to the carbon double bond of the 2-allyloxy benzaldehydes **35**, followed by intramolecular cyclization and 1,2-HAT (hydrogen atom transfer) to obtain the alcohol radical intermediate **40**. Finally, SET oxidation by Ir^{IV} and deprotonation occur to obtain the target products **36**.



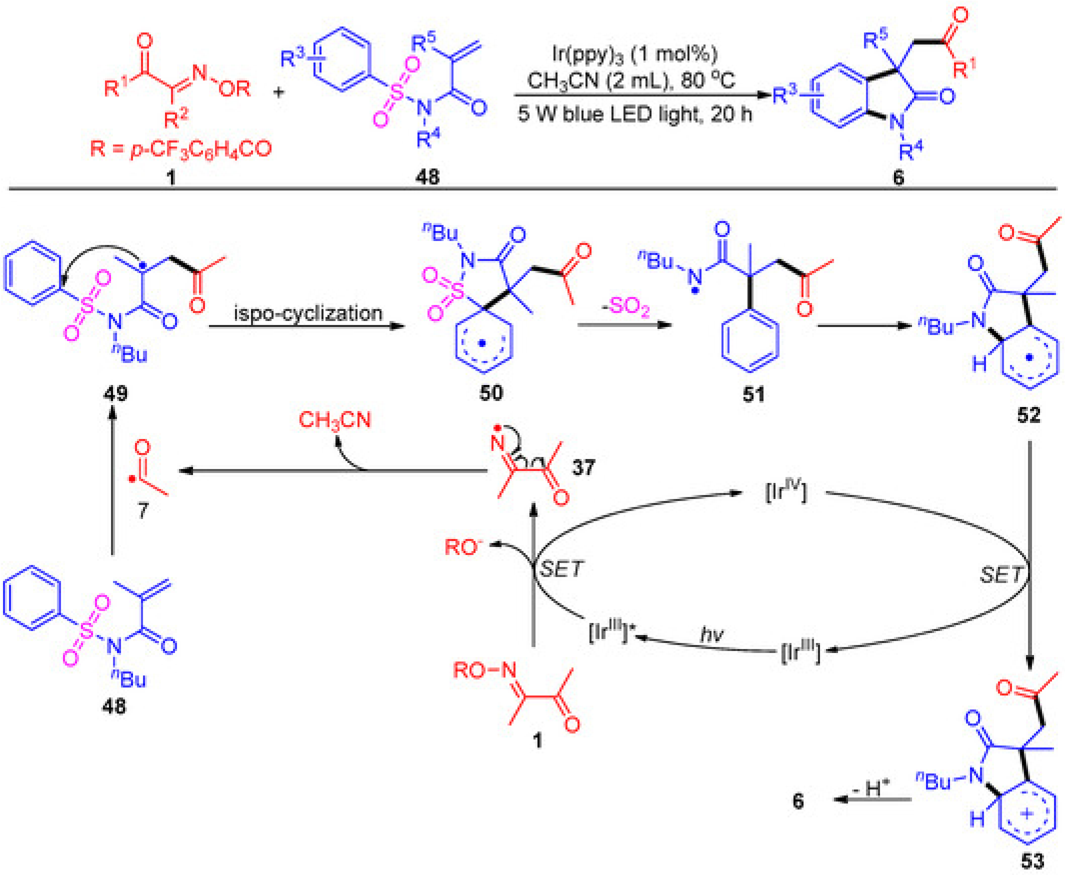
Scheme 6. Visible-light-induced acylation of acyl oxime esters with 2-allyloxy benzaldehydes.

Another acylation/cyclization strategy mediated by a photocatalytic nitrogen-centered radical of acyl oxime esters **1** with activated acrylamides **42** was reported by Liu and Huang's group (Scheme 7) [7]. The authors screened a variety of acyl oximes with different leaving groups, such as 4-$CF_3C_6H_4CO$, 4-$NO_2C_6H_4CO$, C_6F_5CO, CF_3CO, etc., and achieved up to 95% yields with 58 synthetic examples of acylated transformations. The fragmentation of one C–C bond and one N–O bond and the formulation of two new C–C bonds were carried out in one-pot conditions with a low catalyst loading (1 mol%). This protocol represents a simple and green road for the synthesis of acylated indolo/benzimidazo-[2,1,a]isoquinolin-6(5*H*) ones.



Scheme 7. Visible-light-induced acylation of acyl oxime esters with reactive olefins.

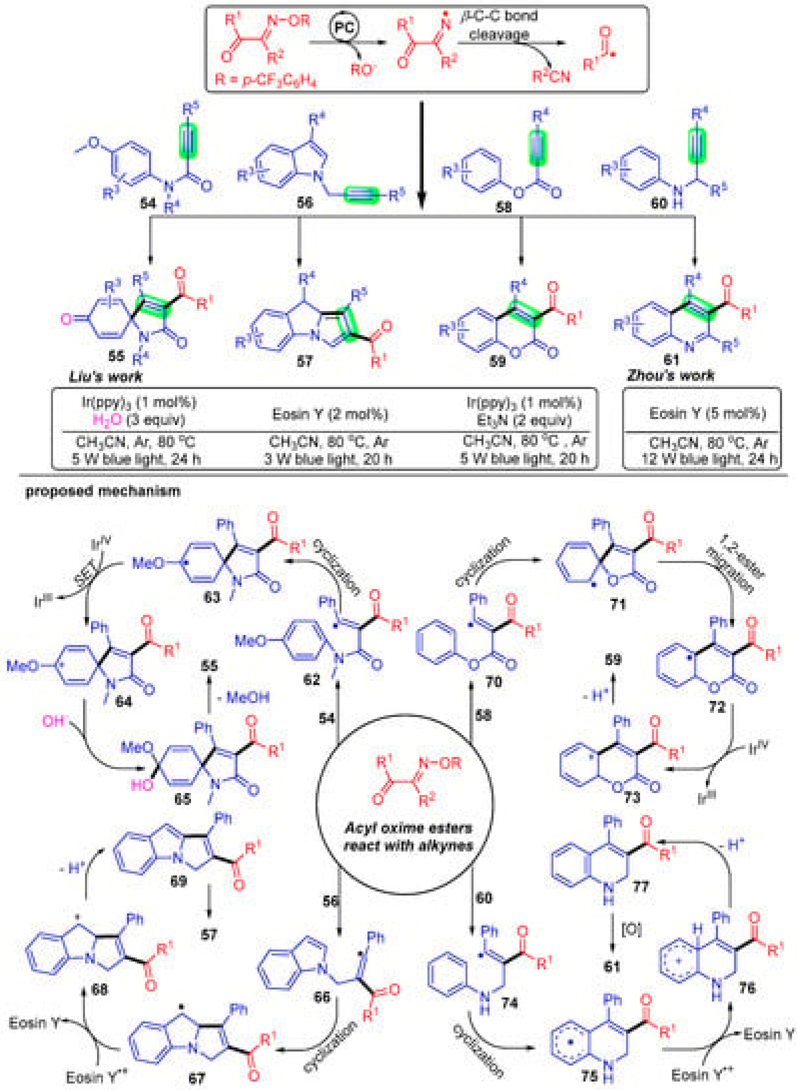
Most recently, the same group uncovered a new acylation reaction of acyl oxime esters with activated *N*-sulfonyl acrylamides **48,** with a broad substrate scope and good functional group compatibility (Scheme 8) [8]. This method provides an effective nitrogen center-mediated approach for the generation of acyl radical intermediates to access acylated oxindole **6**. This acylation transformation proceeds through a normal Smiles rearrangement process that involves cascade intramolecular *ispo*-cyclization (**50**), de-SO_2 (**51**) and re-cyclization (**52**).



Scheme 8. Visible-light-induced acylation of acyl oxime esters with *N*-(arylsulfonyl)acrylamides.

1.2. Acyl Addition to Alkynes

The heterocyclic skeleton presents in commercial drugs and many naturally occurring compounds; thus, the development of convenient and environmentally friendly methods for the construction of this structural motif is an important and promising research field [9][10][11]. Alkynes with specific substituents, such as alkyne amides [12][13][14], *N*-propylindoles [15][16][17], alkyne esters [18][19], alkyne amines [20][21][22], etc., are often used as radical acceptors to construct potential heterocyclic compounds by tandem cyclization. Recently, Liu and Zhou have independently developed a multitude of innovative photocatalytic, nitrogen-centered, radical-mediated acylation strategies of reactive alkynes using acyl oxime esters as acyl sources (Scheme 9) [23][24][25][26].



Scheme 9. Visible-light photoredox-catalyzed acylation of alkynes with acyl oxime esters.

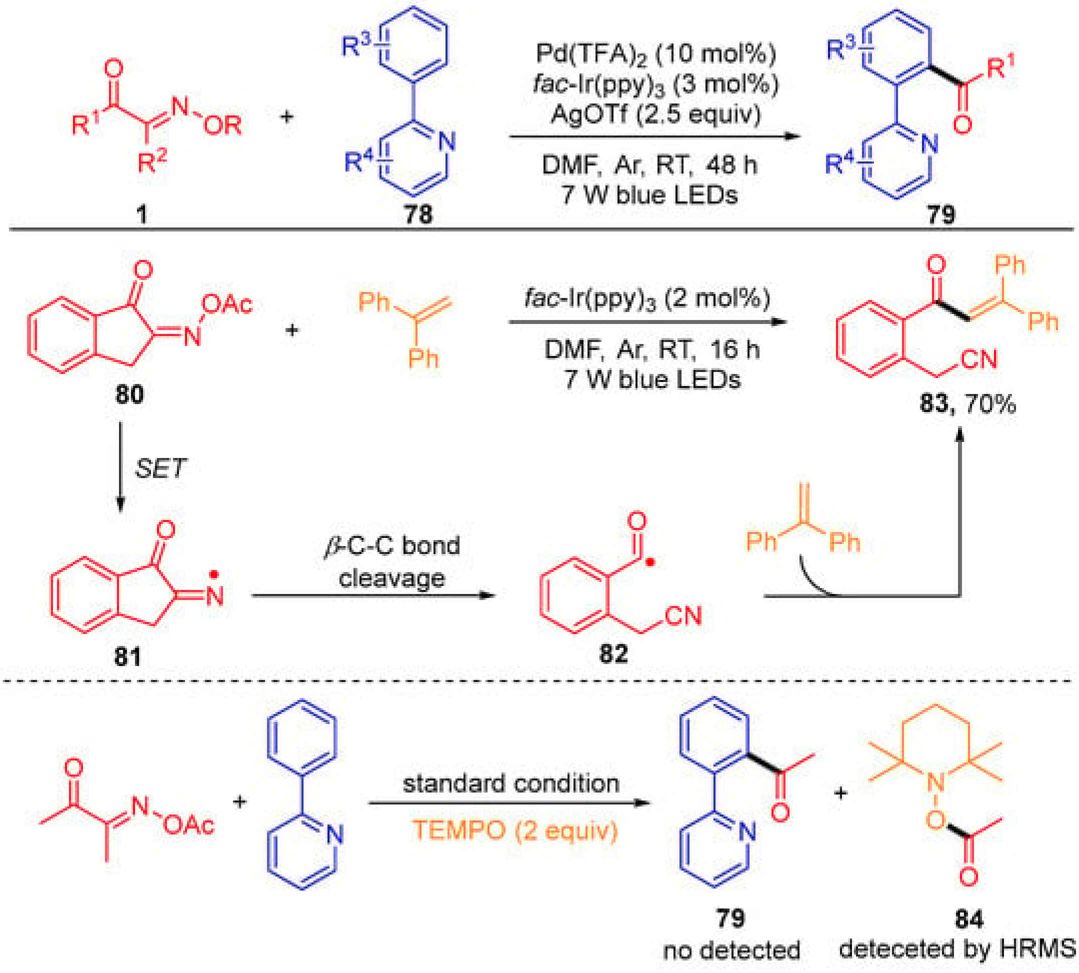
Liu's group pioneered a radical addition strategy of acyl oxime esters **1** with activated alkynes **54** to construct a series of 3-acylated spiro [4,5]trienones derivatives **55** [23]. The acyl radical generated by the C–C bond breakage of acyl oxime esters attacks the carbon–carbon triple bond of propiolamides **54** to give the radical intermediate **62**. The intermediate **62** undergoes intramolecular *ispo*-cyclization and is oxidized to carbocations **64** by Ir^{IV}, followed by the combination with hydroxide anion produced in water to obtain the intermediate **65**. Finally, a methoxy anion and hydrogen ion are removed to obtain the expected trienone product **55**.

Subsequently, Liu's group developed two pragmatic acylation strategies using *N*-propynylindoles **56** [26] and alkynoates **58** [25] under photoexcitation conditions. A large quantity of acylated pyrrolo[1,2-*a*]indole **57** and coumarin **59** derivatives were constructed, and interestingly, both the alkanoyl and aryl groups were well adapted. These studies further developed the application of acyl oxime esters and were of great importance for the development of free radical synthetic chemistry.

Comparably, Zhou’s group has achieved a series of constructions of 3-acyl quinoline skeleton **61** under photocatalytic conditions with *N*-propargyl aromatic amines **60** as radical acceptors [24]. The mechanism of this acylation reaction states that acyl radicals add to the carbon–carbon triple bond of *N*-propargyl aromatic amines **60** for intramolecular cyclization and then proceed to dehydroarylation to give the final quinoline product **61**.

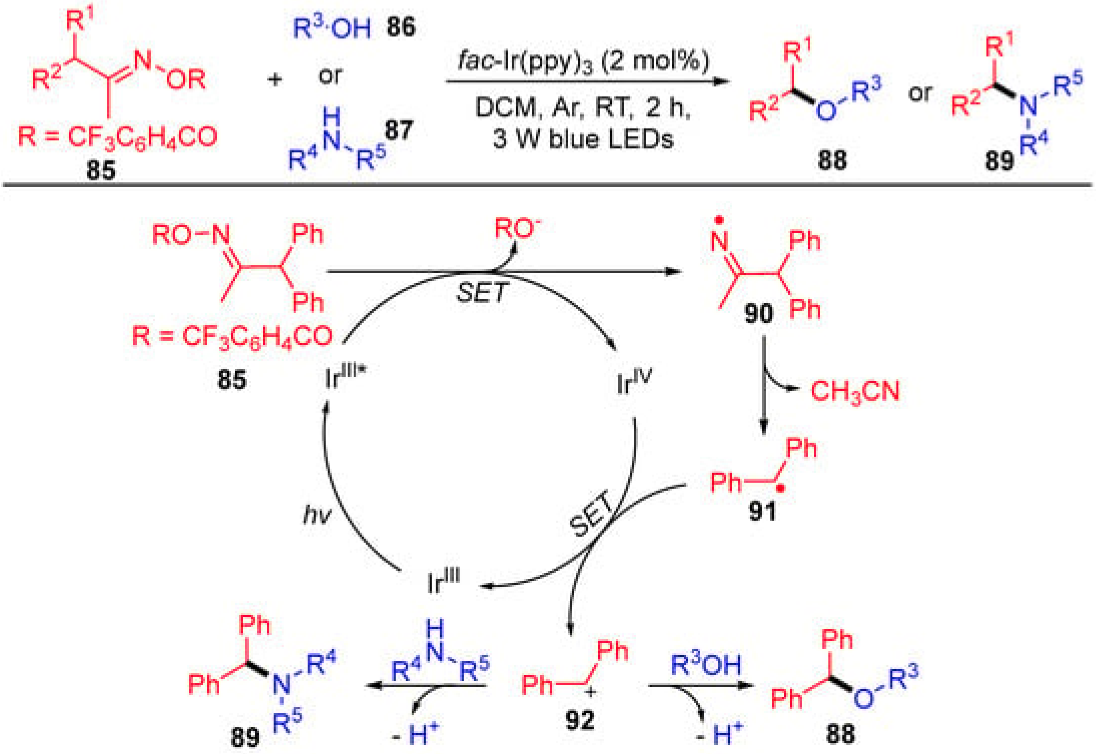
2. Radical Cross-Couple

Recently, the development of the photoredox/palladium-catalyzed C-H acylation of 2-arylpyridines **78** with acyl oxime esters **1** using *fac*-Ir(ppy)$_3$ as a photosensitizer was reported by the Chen group (Scheme 10) [27]. In order to thoroughly study the reaction mechanism, the author carried out some control experiments, including the radical clock reaction using benzocycloketoxime ester **80** with ethene-1,1-diyldibenzene under standard conditions and TEMPO as a radical inhibitor to test the activity of the reaction. The generation of the target product **83** and the detection of the free radical capture product **84** by the HRMS indicate that this acylation reaction contains a free radical mechanism.



Scheme 10. Photoredox/palladium-catalyzed C-H acylation of 2-arylpyridines with acyl oxime esters.

In addition to the above acyl oxime esters, Wu's group reported the benzyl oxime esters **85** with the same reaction mode, i.e., a single electron transfer followed by carbon–carbon bond cleavage to produce the corresponding radical (Scheme 11) [28]. The resulting benzyl radicals **91** are further oxidized to benzyl carbocation **92**, which are then coupled with O and N-nucleophilic reagents to access the target benzyl ethers **88** and benzylamines **89**. This benzylation strategy well tolerates various functional groups under mild conditions, where a wide range of nucleophilic substrates, such as primary and secondary alcohols, amines and even H_2O, worked smoothly.



Scheme 11. Visible-light-induced coupling of benzyl oxime esters with O- and N- nucleophiles.

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