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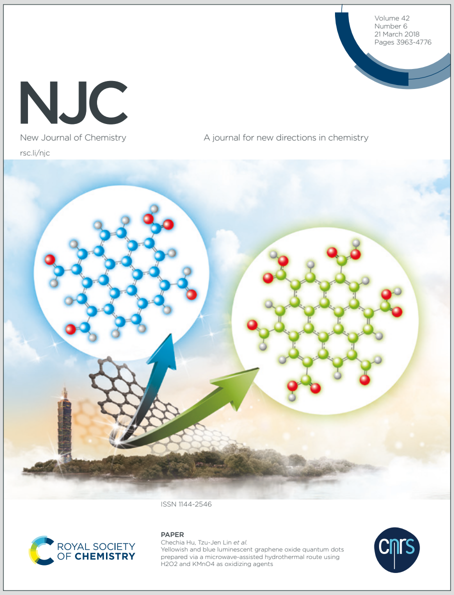

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LETTER

Ir^{III} Catalyzed Direct Syntheses of Amides and Esters Using Nitriles as "Acid Equivalents": A Photochemical Pathway

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Dedicated to Professor Sabyasachi Sarkar on the ocassion of his 70th birthday.

An unprecedented IrIII$[df(CF_3)ppy]_2(dtbbpy)PF_6$ catalyzed simple photochemical process for direct addition of amines and alcohols to relatively less reactive nitrile triple bond is described herein. Various amides and esters are synthesized as the reaction products with nitriles being the "acid equivalent". A mini-library of different types of amides and esters are made using this mild and efficient process which uses only 1 mol% of photocatalysts under visible light irradiation (λ = 445 nm). The reaction strategy is also efficient for gram-scale synthesis.

Introduction

The presence of dense sp electron cloud makes the nucleophilic functionalization of the nitrile triple bond a difficult task. For the sake of their activation selective metal catalysts are deployed often.[1] The involvement of Pd^{II} in this regard is noteworthy.[2] An alternate direct approach for nitrile activation can be the addition of organometallics including Grignard reagents.[3] In parallel, few non-metal catalysts are also used in special cases.[4] Several efforts has been spent for C-radical initiated reaction on nitriles as well.[5] On the other side, amide is always considered as a specially privileged organic functional group which have utmost importance in our day-to-day life.[6-10] Whether it is the protein in food,[6] polyamides in clothing materials[7] or adhesives[8], bio-active molecules in life-saving drugs or drug-precursors,[9] or fertilizers[10a] and herbicides/insecticides[10b-e] in agriculture, the surprising omnipresence of amides is truly a matter of fascination.

Thinking practically, nitriles could be a very popular choice as starting materials which can be directly converted to amides,[11a-e] rather than the other non-nitrile approaches[11f-h] for amide synthesis, including photochemistry[11i-j,12a]. Thus transformation of nitriles to amides has been adapted by several enzymatic biotransformation processes as well.[11k] Apart from the general metal catalyzed invariable "hydration" strategies",[11a-e] metal catalyzed limited number of advance methods are available as well which enable a double-fold access to wide range of amides, with variation in both the nitrile and in amines, replacing water (figure 1)[11l-p], whereas some similar strategies do not require metals at all[11q-s]. The reaction of acid halides with amines is definitely a competitive procedure for amide synthesis, but it often poses problems like requirement of low temperature, uncontrollable vigorous reaction giving side products or commercially non-availability of certain acid chlorides leading to their *in situ* preparation in the laboratory[11t-v], which amide reactions are generally devoid of.

Nevertheless, it is surprising that no photochemical approach towards the rather innocent looking reaction (table 1 scheme) for the synthesis of amide **3a** from **1a** has been made till date. Our ongoing efforts to unleash the "Greener" photochemical power of Ir^{III}[12a-b] or Ru^{II}[12c] transition metal complexes led the present project to discover their photochemical efficiency in synthesizing amides and esters from nitriles by reaction with amines or alcohols respectively for the first time. Here nitriles act as the "acid equivalents".

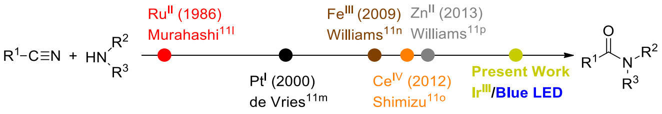

Figure 1 Chronology of metal catalyzed syntheses of amides from nitriles

Results and discussion

When benzyl amine **1a** was irradiated under blue light emitting diodes (λ=445 nm) along with 2 equivalents of CCl_3Br in dry CH_3CN **2a** in presence of only 1 mol% photocatalyst $Ir^{III}[df(CF_3)ppy]_2(dtbbpy)PF_6$[13a-b] at room temperature under inert atmosphere, isacetamide **3a** was formed in 78% yield within 9 hours (table 1, entry 1). Lowering the amount of CCl_3Br resulted in a decrease of the yield of **3a** (entry 2). Using

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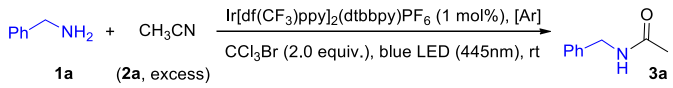
Selectfluor instead of CCl_3Br gave only 64% yield (entry 3). Using $Ru^{II}(bpy)_3Cl_2$[13c] as photocatalyst gave slightly lower yield of the amide (entry 4). Carrying out the reaction under air atmosphere or in presence of CFL light instead of blue LEDs only gave 27% and 10% yields (entries 5 and 6). Under 5 mol% Rose Bengal or Eosin-Y photocatalyst with green LED, the reaction led to only trace amount of product (entries 7 and 8 respectively). Further the use of either basic or acidic additives also afforded less amount of products than the optimized condition (entries 9 and 10 respectively). When the reaction was carried out in complete dark, no reaction was observed (entry 11). Changing the reaction temperature to 50 °C or 0 °C could not result any increment in the yield as well (entries 12 and 13). Carrying out the reaction in DCM or in THF in presence of 4 equivalents of nitrile gave extremely low yield of **3a** (entries 14 and 15), therefore carrying out the reaction under nitrile as solvent was necessary. Lastly, lingering the reaction time to 3 days under optimized condition resulted in no better output (table 1, last entry).

Table 1 Yield optimization in photochemical synthesis of acetamide **3a** from acetonitrile



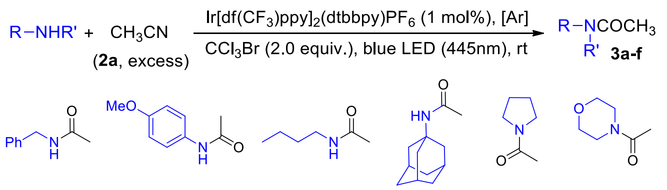
1a (**2a**, excess) **3a**

Entry	Deviation from the Optimized Condition (0.5 mL CH_3CN used for 1 mmol of **1a**)	Time (h)	Yield (%)[a]
1	None	9	78
2	1.0 Equiv. of CCl_3Br used	25	40
3	2.0 Equiv. of Selectfluor used instead of CCl_3Br	28	64
4	1 Mol% $Ru^{II}(bpy)_3Cl_2$ used as photocatalyst	13	70
5	Inert atmosphere not maintained	72	27
6	24-Watt CFL lamp used instead of blue LEDs	72	10
7	Green LEDs are used with 5 mol% Rose Bengal photocatalyst	72	Trace
8	Green LEDs are used with 5 mol% Eosin-Y photocatalyst	72	Trace
9	1.0 Equiv. K_2CO_3 used as base additive	72	Trace
10	1.0 Equiv. *p*-TsOH used as acid additive	72	20
11	Reaction carried out in complete dark	72	0
12	Reaction carried out at 50 °C	8.5	67
13	Reaction carried out at 0 °C	72	44
14	4.0 Equiv. nitrile in DCM solvent	72	16
15	4.0 Equiv. nitrile in THF solvent	72	9
16	None	72	73

[a]All yields mentioned are isolated yields.

Having the optimized condition derived, different amines were reacted with acetonitrile **2a** for synthesizing different N-substituted acetamides and different primary and secondary amine partners were utilized in this regard (table 2). Gratifyingly, p-anisidine also yielded the amide product **3b**, although in lower yield and slow conversion rate due to delocalization of the free radical inside the aromatic ring. Linear primary amine n-butyl amine gave acetamide **3c** in better yield with a faster reaction rate. Structurally constrained adamantane-1-amine gave the corresponding acetamide **3d** in good 82% yield. Secondary amines pyrrolidine and 1,4-morpholine also provided amides **3e** and **3f** in 85% and 88% yields respectively.

Table 2 Substrate studies with different amines for synthesis of acetamides **3a**

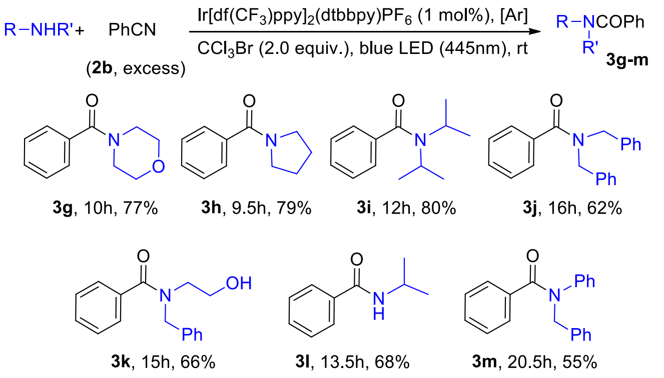


3a, 9h, 78% **3b**, 25h, 40% **3c**, 7.5h, 87% **3d**, 8h, 82% **3e**, 11h, 85% **3f**, 12h, 88%

[a]All yields are isolated yields.

To check the efficiency of the reaction, benzonitrile **2b**, when reacted, gave benzamide **3g** in 77% yield with morpholine (table 3). Other amines like pyrrolidine, diisopropylamine and dibenzylamine yielded the amides with comparable yields (**3h-j**). N-benzyl ethanolamine yielded 66% of the corresponding benzamide (**3k**) and no ester was obtained by the reaction of benzonitrile with the O-centre of N-benzyl ethanolamine. Isopropyl amine gave 68% of the product **3l**. Benzyl protected aniline furnished amide **3m** with the lowest yield in the table.

Table 3 Synthesis of different benzamides with benzonitrile[a]



3g, 10h, 77% **3h**, 9.5h, 79% **3i**, 12h, 80% **3j**, 16h, 62%

3k, 15h, 66% **3l**, 13.5h, 68% **3m**, 20.5h, 55%

[a]All yields are isolated yields.

Then different nitriles were tested with piperidine. Acetonitrile and n-pentanonitrile afforded corresponding amides **3n** and **3o** with 80% and 77% yields respectively (table 4). Amide **3p** resulted through the reaction of cyclohexanecarbonitrile. 3-Phenylpropanenitrile gave amide **3q** in 64% yield. Benzonitrile yielded benzamide **3r** in 72% yield. Highly electron donating or withdrawing substitutions were well tolerated (**3s** and **3t**). Moderate yield with 4-NO_2 substituted benzonitrile is attributed to its high reactivity. 4-Pyridinecarbonitrile afforded the corresponding amide (**3u**) in 69% yield.

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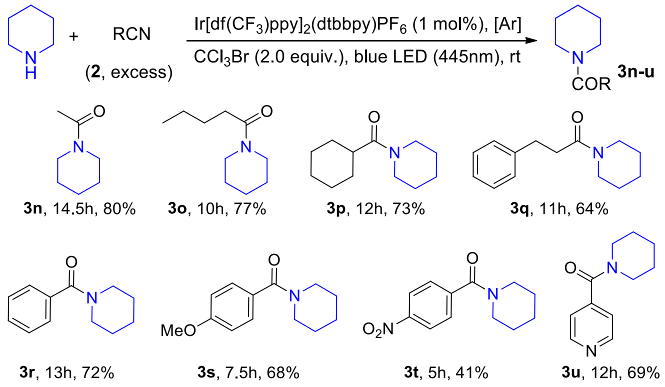
Table 4 Photochemical synthesis of piperidine amides with different nitriles[a,b]



3n, 14.5h, 80% **3o**, 10h, 77% **3p**, 12h, 73% **3q**, 11h, 64%

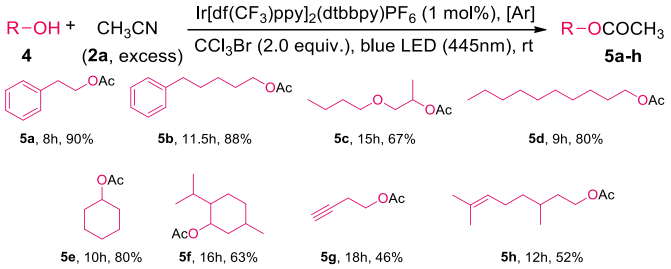
3r, 13h, 72% **3s**, 7.5h, 68% **3t**, 5h, 41% **3u**, 12h, 69%

[a]All yields are isolated yields. [b]For solid nitriles, 0.5 g nitrile was used (for products **3s**, **3t**, **3u**, **5z** and **5aa**).

After synthesizing various amides, the author was urged to observe the reaction outcomes with alcohols. Quite satisfyingly, when different alcohols **4** were taken as substrates, the corresponding acetate esters **5** were formed (table 5). There is no need to introduce their importances, as esters are as important as amides in sustaining human life and culture, which are used as drugs,[14] polymer materials[15] and in cosmetics industry/perfumery[16] for their pleasant odours. Because of such importance many new synthetic procedures are developed recently. Besides the nitriles as starting point (including Pinner reaction),[17] the other available methods involve the reaction of alcohols with acid derivatives[18], oxidative coupling with aldehydes[19], acyl azolium intermediates[20] or with enzymatic methods[21]. Thus, a simple radical functionalization of nitrile triple bonds for the first time to obtain esters will be a great enrichment of its synthetic armoury.

The efficient reaction with 2-phenyl ethanol gave 90% yield of the ester **5a** (table 5). Similarly, high yield of ester **5b** was found with 5-phenyl pentanol. Branched and long aliphatic chained alcohols participated in the reaction quite efficiently (**5c** and **5d**). Substituted (menthol) and unsubstituted cyclic secondary alcohols were also acetylated under the reaction condition (products **5e** and **5f**). Lastly, unsaturated alcohols e.g. but-3-yn-1-ol or citronellol were also photochemically acetylated with CH_3CN (**5g** and **5h** respectively). The lower yields with unsaturated alcohols were probably for the radical mediated side reactions with the multiple bonds. It is noteworthy that tertiary alcohols did not give any product.

Table 5. Photochemical synthesis of acetate esters with acetonitrile **2a**[a]



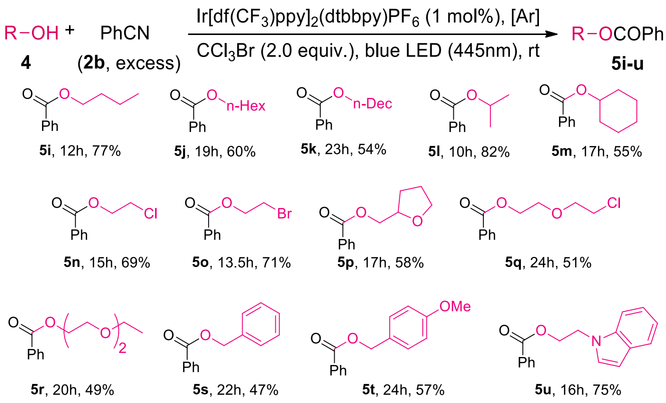
5a, 8h, 90% **5b**, 11.5h, 88% **5c**, 15h, 67% **5d**, 9h, 80%

5e, 10h, 80% **5f**, 16h, 63% **5g**, 18h, 46% **5h**, 12h, 52%

[a]All yields are isolated yields.

When benzonitrile **2b** was reacted with different alcohols under the optimized condition, different benzoates (**5i-u**) were formed (table 6). Aliphatic open chain or cyclic alcohols gave good to moderate yields of esters (**5i-m**). Halogenated ethyl benzoates were also synthesized in good yields (**5n-o**). Etheral alcohols show moderate yields of the corresponding benzoates (**5p-r**). The presence of methoxy group in the benzyl alcohol gave a little better yield of its benzoate ester (**5s** vs **5t**) under this condition. Indole N-substituted ethanol also, was suitable substrate for this photochemical conversion (**5u**, 75%).

Table 6. Synthesis of benzoates from benzonitrile **2b**[a]



5i, 12h, 77% **5j**, 19h, 60% **5k**, 23h, 54% **5l**, 10h, 82% **5m**, 17h, 55%

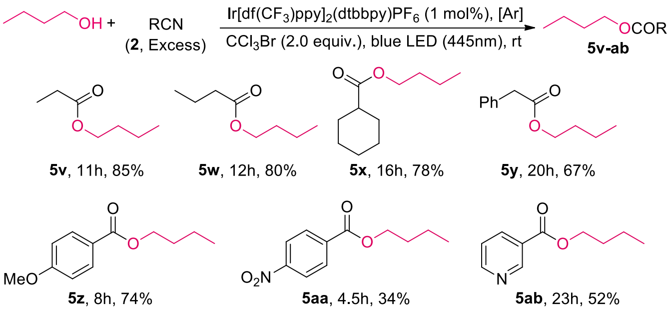
5n, 15h, 69% **5o**, 13.5h, 71% **5p**, 17h, 58% **5q**, 24h, 51%

5r, 20h, 49% **5s**, 22h, 47% **5t**, 24h, 57% **5u**, 16h, 75%

[a]All yields are isolated yields.

Butyl esters (**5v-5ab**) were synthesized using different nitriles (table 7). Aliphatic acyclic nitriles or cyclic secondary nitrile displayed smooth conversion with n-butanol giving good yields of butyl esters **5v-x**. Benzyl cyanide gave moderate yield (67%) the of butyl acetate **5y**. Electron rich methoxy substituted benzonitrile gave ester **5z** in 74% yield. In comparison, highly electron withdrawing 4-NO_2 substituted benzoate ester **5aa** was synthesized albeit in low 34% yield from the corresponding benzonitrile. Similarly, butyl nicotinate (**5ab**) was obtained in 52% yield with 3-pyridine carbonitrile.

Table 7. Synthesis of butyl alkanoates from butanol and nitriles[a]

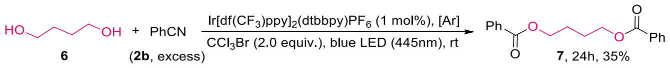


5v, 11h, 85% **5w**, 12h, 80% **5x**, 16h, 78% **5y**, 20h, 67%

5z, 8h, 74% **5aa**, 4.5h, 34% **5ab**, 23h, 52%

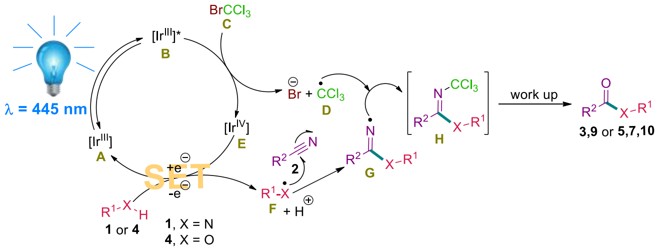
[a]All yields are isolated yields.

An interesting substrate butane-1,4-diol **6** was subjected to this reaction protocol as well, to give diester **7** was with nitrile **2b** in 35% yield after 1 day of irradiation.



Scheme 1 Synthesis of diester **7** from butane-1,4-diol

With the author's previous experience from the photochemical red-ox generation of amides and esters starting from aldehydes,[12a-b] a red-ox neutral reaction mechanism can be drawn as scheme 2 which involves radical[12a]. It commences with photo excitation of Ir^{III} (**A**) to Ir^{III*} (**B**). **B** in turn makes a trichloromethyl radical **D** and bromide anion by donating an electron to CCl_3Br (**C**).[12,22] The photooxidized state of Ir^{IV} (**E**) thus generated is quenched by the amine (**1**) or alcohol (**4**) to reduce **E** and regenerate catalyst **A** by a single electron transfer (SET), unleashing a proton and the amide or oxide radical **F**. Then **F** "attacks" nitrile substrate **2** to form imidamide or imidate radical **G**. **G** adds to trichloromethyl radical **D** to form transient species **H**, which upon workup furnishes amides **3**,**9** or esters **5**,**7**,**10** depending on **F**. Although there is a finite possibility for the $\cdot CCl_3$ radical **D** to abstract H radical from amines or alcohols to give **F**, while the Ir^{V} oxidizing intermediate **G**. In that case there will be bromine in place of $\cdot CCl_3$ in intermediate **H**. But the end bi-products will be the same HBr and the unstable CCl_3OH.



Scheme 2 Mechanism for Ir^{III} photocatalyzed formation of amides (**3**,**9**) and esters (**5**,**7**,**10**) from nitriles under blue LED irradiation

A simultaneous "Proton Coupled Electron Transfer" (PCET) process is also likely to be occurring in parallel to the proposed mechanism in scheme 2 (scheme 3).[23] First a proton transfer occurring between the amine or alcohol and CCl_3Br radical anion (**I**) could generate the amine/alcohol anion along with with the protonated radical of CCl_3Br (**J**). An electron transfer from the anion to Ir^{IV} will make an amine/alcohol radical along with Ir^{III} (**K**). In another pathway, **I** could give rise to an amine/alcohol radical cation by electron transfer process from it to Ir^{IV} giving **L**. Which and **K** are interconvertible by a single proton transfer process from amine/alcohol radical cation to bromide. During the multisite PCET **I** could directly transform to **K** by the synchronized transfer of a proton from free amine/alcohol to CCl_3Br giving CCl_3 radical and hydrogen bromide and transfer of an electron from CCl_3Br radical cation to Ir^{IV}.

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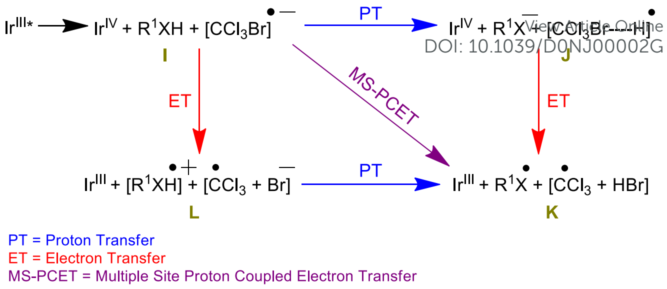
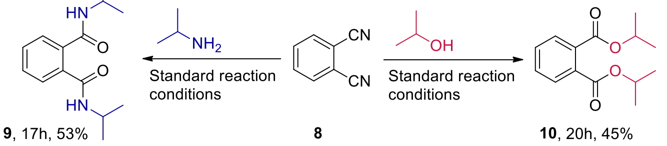


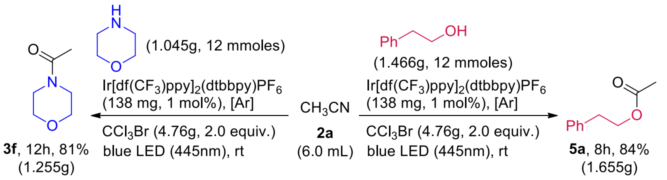
Scheme 3 Schematic diagram of proposed PCET process occurring in photocatalytic amidation/esterification

In order to check the efficiency of the current protocol towards a dinitrile, phthalonitrile **8** was reacted with both isopropyl amine and isopropanol under the optimized conditions. The reaction yielded the bis-amide **9** and diester **10** respectively in moderate yields (scheme 4).



Scheme 4 Photochemical synthesis of bis-amide **9** and diester **10** from dinitrile **8**

Two scale-up reactions were carried out to check the efficiency of this project towards gram-scale syntheses. With acetonitrile **2a**, morpholine and 2-phenylethanol provided amide **3f** and ester **5a** in 81% and 84% yields respectively (scheme 5).



Scheme 5 Gram-scale synthesis of amide **3f** and ester **5a** from nitrile **2a**

Conclusions

In this project a photocatalytic facile synthesis of amides by the addition of amine radicals to nitriles is described. The reaction occur at room temperature under blue LED irradiation in presence of only 1 mol% photocatalyst Ir[df(CF_3)ppy]$_2$(dtbbpy)PF_6. The addition of alkoxide radicals to nitriles furnish the corresponding esters. Diol gives diester and dinitrile forms bis-amide and diester respectively. This is the first report of photochemical nucleophilic functionalization of nitrile triple bonds by N/O radicals. The reaction strategy is also applicable for gram-scale synthesis with almost similar efficiency. Further mechanistic studies and theoretical studies on the proposed PCET process are in progress.

Conflicts of interest

There are no conflicts to declare.

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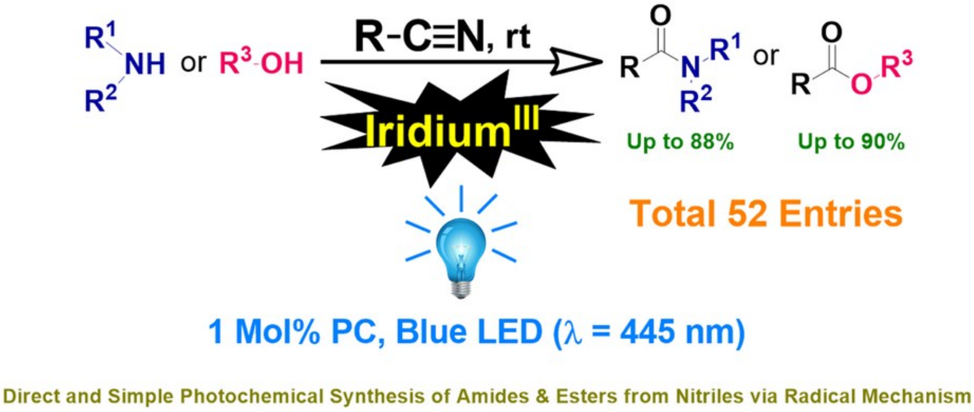

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