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p-Selective (sp²)-C-H Functionalization for Acylation/Alkylation Reaction using Organic Photoredox Catalysis

Ganesh Pandey[a*], Sandip Kumar Tiwari[a], Bhawana Singh[a], Kumar Vanka[b], Shailja Jain[b]

p-Selective (sp²)-C-H functionalization of electron rich arenes have been achieved for acylation and alkylation reaction, respectively, with acyl/alkylselenides by organic photoredox catalysis involving interesting mechanistic pathway.

Arene acylation as well as alkylation is a fundamental C-C bond forming reaction, which are classically, achieved by Friedel-Crafts reaction using stoichiometric or super stoichiometric amount of strong Lewis[1] or Brønsted acid.[2] Owing to regioisomeric and environmental issues associated with these protocols, research has continued in these areas and many new and mechanistically interesting reactions have been discovered[3-5] including many transition metal catalyzed cross-coupling reaction.[6-13] More recently, McMillan[14] and Molander[15] have elegantly developed synergistic dual catalysis (visible-light photoredox catalysis and Ni-catalysis) to bring about such cross-coupling reaction. However, these coupling reactions suffer from the requirements of pre-functionalized arenes, expensive catalysts, bulky ligands, deleterious effects of the metal catalysts and other related environmental and economic issues. Directed (sp2)-C-H bond acylation[16,17] as well alkylation,[18] using expensive catalyst have also appeared recently, however, these approaches, are substrate specific, requires bulky ligands and directing group as an appendage whose removal is often difficult.

Therefore, it was felt necessary to develop a simple, environmentally benign and a catalytic strategy for this fundamental reaction involving regiospecific C(sp²)-H functionalization directly. Keeping these challenges in mind, we conceptualized following (Fig.1) catalytic photoredox cycle using an organic visible-light absorbing photoredox catalyst (DMA) where generation of acyl/alkyl radical from the mesolysis of corresponding acyl/alkyl-SePh⁻ and generation of arene radical

cation by electron transfer from an arene to resultant DMA⁺· was visualized. Cross -coupling of acyl /alkyl radical with arene radical cation[19], followed by aromatization was expected to lead a conceptually new approach for arene alkylation/acylation reaction.

This photoredox cycle was conceptualized by considering our previous experiences[20] and continuing interest[21] in discovering mechanistically interesting and synthetically useful reaction using organic photoredox catalysis.
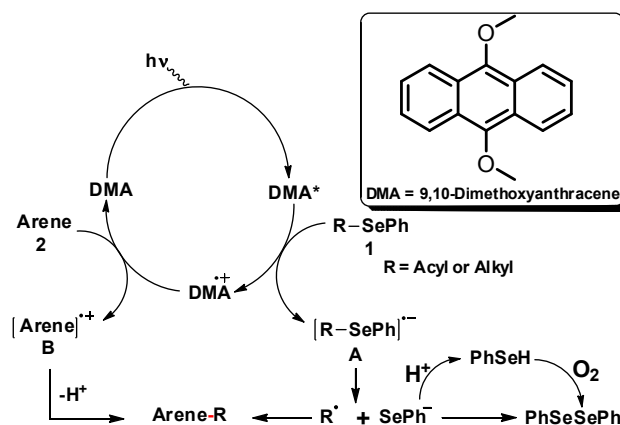
Figure 1. Proposed photoredox cycle for alkylation/acylation of arenes.

We report herein the success of our concept, which involves (sp²)-C-H bond functionalization using a visible-light absorbing organic photoredox catalytic cycle. To the best of our knowledge, this protocol of arene acylation/alkylation is new and carries the promise of a streamlined and sustainable development of fundamental chemistry.

Electron transfer feasibilities, as shown in Fig. 1, between excited state of 9,10-dimethoxy anthracene (DMA*, 0.935 V *vs* SCE, 410 *nm*) and acyl-SePh (**1**) (-0.995 V *vs* SCE, -30.53 kcal/mol) was established using well established protocols.[22] Since electron transfer from DMA* to alkyl-SePh and the mesolysis of the corresponding alkyl-SePh]⁻· was established from our previous studies,[23] to generate alkyl radical (**R•**), it was obvious to presume that acyl-SePh]⁻· mesolysis would generate

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corresponding acyl radical (**R-C•=O**). Similarly, generation of arene radical cation from arenes (**2**) was established by estimating electron transfer processes to resultant DMA$^{+\cdot}$ considering their low oxidation potential (1.495 V *vs* SCE, -6.7 kcal/mol).

To validate our hypothesis, a mixture of **1a** (0.3g, 1.15 mmol) and naphthalene (**2a**) (0.29 g, 2.30 mmol) in the presence of a catalytic amount of DMA (0.04g, 0.17 mmol) were irradiated in acetonitrile utilizing visible light (410 *nm*).[21,24] Progress of the reaction was monitored by following the disappearance of 1 by HPLC (C18 reverse Phase, ACN:H$_2$O/75:25) and GCMS. It was pleasing to note that there were only two product peaks, corresponding to **3a** and **3a'** (8.5:1.5), were observed on chromatogram besides unreacted **1** and DMA. No significant loss in the DMA concentration was noted during or after the reaction. After 18-20 h irradiation, solvent was evaporated and column chromatography of the crude mixture gave **3** [**3a** (85%), **3a'** (15%)], along with diphenyldiselenide (PhSeSePh, 43%). The PhSeSePh is formed by the air oxidation of PhSeH,[25] generated by the protonation of PhSe- during the reaction and is eluted from column chromatography first due to its no-polar character. Since PhSe-SePh, the only side product is formed in this reaction, the same could be recycled to prepare acyl/alkylselenide, making this reaction environmentally benign and atom economy. A control experiments without light and/ or catalyst did not show any reaction.

Identical reaction with toluene (**2b**) and anisole (**2c**) gave exclusively p-substituted acylated product **3b** and **3c**, respectively. However, acylation did not take place with electron deficient arenes such as methyl benzoate, chlorobenzene and bromobenzene (**2d**). In fact, in these reactions acyl radical dimerised into **3d'** instead. Acylation of the simple benzene (2.3 eV) also did not succeed. When these results were analyzed in terms of their redox potentials[26] [methyl benzoate (2.18 eV), chlorobenzene (2.56 eV) and bromobenzene (2.07 eV)] with respect to DMA$^{+\cdot}$, it became clear that electron transfer from 2d to DMA$^{+\cdot}$ was not possible.
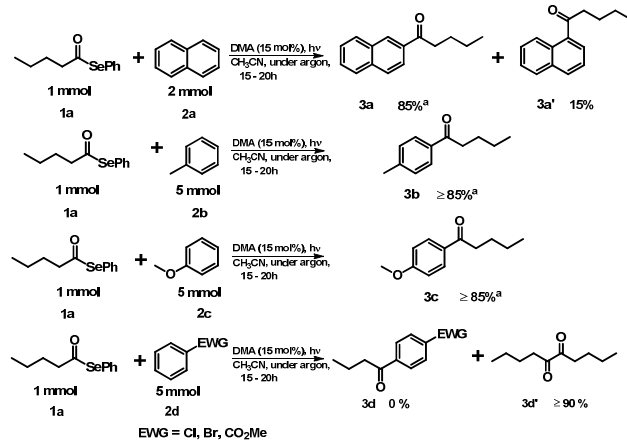
Scheme – 1 Photoredox catalyzed acylation reaction of arenes. a. GC yield.

In order to support the involvement of arene radical cation in the acylation reaction, phenol as well as aniline were included in our study with the premise that these arenes would not acylate

due to rapid deprotonation from the corresponding radical cation as shown in Scheme-2.
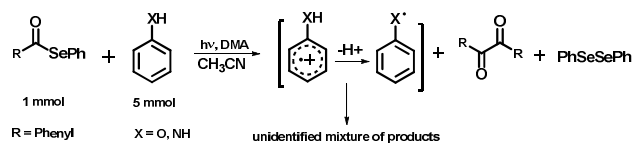
Scheme – 2. Support of the acylation reaction.

More diverse functionalized arenes were included in our study and all of them proved compatible under these photoredox conditions. For example, N,N'-dimethyl aniline (**2o**) on reacting with various acylphenylselenide gave corresponding p-substituted acylated product **3au'**, **3av'**, **3aw'**, **3ax'** and **3ay'**, respectively. Regioselectivity was further studied involving di- and tri-substituted aromatic ring (methyl as well as methoxy). In case of 1,2-disubstituted benzenes (**2h**, **2i**), corresponding **3h**, **3i**, were isolated. Furthermore, reaction with 1,3-disubstituted benzenes (**2f**, **2g**), primarily p-substituted product **3f**, **3g** are formed (<10% o-product was also detected by GCMS). Understandably, reaction with 1,4-disubstituted benzene (**2j**, **2k**) gave o-acylated product (**3j**, **3k**).

Generality of the reaction was established by irradiating **1** in the presence of a wide variety of electron donating **2** under optimized reaction condition and results are shown in Scheme-3. The yields mentioned in the Scheme-3 are the isolated yield.
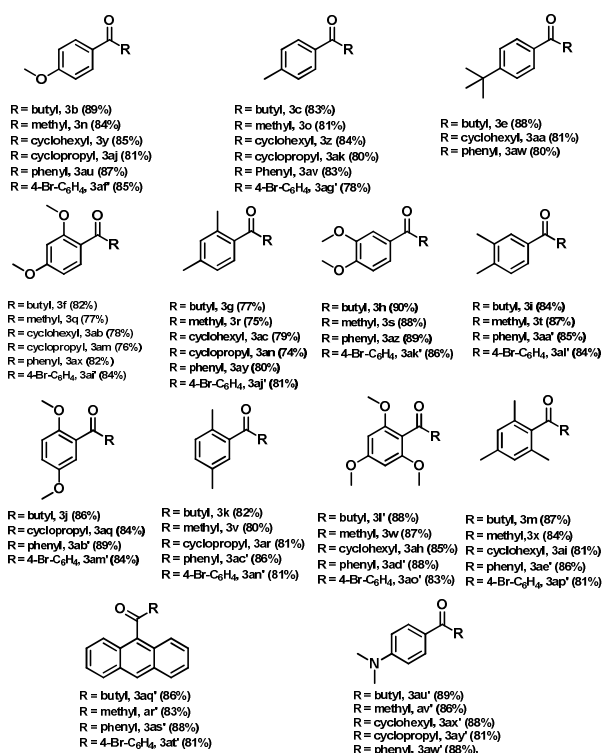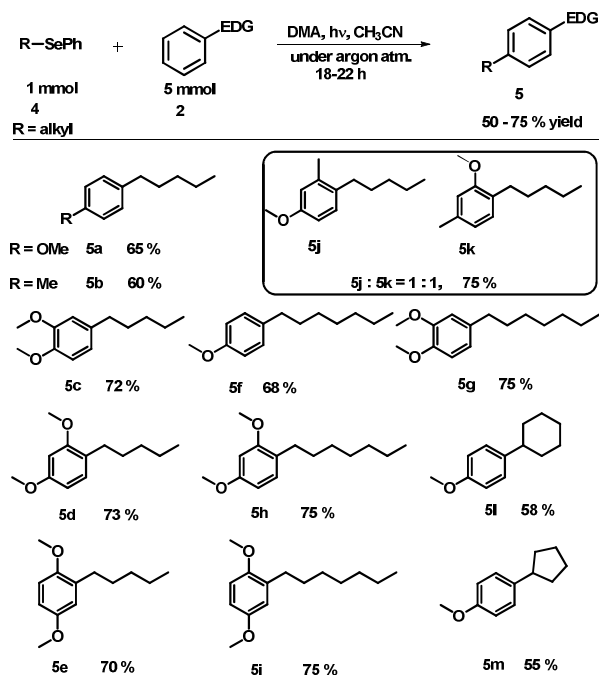

Scheme – 3. Acylation of arenes by acyl selenides by photoredox catalysis. Reaction Conditions: **1** (1 mmol), **2** (2 mmol), DMA (15 mol%), "hν", N$_2$, rt, 18-20h. The isolated yields are based on consumption of 1.

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It may be mentioned here that similar reaction with heteroarenes such as pyridine, pyrrole, furan and thiophene did not succeed.

These successes motivated us to extend this study for alkylation reaction as well. Despite the relevance of alkylbenzenes,[27] the synthetic strategies to prepare these compounds are limited,[28] and therefore, the extension of this approach for the preparation of alkyl arenes appeared an important proposition. Identical reaction, as discussed above for acylation reaction, using alkylphenylselenides gave corresponding p-selective alkyl benzenes.

Further, generalization of this reaction was carried out using different alkyl partners as well as different electron rich aromatic arens are shown in Scheme-4. Anisole (**2a**) and toluene (**2b**) was alkylated at p-position to give **5a**, **5b**. More electron rich arenes such as 1,2-dimethoxy benzenes (**2h, 2i**) gave corresponding p-substituted product **5c** and **5g**, respectively. Similarly, 1,3-dimethoxy benzene (**2f, 2g**) and 1,4-dimethoxy benzene (**2j, 2k**) also got alkylated at p-position (**5d, 5h**) and at o-position (**5e, 5i**), respectively. When reaction was performed using 3-methylanisole, mixture of p-alkylated product **5j** and **5k** were formed in 1:1 ratio. Alkylation with secondary alkyl partner also took place smoothly giving rise to **5l** and **5m**, respectively, in good yield.


Scheme – 4. Alkylation of arenes by alkyl selenides by photoredox catalysis.

It may be appropriate to mention here that acyl/alkyl radical generation by cleavage of –C-SePh bond by tributyltin hydride[29] is known but its use in arene acylation/alkylation remains unexplored. Formation of acyl radical by direct photolysis of corresponding acyl halide[30] in the presence of naphthalene or anthracene, respectively, is also reported but their preparative

application and generalization for arene acylation is not systematically studied. Catalytic photoredox decarboxylation from aromatic carboxylic acid to produce corresponding acyl radical is reported but their application is shown only in the acyl arylation of olefin.[31] Visible-light photoredox catalytic method of arene radical[32] and trifluoromethyl radical[33] from corresponding diaryliodonium salts and trflic chloride, respectively, and their use in arylation and trifluormethylation of arenes and heteroarens are shown, however, much of this reaction remains to be explored. Thus from above results, it is obvious to conclude that this approach of arene acylation as well as alkylation is novel, general and applicable with a variety of different arenes and acyl/alkyl radicals.

To rationalize observed p-selectivity, it is proposed that arene radical cation (**E**) is delocalized to form a distal radical cation (**G**) and (**H**) favouring later by at least 3.1kcal/mol indicating that the para- product would be the preferred one. In order to understand the mechanism of these reactions, calculations have been done with density functional theory (DFT) at the level of TZVP/M06-2X. For further details, please see the Computational Details section in the SI file.

Furthermore, in addition to the thermodynamics, we have also attempted to obtain the barrier at this important step for the formation of the para-product from **J** to **3**, as well as from **I** to **3'** and they indicate that the para-product would be preferred over the ortho. This result therefore corroborates the experimental observations.
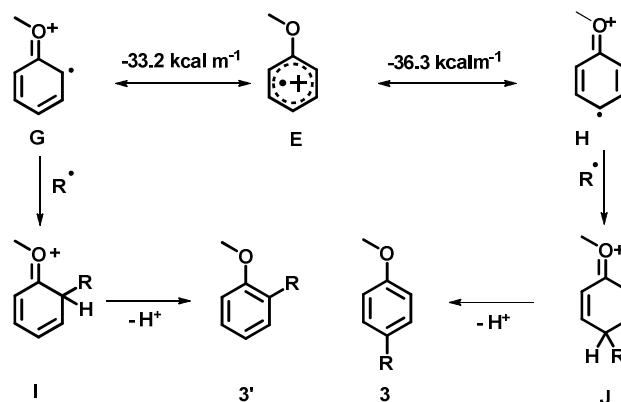
Figure-2. Mechanistic details for acylation/alkylation reaction.

In summary, we have discovered a new strategy of p-selective (sp²)-C-H acylation and alkylation of arenes with acyl/alkyl radical, formed by the mesolysis of the corresponding –C-SePh]⁻ which are generated by using a visible-light absorbing organic photoredox catalysis involving an interesting mechanism. Further study for direct alkynation as well as alkenylation is in progress and will be presented in a full paper in due course.

Conflicts of interest

The author declare no competing financial interest.

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Ganesh Pandey[1*], Sandip Kumar Tiwari[1], Bhawana Singh[1], Kumar Vanka[2], Shailja Jain[2]