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Aldehydes: magnificent acyl equivalents for direct acylation

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Reviews must be:

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- **Jargon free:** Specialist terms and symbols should be defined and fundamental ideas explained so a non-specialist can understand.

PROPOSED TITLE: Aldehydes: magnificent acyl equivalents for direct acylation

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PROPOSED SUBMISSION DATE: A proposed date of submission could be three months after acceptance of the proposal.

PROPOSAL QUESTIONS:
Please complete all sections, ensuring your answers are concise and within the stated word limit.

1) Please comment on why the proposed topic is currently important

The proposed review article sheds light on the use of less toxic, highly durable aldehyde moieties that work as magnificent acylation equivalents for selective acylation of arenes, heteroarenes and alkyls (sp^3, sp^2 and sp C-H bonds) via the proficient utilization of C-H activation strategy. The intention to pen down the recent breakthroughs in this area for enlightening a broad spectrum of readers stems from the non-availability of reviews on the proposed topic. From the viewpoint of greener chemical synthesis, there is a need to disseminate how the cocktail of acylation and activation can play a pivotal role in affording bioactive acylated products in fewer reaction steps, with higher atom-economy and improved selectivity.

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2) What are the implications for the wider scientific community?

This review will provide critical insights on selective acylation for the synthesis of bioactive keto-compounds using non-toxic, readily available aldehydes as acylation surrogates. Gaining an insight into the mechanistic process and approach involved, the academic as well as the industrial researchers will be inspired to design novel bioactive molecules using similar approaches. Special emphasis would be on the propagation of greener chemical synthesis which is the need of the hour in view of minimizing waste, and increasing the economy and efficiency of the protocols.

3) To which communities will your article appeal?

The chemical community on a whole would greatly benefit from the proposed review. In particular, this review is anticipated to appeal the graduates and researchers in the field of organic/medicinal chemistry in general, and particularly to the scientists working in the field of C-H activation.

4) Please comment on any other reviews published on a similar topic, justifying why there is room for another review

Although two review articles were reported on a similar topic that highlight selective acylation via C-H activation using aldehydes as acylation surrogates in 2015[1] and 2016[2], yet, a lot of remarkable advancements have been witnessed in this field since then. Especially, there is room for update on recent reports related to the acylation of arenes, heteroarenes and alkyls (sp^3, sp^2 and sp C-H bonds) that lead to the synthesis of valuable C-C, C-O and C-N bonds that have not been given due coverage in the earlier reviews. Also, these reviews do not present any critical insights into the mechanistic processes involved. In addition, there is a need to review the recent progress on the use of modern green technologies such as continuous flow as well as photochemical approaches that have been integrated with the selective acylation approach for maximizing the benefits.

5) Please provide section headings along with a brief discussion of each section and associated key references. This should:

- **Clearly outline the intended content of the review**
- **Include at least 10 of the core references used to support your review**
- **Ensure that the title and DOI of each reference is included**

Brief description of the sections that are envisioned:

1. Introduction

The concise forging of substituted ketone motifs by means of direct functionalization using C-H activation strategies represents the incredible state of the art in synthetic organic chemistry. Ketones are commonly used ubiquitous structural units for developing pharmaceuticals, dyes, agrochemicals, electronic materials and natural products. Over the course of time, structural diversity of the disubstituted ketone moieties has rapidly expanded as evident from the literature reports. However, the practical challenges associated with the conventional methodologies employed for the synthesis of these significant motifs have in turn engaged the researchers in exploration of improved methods of synthesis. Some of the inherent drawbacks associated with the classical Friedal Crafts acylation reaction include the

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requirement of harsh reaction conditions and super-stoichiometric amounts of Lewis acids, low regioselectivity and the formation of unwanted regioisomers.[3,4] Although other alternative methods have been developed including the oxidation of alcohols[5,6] Grignard/Barbier reaction followed by oxidation[7], or Grignard reaction with nitriles,[8] these methods unfortunately do not match the requirements of appealing methods due to safety concern and environmentally practical considerations.

Transition metal-catalyzed oxidative cross-coupling reactions for the direct functionalization of C-H bonds with high atom-efficiency have emerged as attractive, efficient and straightforward strategies for the formulation of desirable molecules from simple starting materials without the need of any pre-modification or pre-functionalization, thereby improving the overall efficacy of the desired transformations. Therefore, in recent years these oxidative cross-coupling reactions have been extensively explored for the direct synthesis of keto-compounds by means of selective acylation of the starting materials. These approaches are found to be highly advantageous over classical methods used for the acylation of alkyls, aryls or hetroaryls leading to the formation of desirable acylated compounds because of fewer reaction steps, higher atom-economy, improved selectivity and no requirement of pre-functionalization of starting material that cause them to fall under the banner of green chemistry. For the direct acylation by following C-H activation approach, several reagents including aldehydes, benzyl alcohols, α-keto acids, acyl chlorides and toluenes have been explored extensively.[1,2, 9-12] Amongst these acylating surrogates, aldehydes (aliphatic and aromatic) have received profound attention because of their high stability, low toxicity, easy commercial availability, broad substrate scope and low cost. Aldehydes employed in radical acylation and oxidative acylation reactions that lead to the direct formation of new C-C, C-N and C-O bonds with high regioselectivity are shown in **Figure 1**. These routes provide green and versatile alternatives to anhydrides, acyl halides, α-ketoacids and other acylating approaches.

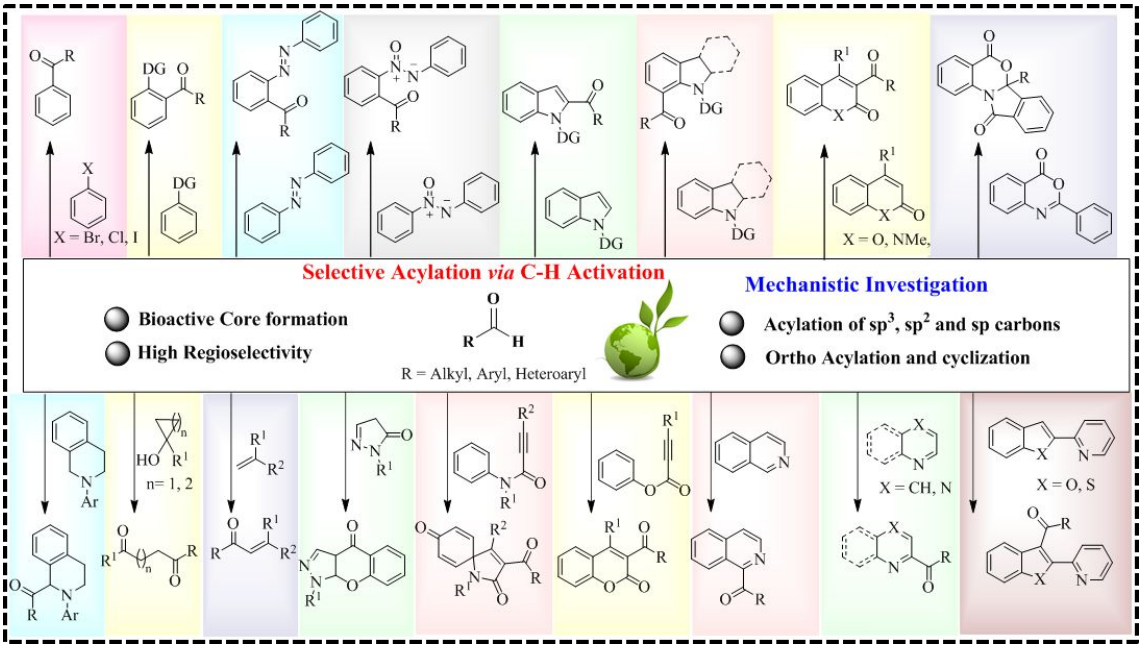

Figure 1. Aldehydes in various acylation reactions.

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2. Scope of the Review

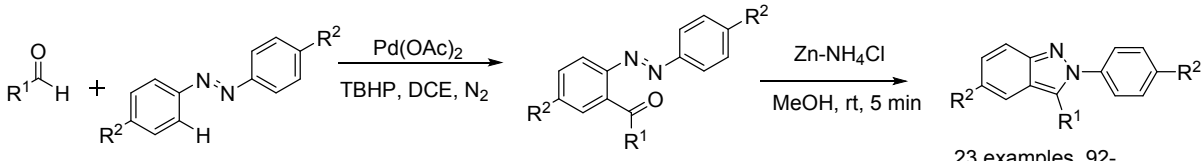
There is a need to disseminate how wondrously the aldehyde moieties are employed in various acylation reactions using C-H activation and how they succumb to provide a greener and versatile alternative to anhydrides, acyl halides and other acylating approaches. Although there are several reviews on C-H activation and transition metal-catalysed reactions, yet, to the best of our knowledge, there is no single review that throws light on the use of aldehydes as magnificent acylation surrogates compiling the acylation of arenes, heteroarenes and alkyls (sp^3, sp^2 and sp C-H bond) leading to the synthesis of valuable C-C, C-O and C-N bonds via the proficient use of C-H activation. This review presents some of the impressive breakthroughs achieved in the past decade in the development of new catalytic reactions, shedding light on some of the latest synthetic tools including flow chemistry and photochemical technologies. It includes a comprehensive discussion on the mechanistic aspects that will enable the researchers to think creatively and work in this area. Through this review, we have the intention of conveying why increasing focus should be directed towards using greener tools and strategies as chemical wastes have a disastrous impact on human health as well as environment.

3. Aldehydes as acylation surrogates

3.1. Acylation of arenes

The use of directing groups (DG) has proven to be one of the most practical methodologies to achieve highly selective functionalization of C-H bonds of arenes through the formation of a metallacyclic intermediate. Consequently, a variety of functionalities has been explored and identified as powerful DGs for accomplishing site-selective C-H activations.

Li and Wang reported an azo-group directed acylation of symmetrically substituted azobenzenes with aldehydes at the 2-position through Pd-catalyzed C-H functionalization.[13] In this case $Pd(OAc)_2$ and TBHP were used as catalyst and oxidant respectively and the desired acylated products were obtained in high yields. Both azobenzene and aldehyde bearing electron releasing as well as electron withdrawing groups delivered the desired products in good yields. The scope of aliphatic and heterocyclic aldehydes also explored under optimized reaction conditions and the corresponding products could be obtained smoothly. Interestingly, the obtained acylated azobenzenes were transformed into the corresponding indazoles using a Zn/NH_4Cl/MeOH reducing system at room temperature within 5 min in quantitative yield (**Scheme 1**).



R^1= Ph, 4-OMePh, 4-MePh, 4-BrPh, 4-ClPh, 4-FPh, 4-CNPh, 4-NO_2Ph, 4-PhPh, 3-OMePh, 2-MePh, 2-ClPh, 2-FPh, naphtyl, 3-NH_2-4-ClPh, 3,5-OMePh, furan, cyclohexyl, propyl

R^2= H, Me, OMe, Cl

Scheme 1 Pd-catalyzed azo-group directed acylation of symmetrically substituted azobenzenes with aldehydes.

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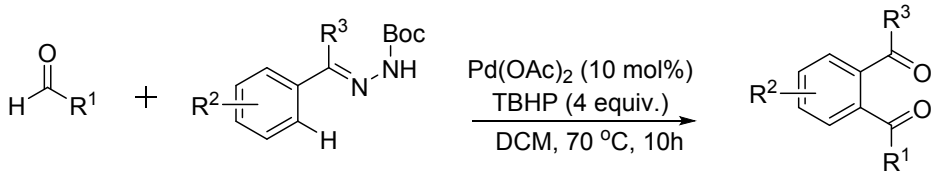
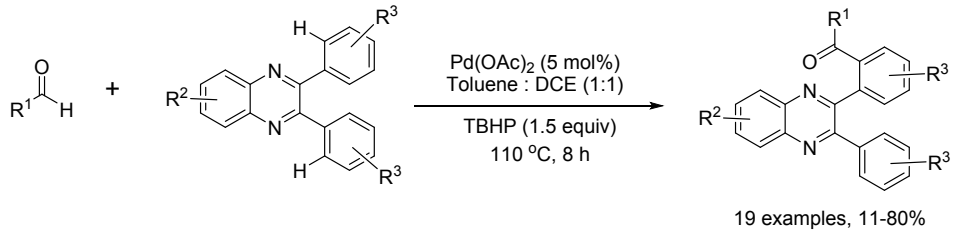
In 2013, Kim with his group reported the first catalytic acylation protocol for the synthesis of 1,2-diacylbenzenes. This method includes the tandem Pd(II)-catalyzed direct regioselective acylation of *N*-Boc hydrazones and *in-situ* cleavage of the directing *N*-Boc hydrazone group in the presence of TBHP as oxidant to afford 1,2-diacylbenzenes (**Scheme 2**).[14] This approach was found to be applicable not only for a wide range of aldehydes but also for various acetophenones and benzophenone *N*-Boc hydrazones. Unfortunately, aliphatic and heterocyclic aryl aldehydes were unable to give the coupling products with this catalytic system.



R^1= Ph, 4-OMePh, 4-OBnPh, 4-MePh, 4-CF_3Ph, 4-FPh, 4-ClPh, 3-OMePh, 2-OMePh, 3,5- ClPh, 2-F-4-OMePh. β-naphthyl
R^2= 4-CF_3, 4-OMe, 4-Br, 4-Cl, 4-F, 4-NO_2, 5-Me, 5-F, 6-F
R^3= Me, Ph

Scheme 2 Pd(II)-catalyzed direct regioselective acylation of *N*-Boc hydrazones to afford 1,2-diacylbenzenes.

Patel and co-workers developed a cross dehydrogenative coupling approach for the 2,3-diarylquinoxaline directed mono *ortho*-acylation of one of the four available *ortho* sp^2 C-H bonds in the two aryl rings of the 2,3-diarylquinoxaline using aromatic aldehydes.[15] The authors developed a small library of 23 derivatives in the presence of $Pd(OAc)_2$ as catalyst, TBHP as oxidant and toluene:DCE (1:1) as solvent system at 110 °C. A variety of functional groups was found to be well tolerated at aromatic aldehyde. Benzaldehdyes having strong electron withdrawing groups such as *p*-COOMe, *p*-NO_2, *m*-NO_2 also provided the desired products in good yields. The substrate scope was further extended to substituted 2,3-diarylquinoxalines with benzaldehdyes and good yields of the corresponding acylated products could be achieved (**Scheme 3**).



R^1= H, 4-MePh, 4-OMePh, 4-OBuPh, 4-PhPh, 4-ClPh, 4-NO_2Ph, 4-CO_2MePh, 3-ClPh, 3-FPh, 3-NO_2Ph, 3.4-OMePh, β-naphtyl, thiophenyl
R^2= H, 6,7-Cl, 6-Me, 6-Cl
R^3= H, 4-Me, 4-Br, 3-Me-4-OMe

Scheme 3 Cross-dehydrogenative coupling for directed mono *ortho*-acylation of sp^2 C-H bonds of 2,3-diarylquinoxalines.

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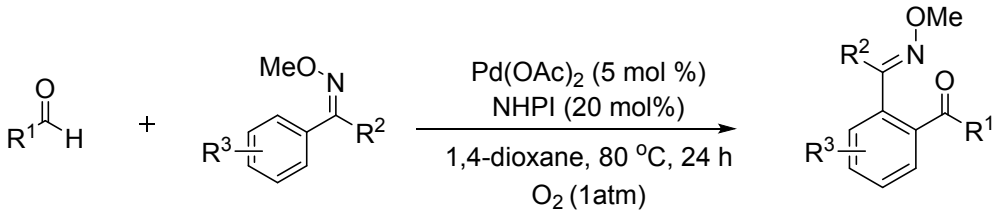
In early 2016, Jiao and co-workers reported *N*-hydroxyphthalimide (NHPI) and palladium co-catalysed radical oxidative acylation of acetophenone *O*-methyl oxime with aldehydes *via* selective C-H functionalization using molecular oxygen as terminal oxidant for C-H acylation.[16] A broad range of *O*-methyl oximes and aldehdyes (alkyl/aryl) was explored and various derivatives were prepared bearing electron withdrawing and releasing groups at 80 °C within 24 h in 1,4-dioxane solvent (**Scheme 4**). The developed acylation reaction conditions were also applied for benzo[*h*]quinolone, 1-phenylpyrazole, 2-phenylpyridine and 2-phenoxypyridine and the corresponding desired products were obtained in moderate to good yields. Unfortunately, azobenzene and acetanilide provided inferior yields of the acylated products and phenyl *N,N*-dimethylcarbamate was found to be unreactive under these reaction conditions. Moreover, the authors successfully converted the acylation product of the oxime ether into isoindoline with the help of $ZrCl_4$ and $NaBH_4$ and 3-hydroxy-3-phenylindanone by removing the directing group with HCl/dioxane followed by intramolecular aldolization with NaOH/DMSO.



R^1= Ph, 4-MePh, 4-*t*-BuPh, 4-ClPh, 4-CF_3Ph, 4-CNPh, 3-FPh, 3-ClPh, 3,4,5-OMePh, 3-Br-4-OMePh, α-naphthyl, β-naphthyl, cyclopropyl, cyclohexyl, pentyl, 1-pentenyl, 2-methyl-1-propeneyl

R^2= Me, Ph, C_2H_5, C_6H_{13} etc.

R^3= 4-OMe, 4-*t*-Bu, 4-*n*-Bu, 4-CF_3, 4-NO_2, 4-Br, 4-Cl

Scheme 4 NHPI and palladium co-catalyzed aerobic oxidative acylation of various *O*-methyl oximes with aryl/alkyl aldehydes.

Zhao and Jiang in 2016 reported a facile and efficient method for the regioselective acylation of 1,4-disubstituted 1,2,3-triazoles using this heterocyclic moiety as directing group. The reactions were carried out using aromatic aldehydes as acyl transfer agent in the presence of Pd-catalyst (**Scheme 5**).[17] 10 mol% of $Pd(OAc)_2$ and 4 equiv of TBHP were used to prepare 27 derivatives in 55-92% yield after 24 h of reaction at 120 °C. The reaction proceeded with almost equal efficacy in the case of aldehydes as well as 1,4-disubstituted 1,2,3-triazoles, but aldehydes with strong electron withdrawing groups (NO_2, MeS=O) afforded relatively lower yield.

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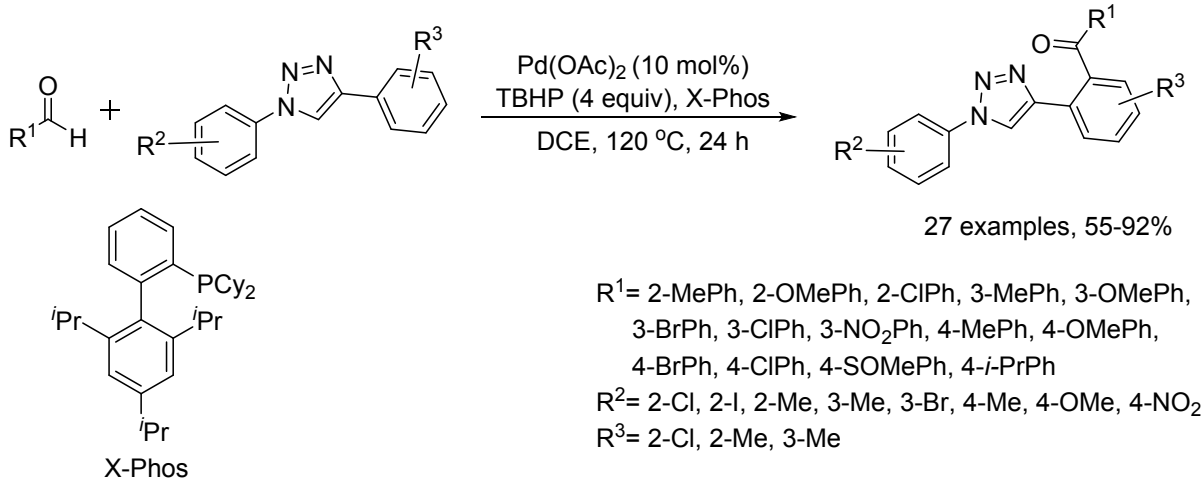
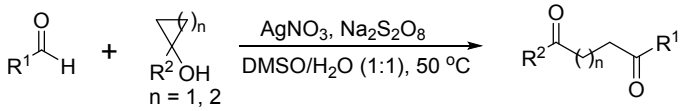


Scheme 5 Regioselective acylation of 1,4-disubstituted 1,2,3-triazoles with aromatic aldehydes.

3.2. Acylation of alkyls

3.2.1. Acylation of sp³ carbons

In 2018 Che *et al.* described a novel silver catalysed ring opening acylation of cyclopropanols and cyclobutanols through intermolecular oxidative radical addition of aromatic aldehdyes under mild and neutral reaction conditions.[18] With the optimized reaction conditions, the substrate scope with respect to cyclopropanols, cyclobutanols and aromatic aldehydes was explored and 32 derivatives were prepared in 36-92% yields at 50 °C (**Scheme 6**). The reactions proceeded smoothly with the applied reaction substrates consisting of distinct functional groups of varying electronic behaviour.



n= 1, 2
R1= Ph, 4-CNPh, 4-CO2MePh, 4-OMe, 4-CHOPh, 4-MsPh, 4-AcPh, 2-CNPh, 4-(C(Et)2OH)Ph
R2= Ph, 2-OMePh, 4-MePh, 4-OMePh, 4-OPhPh, 4-SMePh, 4-FPh, 4-ClPh, 4-BrPh, H, Bn, *n*-Bu, thiophenyl, benzpthiophenyl, benzofuranyl, cyclopropyl, cyclohexyl, cyclobutyl

Scheme 6 Ag-catalyzed ring opening acylation of cyclopropanols and cyclobutanols using aldehydes.

3.2.2. Acylation of sp² carbons

Suresh and co-workers developed an intermolecular tandem Cu-catalyzed *O*-arylation-oxidative acylation protocol to synthesize chromone fused pyrazoles. The reaction was carried out between 2,4-dihydro-3*H*-pyrazol-3-ones and *ortho*-halo aryl carboxaldehydes using air as an ideal oxidant in presence of CuI (0.05 mmol) as catalyst, 1,10-phenanthroline (0.1 mmol) as ligand, K_2CO_3 (1.65 mmol) as base at 120 °C in DMSO solvent.[19] The method was used to prepare 25 chromone-fused pyrazoles in moderate to good yields presenting a countable tolerance towards different substituents in the substrate. During the initial screening of

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substrates 2-bromobenzaldehdye provided better results than 2-chlorobenzaldehdye and 2-iodobenzaldehdye suggesting the bromo group as better leaving group for this transformation. Afterwards the scope of various differently substituted 2-bromobenzaldehdyes was explored for this transformation and it was found that electron donating groups on 2-bromobenzaldehdye were well tolerated and provided the corresponding products in good yields. However, electron withdrawing groups such as fluorine gave the corresponding chromone fused pyrazole in moderate yield. A tetracyclic chromone-fused pyrazole was obtained in 66% yield using 1-bromo-2-naphthaldehdye. On the other hand the reaction of *N*-Boc pyrazolone with 2-bromobenzaldehdye did not give any product. Moreover, this methodology was not found suitable in case of heteroaromtic aldehydes like 2-chloronicotinaldehdye (**Scheme 7**).



Scheme 7 Cu-catalyzed *O*-arylation-oxidative acylation of 2,4-dihydro-3*H*-pyrazol-3-ones with *O*-halo aryl carboxaldehydes.

Recently, an iron catalyzed acyl-azidation of alkenes for the synthesis of unsymmetrical β-azido ketones under mild reaction conditions has been reported by Ge *et al*. Aromatic and aliphatic aldehydes were used as the acyl radical precursors, azidotrimethylsilane ($TMSN_3$) as azido source and TBHP as radical initiator oxidant (**Scheme 8**).[20] Having the optimized reaction conditions in hand, initially the authors investigated the scope of alkenes for the transformation and reactions of *o*-, *m*- and *p*-substituted styrenes (vinylarenes) with benzaldehyde delivering the products in moderate to good yields. Styrenes having alkyl substituents delivered better results than those carrying halogens. Interestingly, vinylarenes containing an ester or a free carboxylic group at the *para*-position also reacted effectively under the optimized reaction conditions and afforded the products in moderate yields. Moreover, heterocyclic compounds, α,β-unsaturated carbonyl compounds and conjugated dienes also resulted in the corresponding azido ketones in moderate yields on treatment with benzaldehyde and $TMSN_3$. Subsequently, the scope of aromatic aldehydes, aliphatic aldehydes and α,β-unsaturated aldehydes was investigated. Aryl aldehydes having either electron-donating or electron-withdrawing groups reacted smoothly with moderate to good yields. However electron-donating groups were found to be more efficient than electron-withdrawing groups.

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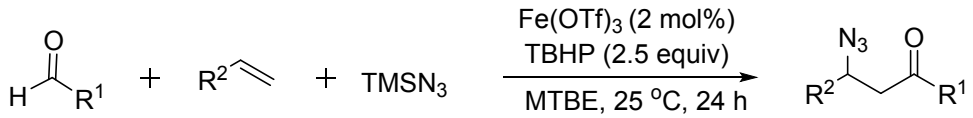

R1= Ph, 4-OMePh, 4-*t*-BuPh, 4-ClPh, 4-OHPh, 2-Cl, 3,4-MePh, 5-Cl-2-FPh, 3-F-6-MePh, α-naphthyl, β-naphthyl, furanyl, thiophenyl, benzofuranyl, benzothiophenyl, 4-((trimethylsilyl)ethynyl)phenyl, 4-morpholinophenyl, cyclopropyl, propyl, cyclohex-3-en-1-yl, 3-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl), etc.

R^2= Ph, 4-MePh, 4-*t*-BuPh, 4-FPh, 4-ClPh, 4-CO_2MePh, 4-CO_2HPh, 3-MePh, 3-ClPh, 2-MePh, 2-ClPh, ethyl, OMe, COOH, OC_6H_{13}, 4-methylthiazolyl, styrenyl, etc.

Scheme 8 Iron-catalyzed acyl-azidation of alkenes.

3.2.3. Acylation of sp carbons

In 2015, Wu and co-workers disclosed a metal-free tandem acylation of alkynoates with aldehydes followed by an intramolecular cyclization leading to 3-acyl-4-arylcoumarins. The reaction proceeded under metal-free conditions in the presence of tetrabutylammonium bromide (TBAB) as additive and $K_2S_2O_8$ as oxidant for the selective synthesis of biologically attractive 3-acylcoumarins.[21] Under the optimized reaction conditions, various differently substituted aldehydes and aryl alkynoates could be coupled in a metal-free acylation/cyclization reaction to obtain the 3-acylcoumarins in moderate to good yields. Aromatic aldehydes having electron-donating groups at the *para*-position of the aromatic ring coupled more efficiently than those bearing electron-withdrawing groups. Although, *ortho*- and *meta*-substituted benzaldehydes were also suitable for this transformation. Moreover, alkyl and cyclic aldehydes could also be used and provided the corresponding coumarin derivatives in moderate yields.

Similarly, the aryl alkynoates with either an electron-rich or electron-poor substituent at the *para*-position of the phenoxy ring reacted well and the corresponding products were obtained in good yields. However, in the presence of the strong-electron withdrawing CF_3 group on the phenoxy ring only 38% yield of the product was obtained, whereas no product was formed for the *ortho*-substituted system. Furthermore, aryl alkynoates with a methyl group at the *meta*-position of the phenoxy ring resulted into a mixture of two regioisomers in a 1.6:1 ratio. However, with a methoxy group at the *meta*-position only one isomer was obtained in 76% yield (**Scheme 9**).

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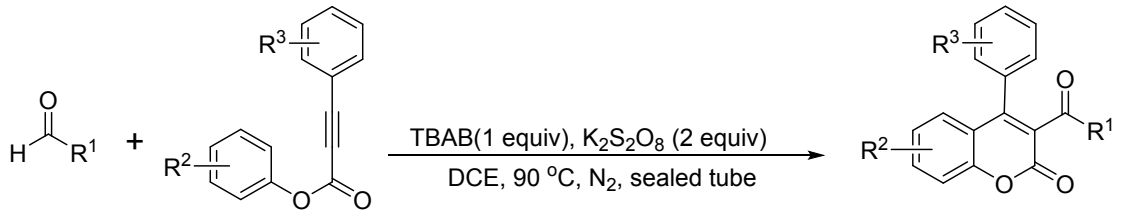

35 examples, 37-86%

R^1= Ph, 4-MePh, 4-OMePh, 4-IPh, 4-ClPh, 4-ClPh, 4-BrPh, 4-CF_3Ph, 3-MePh, 3-OMePh, 3-ClPh, 2,4-ClPh, 2-MePh, 2-OHPh, *n*-Pr, *i*-Bu, cyclopropyl

R^2= 5,7-Me, 6-Me, 6-t-Bu, 6-OMe, 6-OPh, 6-F, 6-Cl, 6-Br, 6-CF_3, 5-Me, 8-Me, 7-OMe

R^3= H

Scheme 9 Metal-free tandem acylation of alkynoates with aldehydes followed by an intramolecular cyclization.

3.3. Acylation of heteroarenes/heteroaryls

Heterocyclic compounds constitute the largest and one of the most vital classes of organic compounds used in many biological fields due to their importance in the treatment of multiple illnesses. Presently, lots of heterocyclic compounds are known and due to the enormous synthetic research as well as their synthetic utility the number of heterocyclic molecules is increasing rapidly day-by-day. Heterocyclic compounds play a role in almost all fields of science such as medicinal chemistry, biochemistry, synthetic chemistry, and widely distributed in natural products, biomolecules and other bioactive molecules. These scaffolds are major constituents of biological molecules such as DNA, RNA, vitamins, enzymes, chlorophyll, haemoglobin and many more. Therefore, pharmaceutical and organic chemists have been making extensive efforts for the construction and functionalization of heterocyclic molecules through developing versatile, atom- and step-economical efficient synthetic strategies.

Wu and his team described a one-pot procedure for the selective formation of 8-acylated-2-quinolinones starting from quinilone-*N*-oxides and aldehydes using a palladium-based catalyst and TBHP oxidant through the formation of an *N*-oxide-chelated palladacycle.[22] While evaluating the reaction parameters, the authors found that the best conditions involved the stirring of a mixture of quinoline-*N*-oxide (0.2 mmol) with benzaldehyde (0.6 mmol) in the presence of $PdCl_2$ (10 mol %), TBHP (0.9 mmol, 5-6 M in decane), water (100 μL) as additive, DCE (1.5 mL) as solvent at 140 °C for 24 h. A total 26 8-acylated-2-quinolinones were prepared in good to excellent yields by this strategy starting from various quinoline-*N*-oxides and benzaldehydes (**Scheme 10**). Benzaldehydes having electron-donating (Me and OMe) and weak electron-withdrawing substituents (F, Cl and Br) at the *para*-position of the aryl gave the corresponding products in good to excellent yields. However, the efficiency of the acylation was slightly affected by steric hindrance as *p*-methylbenzaldehyde gave a slightly higher yield relative to *o*- and *m*-methylbenzaldehyde and a similar trend was observed for methoxy and halogen-substituted benzadehydes. 3-(Trifluoromethyl)benzaldehyde provided the acylated product in only 43% yield. Furthermore, disubstituted aromatic aldehydes also provided good yields of the desired products. Substituted quinoline-*N*-oxides were also coupled smoothly with benzaldehyde and the position of the substituents did not influence the formation of the products significantly, expanding the synthetic utility of the current acylation protocol.

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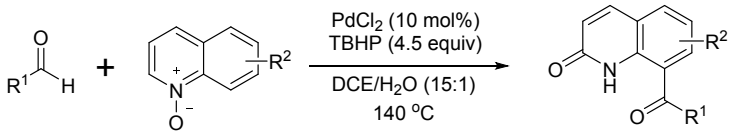


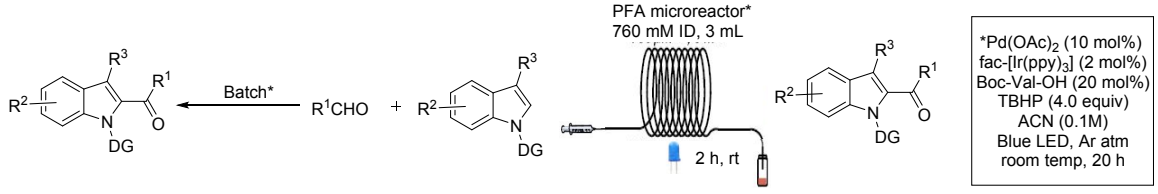
26 examples, 30-95%

R^1= Ph, 4-MePh, 4-OMePh, 4-FPh, 4-ClPh, 4-BrPh, 2-MePh, 2-OMePh, 2-FPh, 2-ClPh, 2-BrPh, 3-MePh, 3-OMePh, 3-FPh, 3-ClPh, 3-BrPh, 3-CF_3Ph, 3,4-MePh, 2,4-ClPh, a-naphthyl

R^2= 3-Me, 6-Me, 5-OMe, 3-Br, 6-F, 6-Cl

Scheme 10 Pd-catalyzed selective C-8 acylation of quinilone-*N*-oxides using aldehydes.

Van der Eycken and his group established a mild and versatile method for the C2 C-H acylation of *N*-pyrimidylindoles with aldehdyes *via* dual photoredox/transition-metal catalysis in batch and flow at room temperature.[23] Initially, the authors explored various reaction parameters including solvent, catalysts, photocatalysts and ligands to achieve optimal reaction conditions. Finally, the use of 10 mol% $Pd(OAc)_2$ catalyst, 2 mol% of photocatalyst *fac*-[$Ir(ppy)_3$], 20 mol% Boc-Val-OH ligand and 4 equiv of 0.1 M TBHP in acetonitrile delivered the best outcome in the presence of blue LED light after 20 h in a batch process. Whereas in a flow process only 0.5 mol% of photocatalyst *fac*-[$Ir(ppy)_3$] with slight excess of oxidant (6 equiv of 0.2 M TBHP in acetonitrile) along with the rest of the other reagents was found to be enough to give good product yields in just 2 h. With these optimized reaction conditions in hand, the scope of the reaction was determined by exploring various substituted benzaldehydes as coupling partners of *N*-protected indoles. C2-acylation of indole derivatives with benzaldehyde bearing alkyl/aryl groups or a methoxy group smoothly proceeded with good product yields. However, hydroxylated benzaldehydes delivered inferior yields. Furthermore, the acylated products were obtained in good yields (54-89%) when benzaldehyde contained electron withdrawing groups such as Br, CN, NO_2, CF_3. Interestingly, heterocyclic aromatic aldehydes, aliphatic acyclic and cyclic/heterocyclic aldehydes reacted efficiently to afford C2-acylated *N*-pyrimidylindoles in good to excellent yields (**Scheme 11**).



DG= pyrimidinyl, pyridinyl, Boc, methyl

29 examples, 0-81%

R^1= Ph, 4- MePh, 4-PhPh, 4-OMePh, 4-OHPh, 4-FPh, 4-CF_3Ph, 4-BrPh, 4-NO_2Ph, 4-CNPh, 2,4,6-MePh, 3-OHPh, 3-BrPh, 3-IPh, 3-NO_2Ph, b-naphtyl, furanyl, thiophenyl, 2,6-dimethylhept-2-enyl, cyclohexyl

R^2= H, 5-OMe, 5-F, 6-F, 7-Me

R^3= H, Me

18 examples, 0-95%

R1= 4- MePh, 4-OMePh, 4-OHPh, 4-FPh, 4-CF_3Ph, 4-CNPh, 3-IPh, 3-NO_2Ph, b-naphtyl, furanyl, furan-2-ylmethanol, 2,6-dimethylhept-2-enyl, 2,6-dimethylheptan-2-ol, cyclohexyl, *tert*-butyl piperidine-1-carboxylate, *tert*-butyl pyrrolidine-1-carboxylate,

R^2= H, 6-F

R^3= H

Scheme 11 Acylation of N-pyrimidylindoles with aldehdyes *via* dual photoredox/transition-metal catalysis in batch and flow.

Recently, Singh and co-workers have developed a highly efficient, metal-free approach for the regioselective C3-acylation of coumarin with aromatic aldehydes using *tert*-butyl peroxybenoate (TBPB) as free radical initiator.[10] Various differently substituted aromatic aldehydes having electron-withdrawing and electron-donating groups were reacted with 7-

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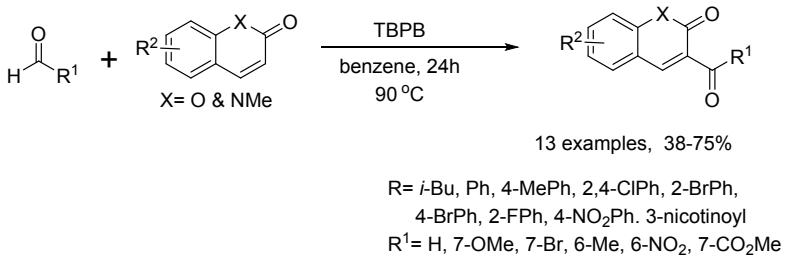
methoxy coumarin under the optimized reaction conditions. All applied aromatic aldehydes delivered the desired products in moderate to good yields at 90 °C after 24h. Also, other derivatives of coumarin produced the desired products in good yields upon treatment with benzaldehyde. Unfortunately, neither aromatic aldehyde nor coumarin bearing a strong electron-withdrawing NO_2-group furnished the corresponding acylated compound. Moreover, isobutyraldehyde and pyridine-2-carbaldehyde also resulted in the acylation of coumarin at the C3-position in 41% and 60% yield, respectively. Furthermore, *N*-methylquinolone delivered the C3-acylated product upon treatment with benzaldehyde under the optimized reaction conditions (**Scheme 12**).



Scheme 12 Regioselective C3-acylation of coumarin with aldehydes.

4. Miscellaneous

In 2014, Luo and Liang developed a metal-free one-pot cascade cyclization of 1,6-enynes with aldehydes involving simultaneous formation of one C(sp^2)-C(sp^2) and two C(sp^2)-C(sp^3) bonds resulting in the synthesis of carbonylated tricyclic fluorene derivatives by using PivOH and TBHP.[24] The conditions were optimized as the reaction of a 1,6-enyne (0.2 mmol) with an aldehyde (1.0 mmol) in the presence of the oxidant TBHP (0.4 mmol, 70% aqueous solution), the additive PivOH (0.4 mmol) in acetonitrile (1 mL) as solvent at 120 °C for 48 h under argon atmosphere. These reaction conditions were initially examined for the exploitation of aldehydes in this cascade oxidative cyclization process. Various aromatic aldehydes containing electron-donating and electron-withdrawing groups were able to participate in this reaction to afford the desired fluorene derivatives in good yields regardless the position of the substituents on the aryl ring of aldehydes (**Scheme 13**). Aliphatic aldehydes were not suited in this transformation as only trace amount of the products could be obtained. Remarkably, benzo[*d*][1,3]dioxole-5-carbaldehyde and thiophene-2-carboxyaldehyde could also undergo the reaction giving the products in 45% and 35% yields, respectively.

Delighted by these promising results, the scope of 1,6-enyne substrates was examined with benzaldehyde and the reaction proceeded smoothly in most of the cases giving the desired products in moderate to good yields (**Scheme 13**). 1,6-Enynes substituted with electron-donating alkyl or alkoxy groups at the *ortho*, *meta* or *para*-position or containing either halogen or an electron-withdrawing COOMe, CN group at the *para*-position were comfortable the reaction to afford the corresponding carbonylated flurenes. The tosylamides could also react with benzaldehyde to give the products in moderate yields, whereas only trace amounts of the product (9,9-dimethyl-1,3,9,9a-tetrahydroindeno[2,1-*c*]pyran-4-yl)(phenyl)methanone were obtained from the corresponding enyne substrate.

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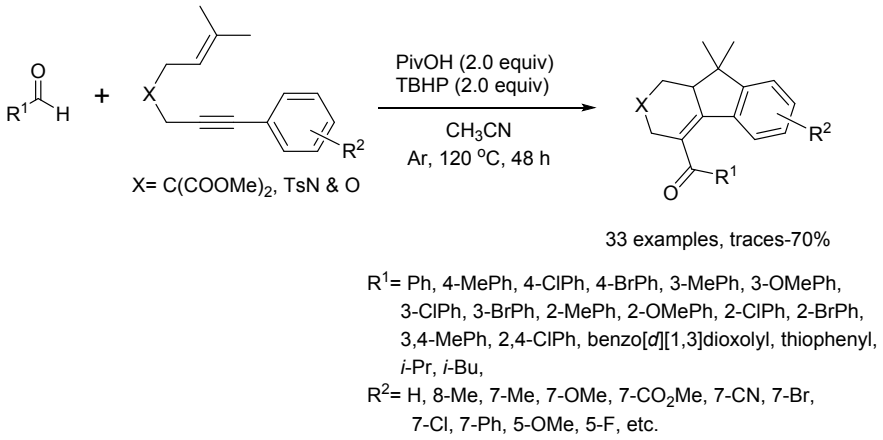

Scheme 13 Metal-free one-pot cascade cyclization of 1,6-enynes with aldehydes.

Later in 2017, Zheng and Ma published a direct oxidative *N*-acylation reaction of primary amines with aryl/α,β-unsaturated aldehydes in the presence of the azolium salt of an *N*-heterocyclic carbine, using ^{t}BuOK or NaH as base and 3,3',5,5'-*tetra*-*tert*-butyldiphenoquinone (DPQ) as oxidant at 25 °C.[25] This methodology provided a proficient approach for the synthesis of *N*-sulfonylcarboxamides, *N*-sulfinylcarboxamides and dicarboxyimides in good yields. The scope of the primary amines with aldehydes was investigated by synthesizing 24 *N*-acylated derivatives of amines in high yields. Aryl aldehydes bearing various substituents such as F, Cl, OMe and NO_2 at different positions (*ortho*-, *meta*- and *para*-) of the aryl ring participated in the reaction with toslyamide to give the respective *N*-tosylcarboxamindes in high yields. Delightfully, thiophene-2-carbaldehyde and 2-naphthaldehyde provided the respective imides in 87% and 91% yield with these newly developed conditions (**Scheme 14**). Moreover, α,β-unsaturated aldehydes including enals and ynals, also fitted suitably in this direct *N*-acylation protocol of tosylamide and conjugated ynals bearing an aliphatic or aromatic substituent exhibited a wide scope resulting in 71-87% yields of the products. Unfortunately, alkylated aldehydes were found to be inactive under the current reaction conditions and could not afford the imide products probably due to competing enolization of the ldehyde substrate.

To expand the synthetic utility of this methodology, other amide substrates were examined. Electron-rich (unsubstituted) as well as electron-poor (*p*-NO_2 and *p*-Cl substituted) aryl sulfonamides upon reaction with 4-chlorobenzaldehyde delivered excellent 93-96% yields of the corresponding products. Besides, methanesulfonamide was also witnessed as a competent reaction partner since 92% yield of the product could be obtained in this case. Additionally, benzamide and its *p*-chloro and *p*-nitro derivatives could also be employed effortlessly for the formation of dicarboxyamides using the stronger base NaH (3.0 equivalent) instead ^{t}BuOK, due to the inferior acidity of carboxamides compared to sulfonamides. Interestingly, (*S*)-*tert*-butylsulfinamide (99% ee) fitted efficiently in this protocol and yielded the (*S*)-*tert*-butylsulfinamide-4-chlorobenzamide in 81% yield with almost complete retention (98% ee) of configuration (**Scheme 14**).

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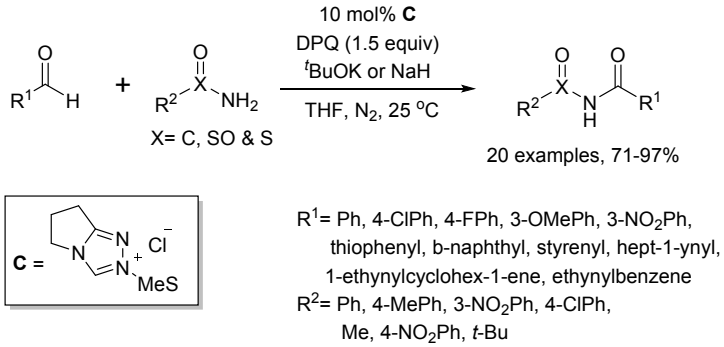

Scheme 14 *N*-acylation reaction of primary amines with aryl/α,β-unsaturated aldehydes using azolium salt of an *N*-heterocyclic carbene.

Hu and co-workers divulged a facile and efficient $PhI(OAc)_2$-promoted double acylation (*N*- and *O*-acylation) of hydroxylamines with aldehydes at room temperature in acetic acid for the synthesis of *N*-acetoxy-*N*-arylamides in good to excellent yields.[26] The acylation of *N*-atom of the hydroxylamines is due to the acyl group of aldehyde, whereas the O-atom gets acylated by the acetyl group of $PhI(OAc)_2$. This transformation exhibited great substrate scope under the optimized reaction conditions. Initially, the effect of aromatic aldehydes was explored with *N*-phenylhydroxylamine and all the selected aryl aldehydes could give the desired products regardless the nature (electron-releasing or electron-donating) of the substituents present on aromatic ring. However, in some cases the position of the substituents on the aryl ring of the bezaldehyde was found to influence the reaction yield. For example, *m*-nitrobenzaldehyde delivered 85% yield whereas *p*-nitrobenzaldehyde resulted in 73% yield, but unfortunately no product formation took place with *o*-nitrobenzaldehyde. 2-Furaldehyde and pyridine-2-carboxaldehyde offered their respective products in good yields, while on the other hand no product formation was observed with aliphatic aldehydes (**Scheme 15**).

Similarly, the applicability of various *N*-aromatic hydroxylamines bearing an electron-rich methyl group or an electro-poor chloro, bromo, acetyl or ester group was evaluated with benzaldehyde, and the corresponding products were obtained in 45-75% yields. However, no product could be obtained with aliphatic hydroxylamines such as *N*-methylhydroxylamine and *N*-(*t*-butyl) hydroxylamine. Next, the compatibility of simultaneous presence of substituents on the aromatic aldehyde and the aromatic hydroxylamine was exploited. Aromatic aldehydes delivered higher product yields when electron-withdrawing groups were present. On the other hand, aromatic hydroxylamines with electron-donating groups on their phenyl ring resulted in higher product yields (**Scheme 15**).

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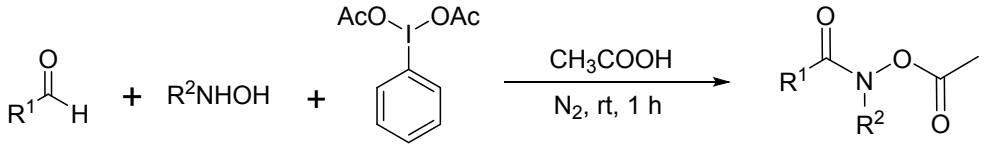


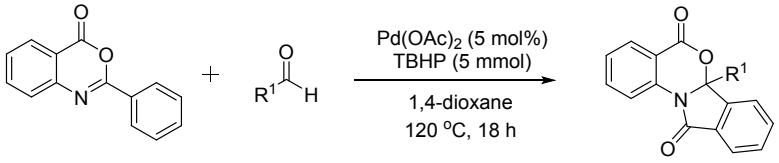
35 examples, 0-96%

R^1= Ph, 2-MePh, 3-MePh, 4-MePh, 3-OMePh, 4-OMePh, 2-ClPh, 3-ClPh, 4-ClPh, 2-NO_2Ph, 3-NO_2Ph, 4-NO_2Ph, 4-CNPh, furanyl, pyridinyl, propyl, 4-CF_3Ph

R^2= Ph, Me, *t*-Bu, 2-MePh, 3-MePh, 4-MePh, 2-ClPh, 3-ClPh, 4-ClPh, 4-BrPh, 4-AcPh, 4-($CO_2C_2H_5$)Ph

Scheme 15 PhI$(OAc)_2$-promoted double acylation (*N*- and *O*-acylation) of hydroxylamines with aldehydes.

Recently in 2018, Kumar *et al.* disclosed a radical-induced Pd-catalyzed approach for the direct functionalization of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones with aldehydes. The reaction proceeded through the formation of the *o*-acylated 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one intermediate to give 6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones in the presence of TBHP as oxidant.[11] Various aryl aldehydes with electron-rdonating groups (Me, OMe) and electron-withdrawing groups (F, Cl, Br, etc.) reacted smoothly with 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one in the presence of $Pd(OAc)_2$ (5 mol%) as catalyst using TBHP (5 mmol) as oxidant in 1,4-dioxane as solvent at 120 ^oC for 18 h to afford 19 derivatives in 21-79% yield (**Scheme 16**). Aliphatic aldehydes such as cyclohexanecarboxaldehyde and isobutyraldehyde delivered the corresponding products in 48% and 33% yields, respectively.



18 examples, 22-79%

R^1= Ph, 2-FPh, 2-ClPh, 2-BrPh, 4-MePh, 4-OMePh, 4-FPh, 4-ClPh, 4-BrPh, 3,4-MePh, 3,4-OMePh, 3-ClPh, 2,4-FPh, 2,6-FPh, 2-F-4-ClPh, 2-F-4-BrPh, cyclohexyl, isopropyl

Scheme 16 Pd-catalyzed direct functionalization of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones with aldehydes.

Further progress in this field is underway.

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Dr. Prashant Kumar is currently an Assistant professor at SRM University, Sonipat, India. He completed his Ph.D. in 2018 from the Department of Chemistry, University of Delhi. Since then he has been actively involved in research and teaching students pursuing Bachelors' as well as Masters'

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Degree in Chemistry. He has taught in various colleges and institutes including Acharya Narendra Dev College, University of Delhi, SGT University, India. Dr. Kumar holds good expertise in organic chemistry and is a recipient of prestigious awards like UGC-JRF, UGC-SRF awarded by university grants commission, government of India, India. He has worked extensively on metal catalyzed and metal free C-H activation reactions that are of utmost significance in synthetic organic chemistry. He has also worked on the synthesis of biologically active molecules and this work has been published in reputed international journals like Advanced Synthesis and Catalysis, European Journal of Chemistry, ACS Sustainable Chemistry & Engineering, Nature Scientific Reports, etc.

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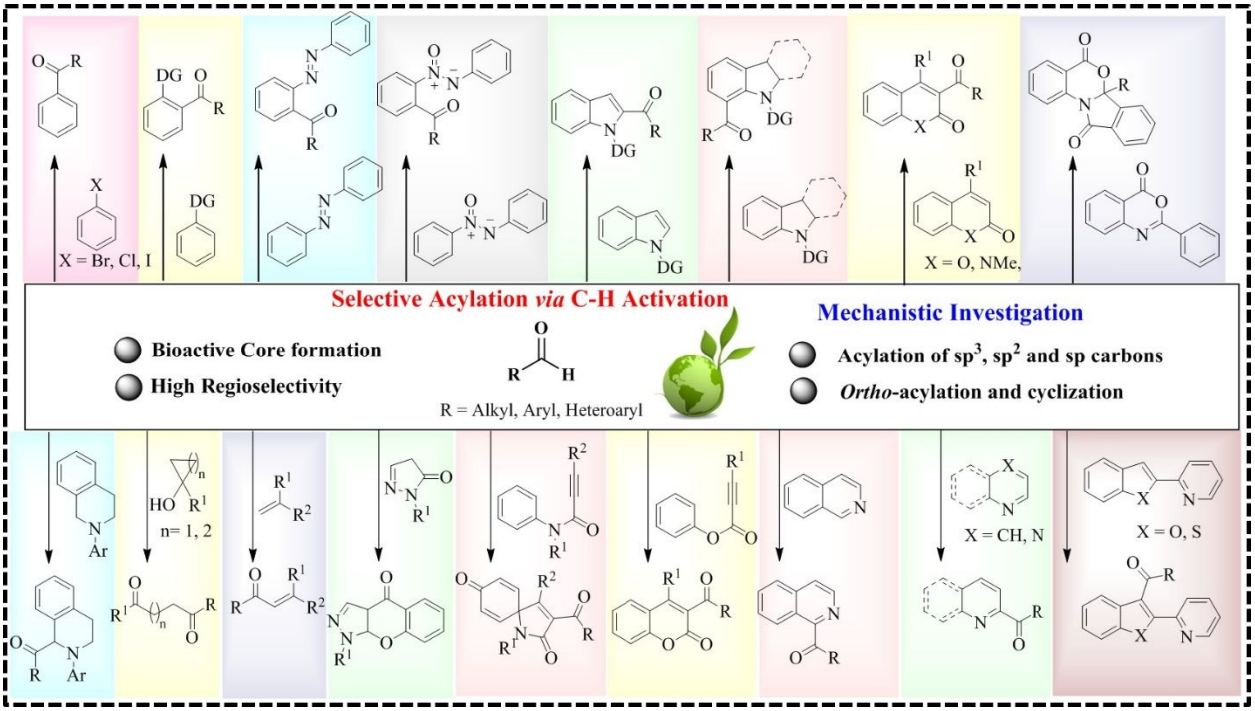
Table of contents

This review sheds light on the use of aldehydes in selective acylation of arenes, heteroarenes and alkyls (sp^3, sp^2 and sp) C-H bonds by proficient utilization of C-H activation strategy.



ARTICLE

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Aldehydes: magnificent acyl equivalents for direct acylation

Prashant Kumar*[a,b] Sriparna Dutta,[b] Sandeep Kumar,[b] Vijay Bahadur,[a,b] Erik V. Van der Eycken,[c,d] Karani S Vimaleswaran,[e] Virinder S. Parmar[f] and Brajendra K. Singh*[b]

From the viewpoint of meeting the current Green Chemistry challenges in chemical synthesis, there is a need to disseminate how the cocktail of acylation and activation can play a pivotal role in affording bioactive acylated products comprising of substituted ketone motifs in fewer reaction steps, with higher atom-economy and improved selectivity. In recent years, a significant number of articles employing the title compounds "aldehydes" as magnificent acylation surrogates have been developed which are less toxic and widely applicable. This review sheds light on their use for selective acylation of arenes, heteroarenes and alkyls (sp^3, sp^2 and sp) C-H bonds by proficient utilization of C-H activation strategy. Critical insights on selective acylation of diverse moieties for the synthesis of bioactive compounds are presented in this review that will enable the academic as well as the industrial researchers to understand the mechanistic aspects involved and fruitfully employ these strategies in designing novel molecules.

1. Introduction

The concise forging of substituted ketone motifs by means of direct functionalization using C-H activation strategies presents the incredible state of the art in synthetic organic chemistry. Ketones are commonly used ubiquitous structural units for developing pharmaceuticals, dyes, agrochemicals, electronic materials and natural products. These are the fundamental building blocks of various bioactive molecules and drugs such as tiaprofenic acid and ketoprofen which are used as anti-photoallergic agents[1] and nonsteroidal anti-inflammatory drugs,[2] fenofibrate that is used as the classical lipid regulating agent[3], benzbromarone (BBR) which is employed as a uricosuric agent[4], and mebendazole that works as a broad-spectrum human anthelmintic agent.[5] Over the course of time, structural diversity of the disubstituted ketone moieties has rapidly expanded as evident from the literature reports. However, the practical challenges associated with the conventional methodologies employed for the synthesis of these significant motifs have in turn engaged the researchers in exploration of improved methods of synthesis. Some of the inherent drawbacks associated with the classical Friedel-Crafts acylation reaction include requirement of harsh reaction conditions and super stoichiometric amounts of Lewis acids, low regioselectivity and the formation of unwanted regioisomers.[6,7] Although other alternative methods have been established over the years comprising of the oxidation of alcohols,[8,9] Grignard/Barbier reaction followed by oxidation,[10] and reaction of Grignard reagents with nitriles,[10f] these methods do not match the current Green Chemistry requirements due to issues related to safety and economy.

Transition metal-catalyzed oxidative cross-coupling reactions for the direct functionalization of C-H bonds with high atom-efficiency have emerged as attractive, efficient and straightforward strategies for access to desirable molecules from simple reaction substrates without any pre-modification or pre-functionalization, thereby increasing the efficacy of the anticipated transformations. Therefore, in recent years these cross-coupling strategies have been extensively explored for the direct synthesis of keto compounds by means of selective acylation of the starting materials. These approaches are found to be highly advantageous over classical methods used for the acylation of alkyl, aryl or heteroaryls leading to the formation of desirable acylated compounds because of fewer reaction steps, higher atom-economy, improved selectivity and non-requirement of pre-functionalization of the starting materials. For direct acylation by following the C-H activation approach, several reagents including aldehydes, benzyl alcohols, α-keto acids, acyl chlorides, etc. have been explored extensively.[11-14] Amongst these acylating surrogates, aldehydes (aliphatic and aromatic) have received profound

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attention because of their high stability, less toxicity, ease of availability, broad substrate scope and low cost.

In fact, aldehydes consist of an important class of molecules that are found extensively in nature. Amongst the aldehydes, benzaldehyde is one of the most important motifs, which is widely used in food industry as an ingredient in cherry and other natural fruity flavours. Naturally, aldehyde motifs are present in peach, black tea, bitter almond, and apricot kernel.[15] Benzaldehyde has been reported to act as an anti-tumour agent for various kinds of tumours occurring in humans[16] and mice.[17] The mechanism for the anti-tumour behaviour of benzaldehyde for cell growth inhibition has been well established using human NHIK 3025 cells.[18] Aldehydes can be formed endogenously by amine oxidases, carbohydrate or ascorbate autoxidation, lipid peroxidation, myeloperoxidase-catalyzed metabolic activation, carbohydrate metabolism or by cytochrome P-450s, etc.[19,20] In the year 1946, the first review[21], which was published by Lloyd N. Fergusoy from the University of California, on the synthesis of aromatic aldehydes, covered essential information pertaining to both the direct as well as indirect method for the introduction of the formyl (CHO) group into the aromatic nucleus. It was highlighted in this review that Gattermann and Koch[22] for the first time prepared aromatic aldehydes *via* reaction between benzene and its derivatives, CO and HCl, using anhydrous $AlCl_3$ as a catalyst. Thereafter, this protocol was modified further by Gattermann[23] himself, where he used cyanide instead of CO and produced aldimine hydrochloride as an intermediate that was hydrolysed to the aldehyde. In due course, several other methods were established for aldehyde synthesis. Also, meanwhile attempts were made towards utilizing aldehydes for their transformation into valuable compounds. For instance, it was found that benzaldehyde could react with pyruvate and get transformed into a chiral compound (*R*)-phenylacetylcarbinol [(*R*)-PAC] with the help of pyruvate decarboxylase (PDC) enzyme (**Fig. 1**).[24,25]

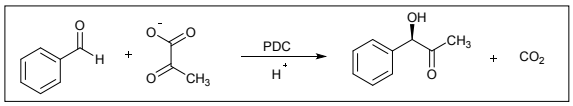

Fig. 1 Transformation of benzaldehyde and pyruvate into (R)-phenylacetylcarbinol using pyruvate decarboxylase.

Henceforth, aldehydes were employed as starting materials in important organic reactions such as addition, condensation, hydrogenation, coupling, etc.[26-31] Over the course of time, aldehydes were also employed in radical acylation and oxidative acylation reactions that result in the direct regioselective formation of new C-C and C-N bonds. These routes provided better alternatives to anhydrides, acyl halides, α-ketoacids and other acylating agents.[32-34] Ideally, it is well known that green chemistry helps in achieving reduction of waste at source by redesigning existing processes at the molecular level. These acylation reactions add to the credentials of green chemistry. A major breakthrough in the use of aldehydes as acylating agents was achieved when Cheng *et al.* in 2009 reported the first direct oxidative acylation of a C-H bond applying aromatic aldehydes as acyl equivalents in the presence of a Pd-catalyst.[35] During mechanistic investigation of the radical induced acylation reactions, it was postulated that the aldehyde moiety gets converted first into an acyl radical **(Fig. 2)** which then combines to give the corresponding acylated product.

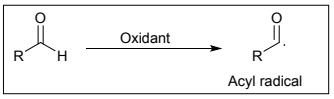

Fig. 2 Acyl radical formation from the aldehydes.

The use of benzaldehydes in radical mediated as well as oxidative cross-coupling reactions was reviewed by Xiao-Feng Wu in 2015.[33] This mini-review sheds light on recent work in transition metal catalysed acylation of aryls, heteroaryls/heteroarenes. Thereafter, in 2016, Kim and co-workers published a review summarizing the recent progress in oxidative and decarboxylative transition metal-catalysed acylation reactions by C-H activation.[34]

2. Scope of Review

There is a need to disseminate how wondrously the aldehyde moieties are employed in various acylation reactions using C-H activation and how they succumb to provide a better substitute of the irritating and toxic anhydrides, acyl halides and other acylating reagents. Although there are several reviews on C-H bonds activation and transition metal-catalysed reactions, yet, to the best of our knowledge, there is no single review that throws light on the use of aldehydes as magnificent acylation surrogates compiling the acylation of arenes, heteroarenes and alkyls (sp^3, sp^2 and sp) C-H bonds resulting in the synthesis of valuable C-X (X=C, O, N) bonds by proficient use of C-H activation. This review presents some of the exciting discoveries accomplished during the past few years in the development of novel catalytic protocols, shedding light on some of the latest synthetic tools including flow chemistry and photochemical methodologies. It includes a comprehensive discussion on the mechanistic aspects that will enable the researchers to think creatively and work in this exciting area. This review focusses on using greener tools and strategies, given that chemical waste has a disastrous impact

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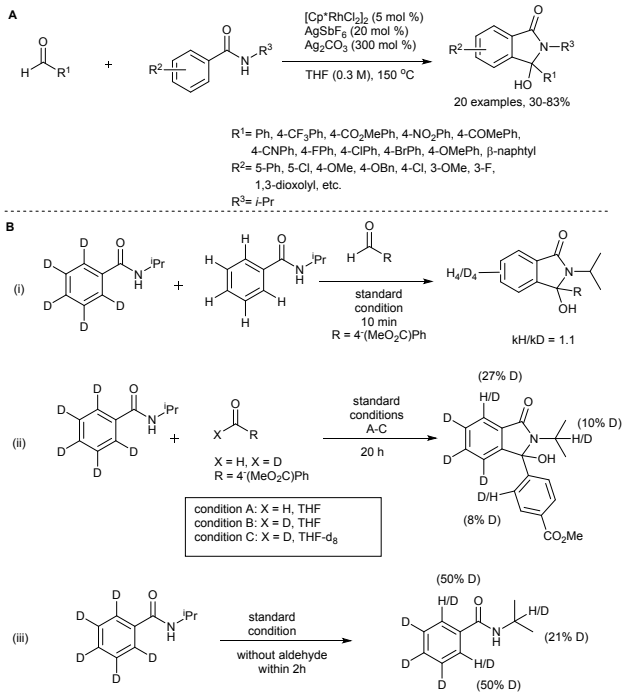
on human health as well as on the environment and eco-systems.

3. Aldehydes in acylation reactions

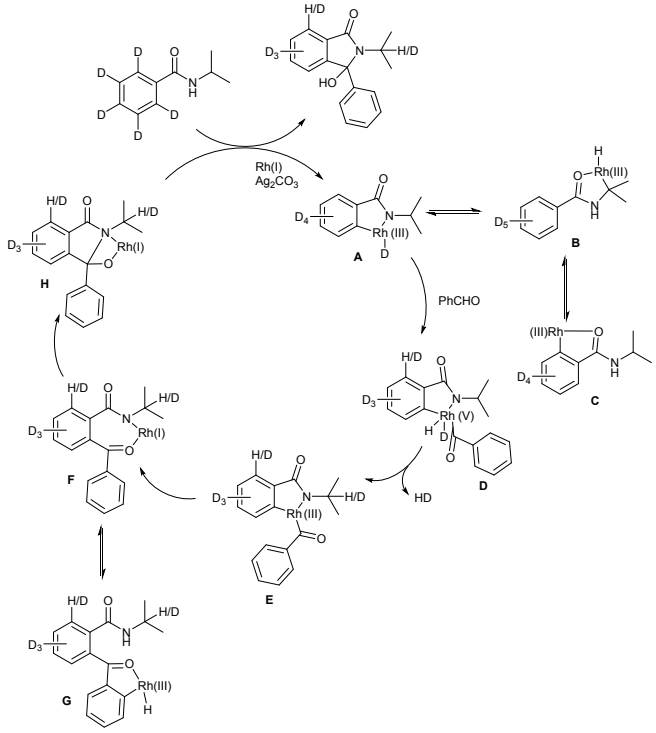
3.1. Acylation of arenes

In 2012, Kim and his team described the Rh-catalyzed regioselective acylation of secondary benzamides using aromatic aldehydes, which on subsequent intramolecular cyclization afforded 3-hydroxyisoindolin-1-ones (**Scheme 1**).[36] Authors have synthesized 21 derivatives of 3-hydroxyisoindolin-1-one by reacting several differently substituted benzamides with aldehydes. Benzaldehydes having electron-withdrawing groups such as NO_2, CF_3, COOMe, CN, etc. delivered the 3-hydroxyisoindolin-1-ones in high yields. On the other hand, aldehydes carrying the electron-releasing OMe group displayed inferior reactivity. Benzamides having electron-releasing groups delivered high yields in comparison to those bearing electron-withdrawing groups.



Scheme 1: Rh-catalyzed regioselective sp^2 C-H acylation of secondary benzamides using aryl aldehydes with intramolecular cyclization and mechanistic studies.

To probe the catalytic reaction pathway for this transformation, authors carried out intermolecular kinetic isotope experiment by treating equimolar amounts of deuterated benzamide and simple benzamide with methyl terephthalaldehydate under standard reaction conditions for 10 min and a 1.1 k_H/k_D value was observed (**Scheme 1B**). Other deuterium-labelling control experiments suggested the rapid and reversible metalation-proto(deutero)demetalation before the cross-coupling reaction. This also suggested that addition of the aldehyde to the cyclo-rhodated intermediate is involved in the rate-limiting step of this conversion. A possible reaction mechanism is depicted in **Scheme 2**.

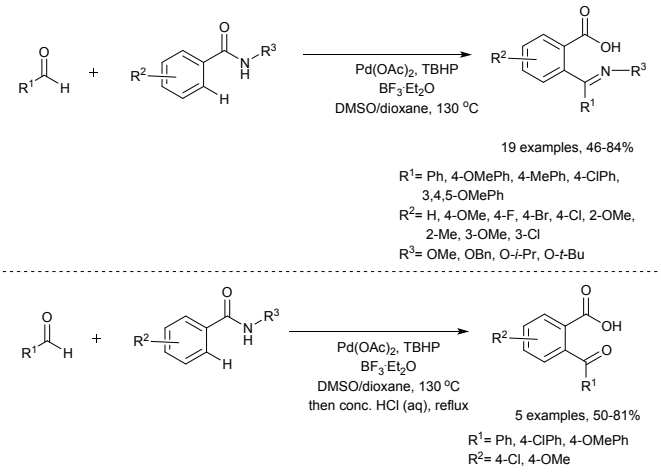


Scheme 2: Plausible reaction mechanism of the Rh-catalyzed regioselective sp^2 C-H acylation process for the secondary benzamides with aryl aldehydes.

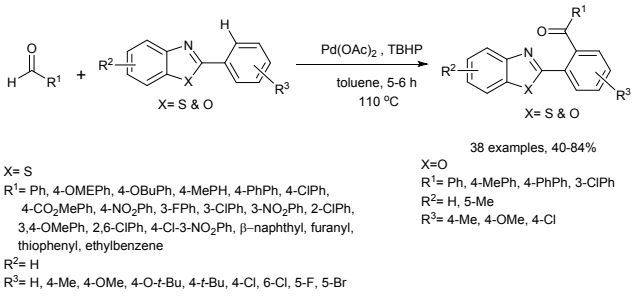
In 2013, Zhang *et al.* developed a Pd-catalysed protocol for the synthesis of keto-carboxylic acids through an aryl amide directed C-H functionalization approach. The reaction proceeded by oxidative coupling between aryl amides and aldehydes using TBHP as oxidant and resulted in imino carboxylic acids, which on subsequent treatment with HCl solution gave keto carboxylic acids.[37] The reactions progressed through benzamide directed *o*-acylation followed by ring closing and opening to give keto-carboxylic acids. Both benzamides as well as aldehydes bearing electron-releasing groups and electron-withdrawing groups were compatible for the reaction irrespective of the positions of the functional groups. The authors prepared 19 imino carboxylic acid derivatives in 46-84% yield and five keto-carboxylic acid derivatives in 50-80% yield (**Scheme 3**).

Two closely related studies were disclosed by Patel *et al.* and Wu *et al.* in 2013 using Pd(II) catalyst and TBHP oxidant for direct *o*-acylation of 2-arylbenzothiazoles and 2-arylbenzoxazoles. In the first study,[38] the authors reacted benzothiazoles or benzoxazoles with aldehydes using $Pd(OAc)_2$ as catalyst and TBHP as oxidant in toluene as solvent (**Scheme 4**). A set of 38 *o*-acylated benzothiazoles and

benzoxazoles were prepared in moderate to good yields. The developed method was robust and adequate for diverse azoles and aldehydes. The method seemed to be insensitive to the electronic behaviour of the substituents present either on azoles or aldehydes.



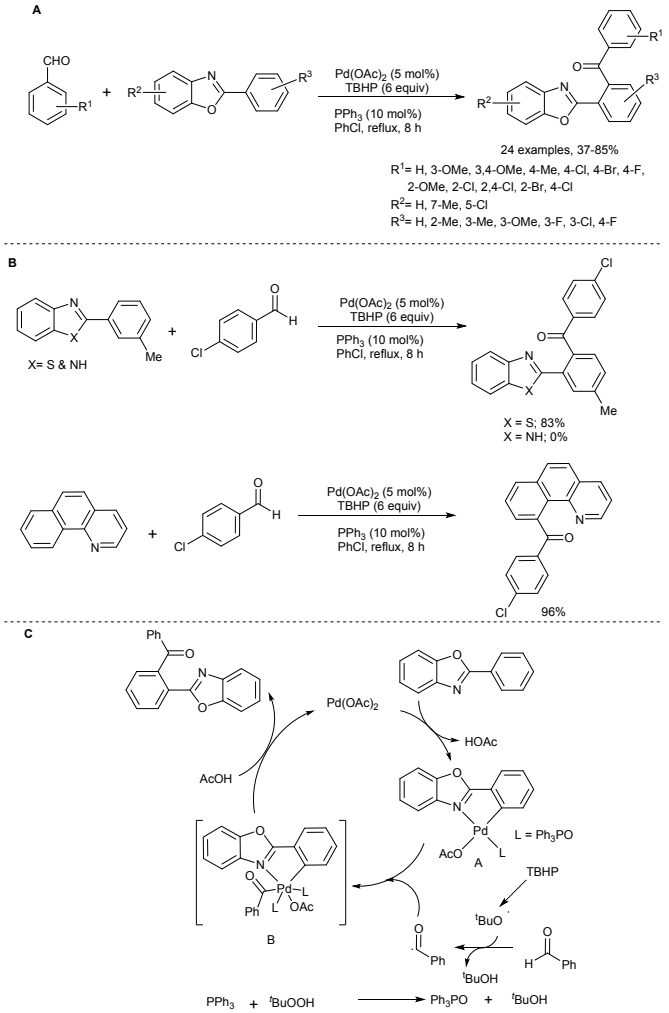
Scheme 3: Pd-catalyzed synthesis of imino carboxylic acids and keto-carboxylic acids *via* aryl amide directed C-H activation reaction.



Scheme 4: Pd(II)-catalyzed direct ortho-acylation of 2-arylbenzothiazoles and 2-arylbenzoxazoles.

In a second study,[39] the authors reported the *o*-acylation of 2-arylbenzoxazoles using aldehydes as coupling partner in the presence of $Pd(OAc)_2$ catalyst, PPh_3 as ligand and TBHP as oxidant (**Scheme 5)**. 24 *ortho*-acylated benzoxazole derivatives were obtained in 37-85% yield. Benzothiazole and benzo[*h*]quinoline were efficiently coupled with *p*-chlorobenzaldehyde giving the respective *ortho*-acylated products in 83% and 96% yield after 8 h at refluxed temperature. Unfortunately, 2-(3-methylphenyl)benzimidazole was unable to give the acylated product under the optimized reaction conditions.

Remarkably, 2-arylbenzoxazoles having substituents on the *meta*-position of the benzene ring exhibited high regioselectivity and acylation achieved at the less crowded *ortho*-C-H bond of the directing group. The steric hindrance at the *ortho*-position of aromatic aldehydes influenced the reaction efficiency and resulted in a lower yield of the corresponding acylated products.



Scheme 5: Pd-catalyzed *ortho*-acylation of 2-arylbenzoxazoles/ 2-arylbenzothiazoles/2-arylbenzimdazoles and plausible reaction mechanism.

For both the reactions similar reaction pathway was suggested as presented in **Scheme 5C**. Mechanism starts with cyclopalladation of the 2-arylbenzoxazole or 2-arylbenzothiazole to give intermediate **A**. In the second step, the *in-situ* generated acyl radical reacts with intermediate A to form either reactive Pd^{IV} or dimeric Pd^{III} intermediate **B**. In the last step, reductive elimination resulted *o*-acylated derivatives of 2-arylbenzoxazole and redeveloped Pd^{II} salt to maintain the catalytic cycle.

Kim and his group in 2013 reported the first catalytic acylation protocol to synthesize 1,2-diacylbenzenes from *N*-Boc hydrazones.[40] This method involves the Pd(II)-catalysed tandem regioselective acylation of *N*-Boc hydrazones and *in-situ* dissociation of the directing *N*-Boc hydrazone group in the presence of TBHP as oxidant delivering 1,2-diacylbenzenes (**Scheme 6**). This approach was set up not only for various aldehydes but also for several acetophenones and benzophenone *N*-Boc hydrazones. Unfortunately, aliphatic and heterocyclic aryl aldehydes were unable to give the coupling products with this catalytic system. To acquire

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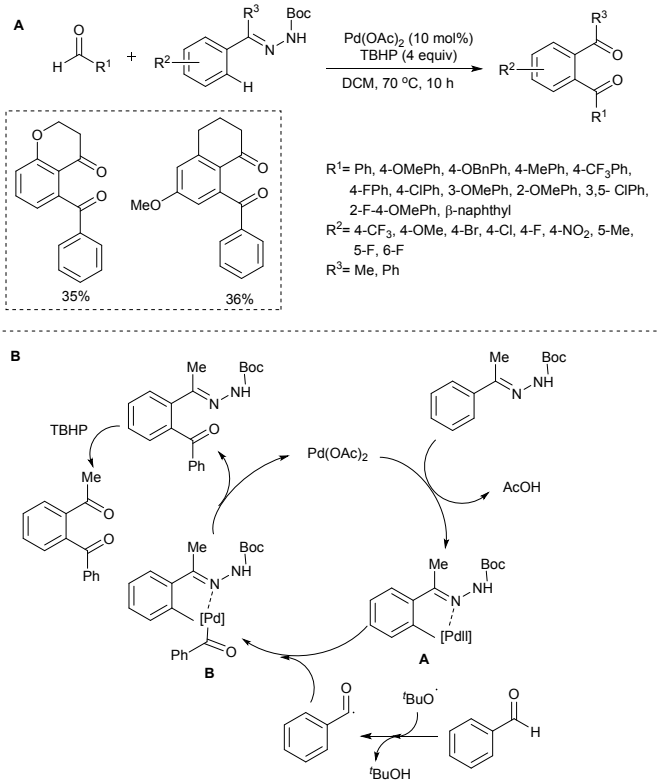
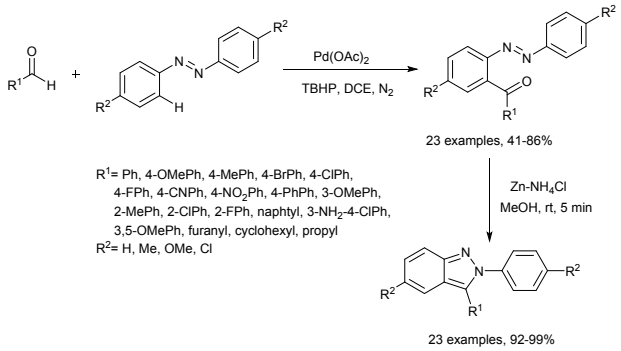
greater understanding of the reaction pathway, various experiments were carried out. The observations suggested that the *N*-Boc hydrazone moiety is acting as directing group. The rate of the acylation reaction was found to be significantly faster than that of the hydrolysis step. **Scheme 6B** also outlines the mechanism of this transformation.



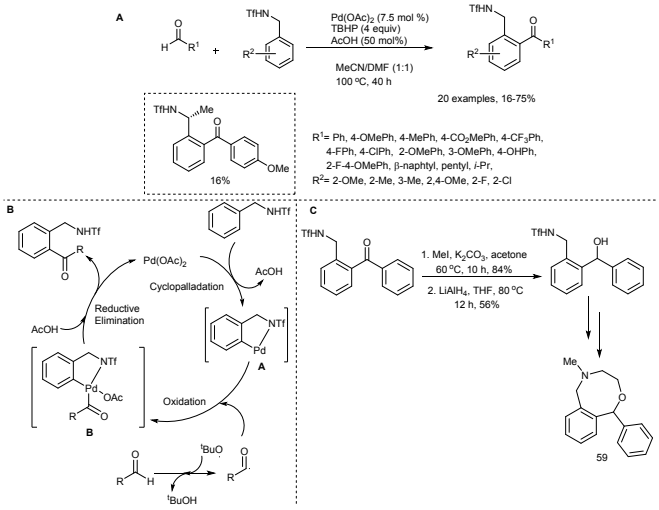
Scheme 6: Pd(II)-catalyzed direct regioselective acylation of N-Boc hydrazones and plausible reaction mechanism.

In 2013, Li *et al.* reported an azo-group directed selective acylation of symmetrically substituted azobenzenes by aldehydes involving a Pd-catalysed C-H activation method.[41] Using optimized reaction conditions, the scope of various azobenzenes and aldehydes was explored using $Pd(OAc)_2$ and TBHP. Aromatic aldehydes containing strong electron-withdrawing groups such as CN, NO_2 at the *para*-position of the aryl ring provided higher yields than those containing electron-releasing groups (Me, OMe) at the *para*-position. Reactions of azobenzene with α-naphthaldehyde as well as furan-2-carbaldehyde delivered the products in 86% and 66% yield, respectively. Cyclohexanecarbaldehyde and propionaldehyde also reacted smoothly to give the corresponding reaction products in 59% and 64% yield, respectively. The synthesized acylated azobenzenes were converted into the indazoles using Zn/NH_4Cl/MeOH as reducing system at room temperature in just 5 min (**Scheme 7**).



Scheme 7: Pd-catalyzed azo group directed acylation of symmetrically substituted azobenzenes with aldehydes.

Meanwhile, Sharma *et al.* reported a Pd-catalyzed oxidative *o*-acylation of triflamide-protected benzylamines using aliphatic and aromatic aldehydes *via* C-H activation strategy. It was observed that benzylamines having triflamide as directing group delivered *o*-acyl-*N*-benzyltriflamides with high regioselectivity applying $Pd(OAc)_2$ as catalyst and TBHP as ideal oxidant. They used AcOH as an additive and the reactions were carried out in the binary solvent system MeCN/DMF (1:1) (**Scheme 8A**).[42]

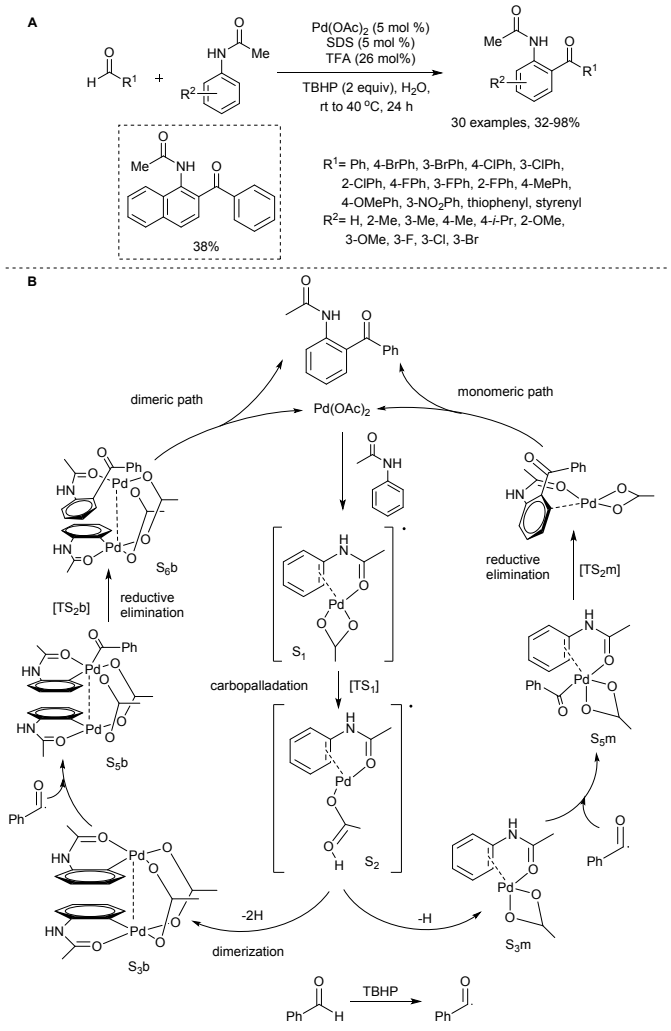


Scheme 8: (A) Pd-catalyzed oxidative acylation of *N*-benzyltriflamides with aldehdyes *via* C-H activation; (B) plausible reaction mechanism; (C) transformation of triflamides.

The substrate scope examination revealed that electron poor aromatic aldehydes were less reactive in comparison to electron rich aromatic aldehydes. In order to examine a plausible reaction mechanism for this transformation, the radical scavenger, ascorbic acid, was added in a dose-dependent manner and it was found that the reaction proceeds *via* a radical pathway as shown in **Scheme 8B**. They have also established that *o*-acyl-*N*-benzyltriflamides are effective synthetic precursors for the construction of the analgesic drug nefopam and analogous (**Scheme 8C**).

Novàk and co-workers reported a Pd-catalysed cross-dehydrogenative coupling of anilides with aromatic aldehydes

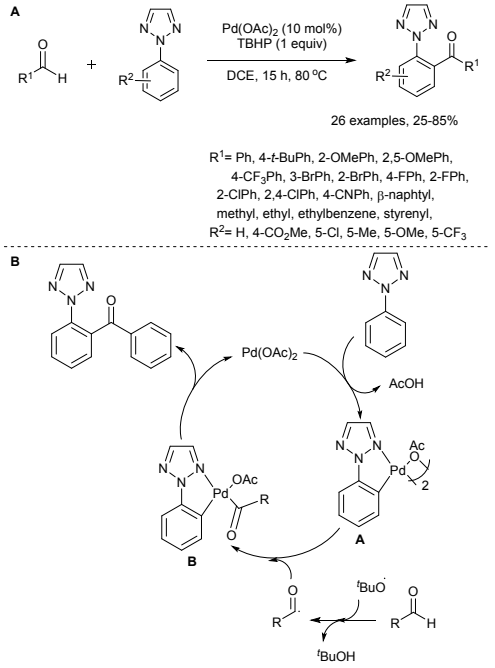
using mild reaction conditions for the selective *o*-acylation of anilides (**Scheme 9**).[43]



Scheme 9: Pd-catalyzed cross-dehydrogenative coupling between anilides and benzaldehydes and proposed reaction mechanism.

Remarkably, this reaction was accomplished at 25-40 °C temperature under aqueous conditions in 24 h. Utilization of the surfactant dodecyl sulphate (SDS) helped to upturn the solubility of the reaction substrates in water, and trifluoroacetic acid (TFA) accelerated the reaction in water. The presence of electron releasing or electron withdrawing groups on the anilide does not affect the reaction outcome and resulted in high yield of the products. Aromatic aldehydes with weak electron-withdrawing groups (F, Cl, Br etc.) provided higher product yield, than those containing electron-releasing groups (Me, OMe). 3-nitrobenzaldehdye delivered the desired product in just 39% yield. In order to support the hypothesis regarding the probable reaction mechanism, authors have performed quantum mechanical density functional calculations, which suggested the preference of bimetallic catalysis over a monomeric route (**Scheme 9B**).

In 2014, Kuang and co-workers described the acylation of 2-aryl-1,2,3-triazole scaffolds with differently substituted aryl and alkyl aldehydes using $Pd(OAc)_2$ as effective catalyst and TBHP as oxidant (**Scheme 10A**).[44] All the used substrates delivered the anticipated products in moderate to good yields regardless the nature of the substituents. Noticeably, 2-aryl-1,2,3-triazole and benzaldehyde both containing strong electron withdrawing groups such as COOMe (on triazole) and CN (on benzaldehyde) gave the corresponding product in 82% yield. However, the highest yield (85%) was obtained in two cases: 1) when unsubstituted 2-aryl-1,2,3-triazole was treated with benzaldehdye and 2) coupling of benzaldehyde bearing a strong withdrawing cyano (CN) group with 2-aryl-1,2,3-triazole having strong electron donating methoxy (OMe) group. Interestingly, high regioselectivity was observed with *meta*-substituted 2-aryl-1,2,3-triazole and acylation at the *para*-position with respect to the *meta*-substituent was achieved instead of *ortho*-position due to steric hindrance.



Scheme 10: Pd-catalyzed acylation of 2-aryl-1,2,3-triazole scaffolds with differently substituted aryl and alkyl aldehydes and plausible reaction mechanism.

Based on the available reports and observations, the authors designed a plausible reaction mechanism that starts with the formation of a five membered cyclopalladation intermediate **A** between 2-aryl-1,2,3-triazole and the Pd-catalyst. Subsequently, the generated benzoyl radical reacts with intermediate **A** resulting in conversion of Pd(II) to the dimeric Pd(III) or Pd(IV) complex **B**. Lastly, this complex **B** undergoes reductive elimination leading to the acylated product and Pd(II) get regenerated for the subsequent cycle (**Scheme 10B**).

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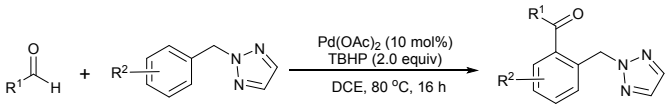
In August 2014, Kuang *et al.* reported the first example of a Pd-catalysed direct *ortho*-acylation of 2-benzyl-1,2,3-triazoles by aldehydes *via* C-H bond activation in the presence of $Pd(OAc)_2$ as catalyst and TBHP as oxidant.[45] Using the optimized reaction conditions, the substrate scope with respect to aldehydes as effective acyl source, and 2-benzyl-1,2,3-triazoles was explored, and 26 derivatives were prepared with 56-85% yield. The reaction proceeded successfully with substrates having electron donating or electron withdrawing groups. However, 2-benzyl-1,2,3-triazole bearing a nitro group at the *para*-position was not found to be reactive and no acylated product was obtained (**Scheme 11**). The reaction was found to progress following the reaction pathway as shown by Kuang *et al.* (**Scheme 10B**).

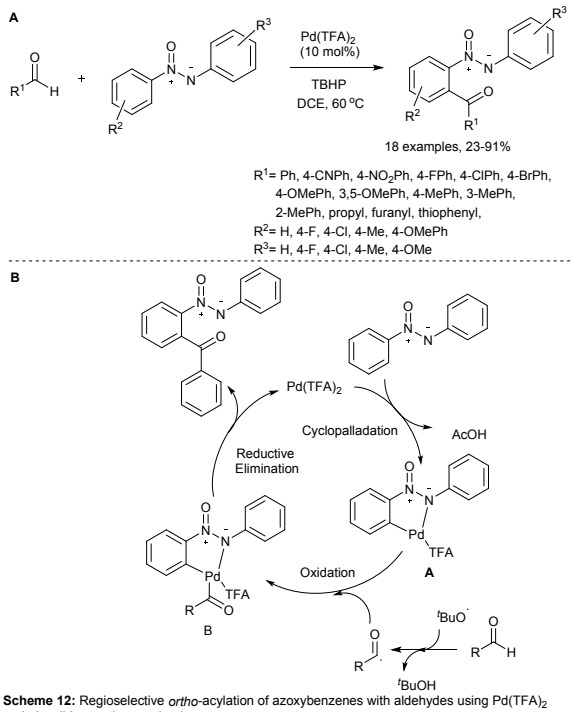


26 examples, 56-85%

R^1= Ph, 2-OMePh, 2,5-OMePh, 2-FPh, 4-FPh, 4-ClPh, 3-BrPh, 4-CNPh, 2-NO_2Ph, 4-*i*-Pr, furanyl, styrenyl, ethylbenzene, ethyl
R^2= H, 5-Me, 3-Me, 5-OMe, 5-F, 5-Cl, 4,5-ClPh, 5-CF_3, 5-NO_2

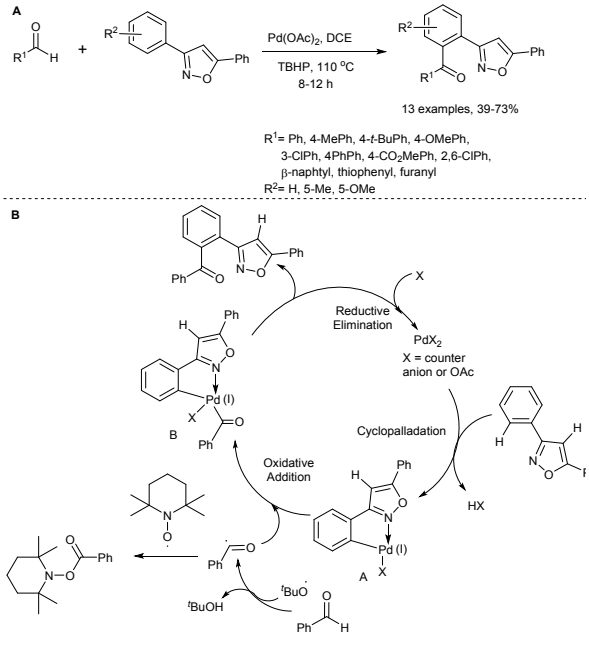
Scheme 11: Pd-catalyzed direct *ortho*-acylation of 2-benzyl-1,2,3-triazoles.

Sun *et al.* in 2014 introduced azoxy compounds for selective acylation. The authors developed an interesting approach for the selective *ortho*-acylation of azoxybenzenes using various aromatic, heteroaromatic and aliphatic aldehydes in the presence of $Pd(TFA)_2$ as catalyst and TBHP as oxidant.[46] They prepared 19 different mono-acylated azoxybenzenes with 23-87% yield in 24 h at 60 °C. The presence of mild electron-withdrawing groups (F, Cl, Br) at the *para*-position of the benzaldehydes positively affected the reaction giving higher yields of the mono-acylated derivatives. However, strong electron-withdrawing groups (CN, NO_2) had a reverse effect resulting in very poor yields of the corresponding products. Unfortunately, other electron-withdrawing groups like CF_3 and CO_2Me were not suitable for this transformation as no desired products were obtained. Besides the presence of two *ortho*-C-H bonds, the reaction afforded exclusively the mono-acylation in the ring directly attached to the N=O group (**Scheme 12A**). The *ortho*-acylation product was converted into the indazole analogue by a reduction process. The reaction was found to progress through a free radical pathway (**Scheme 12B**).



Scheme 12: Regioselective *ortho*-acylation of azoxybenzenes with aldehydes using $Pd(TFA)_2$ and plausible reaction mechanism.

In 2014, Patel and his team established a strategy for the regioselective *ortho* sp^2 C-H acylation of 3,5-diarylisoxazole.[47] From four sp^2 C-H bonds and one interior sp^2 C-H bond, the functionalization occurred at one of the *ortho* C-H bonds near to the *N*-atom in the presence of $Pd(OAc)_2$ as catalyst and TBHP as oxidant(**Scheme 13A**).



Scheme 13: Pd-catalyzed selective N-directed ortho-acylation of 3,5-diarylisoxazole and proposed reactior mechanism.

Authors reported 13 acylated products with high regioselectivity in 39-73% yield at 110 °C after 8-12 h in dichloroethane (DCE) as solvent. The reaction progressed

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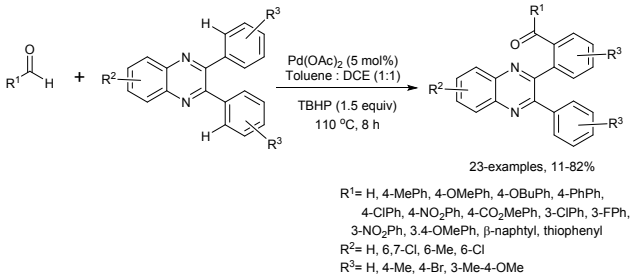
smoothly with the applied substrates and was found compatible with all kinds of functional groups present on the aldehydes. Nevertheless, the electron-withdrawing groups such as *o*-NO_2, *p*-Cl, *m*-F in 3-aryl ring of 3,5-diarylisoxazole suppressed the product formation completely under these reaction conditions. The reaction mechanism was not thoroughly probed but expected to proceed as outlined in **Scheme 13B**.

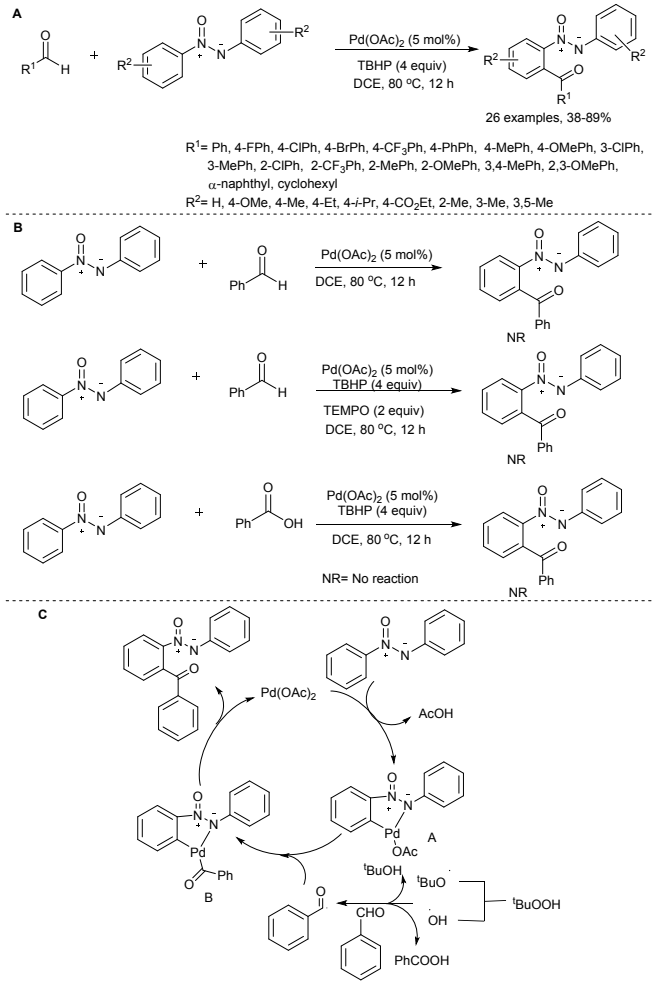
In continuation of their work on selective *N*-directed acylation reactions, Patel and co-workers reported a cross dehydrogenative coupling methodology for the selective mono *ortho*-acylation of the sp^2 C-H bond of 2,3-diarylquinoxalines using aromatic aldehydes.[48] The authors developed a small library of 23 derivatives employing $Pd(OAc)_2$, TBHP and toluene:DCE (1:1) at 110 °C. Various functional groups were well tolerated on the benzaldehyde and *p*-chlorobenzadehyde provided the highest yield (82%). Benzaldehydes bearing strong electron-withdrawing groups like *p*-COOMe, *p*-NO_2, *m*-NO_2 also provided the desired products in good yields. The substrate scope was further extended to substituted 2,3-diarylquinoxalines with benzaldehydes and good yield of the desired products were achieved (**Scheme 14**).



Scheme 14: Cross dehydrogenative coupling for directed mono *ortho*-acylation of sp^2 C-H bonds of 2,3-diarylquinoxaline.

Methyl and chloro substituted unsymmetrical 2,3-diarylquinoxalines after reaction with benzaldehyde provided inseparable mono-acylated products in a ratio of 5:4 and 5:3, respectively. Furthermore, when the reaction with 2,3-diarylquinoxaline having two electron-releasing groups (-Me and -OMe) in one of the aryl ring was performed, mono *ortho*-acylated products were obtained in a 6.7:1 ratio, revealing the favoured oxidative palladation at the more electron rich aryl ring. However, in the presence of bromine in one of the aryl rings, *ortho*-acylation was accomplished at the unsubstituted aryl ring, resulting in only one product and reconfirming the favoured oxidative palladation of more electron rich aryl ring (**Scheme 14**).

The reaction conditions applied in regioselective acylation of azobenzenes (**Scheme 15**) were effectively installed by Wu and co-workers in 2015 during the acylation of azoxybenzenes by aldehydes using $Pd(OAc)_2$ as catalyst at 80 °C in the presence of TBHP as oxidant (**Scheme 15A**).[49] The authors have prepared a library of derivatives using differently substituted azoxybenzenes and aryl/alkyl aldehydes. However, in comparison to Sun's protocol[46], aliphatic aldehydes gave inferior yields and heterocyclic aldehydes could not be applied for this transformation, which shows the significance of the reaction temperature. The authors also performed some control experiments to investigate the reaction mechanism. When the reaction was carried out in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) no acylation product was obtained revealing a free radical pathway (**Scheme 15B**). The probable reaction route for this conversion is shown in **Scheme 15C**.



Scheme 15: (A) Regioselective *ortho*-acylation of azoxybenzenes with aldehydes; (B) Control experiments; (C) plausible reaction mechanism.

In 2015 Xiao *et al.*, successfully carried out the acylation of the aryl ring of acetophenone *O*-methyl oxime with aromatic aldehydes using almost similar reaction conditions as was used by Novàk's and co-workers as given in **Scheme 9**.[50] In this

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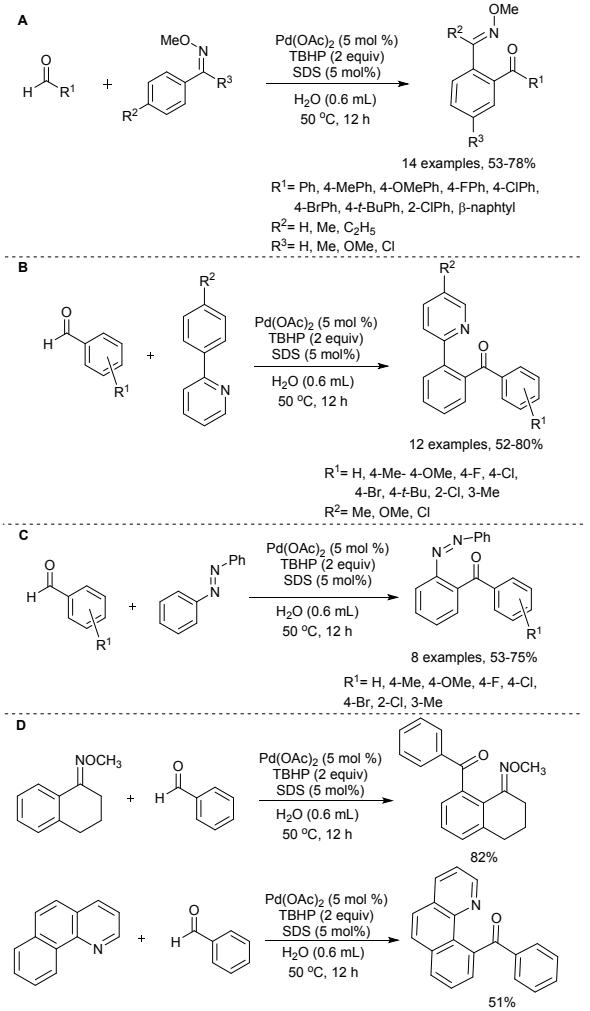
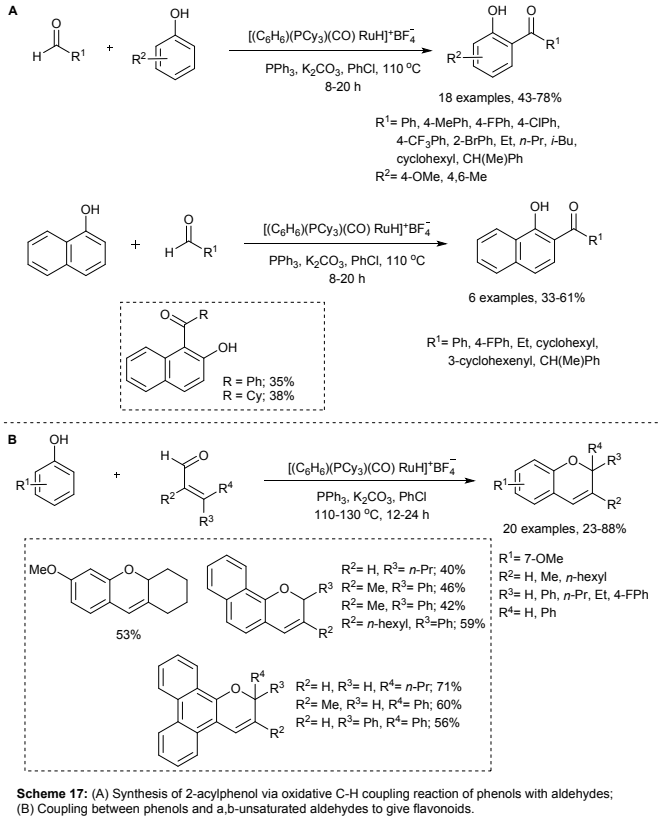
case reactions were carried out at 50 °C for 12 h and the targeted products were achieved in 53-80% yields. The authors extended the application of the reaction conditions for the acylation of the aryl ring of 2-phenylpyridines, diphenyldiazenes, aromatic azo-compounds and other aryl ketone oximes with aromatic aldehydes (**Scheme 16A-D**). The reactions proceeded effectively in all these cases and electron-releasing or electron-withdrawing groups were compatible under standard reaction conditions.



Scheme 16: Pd-catalyzed acylation of aryl ring (A) acetophenone *O*-methyl oximes; (B) 2-phenylpyridines; (C) diphenyldiazenes; (D) aryl ketone oxime and aza phenanthrene with aromatic aldehydes.

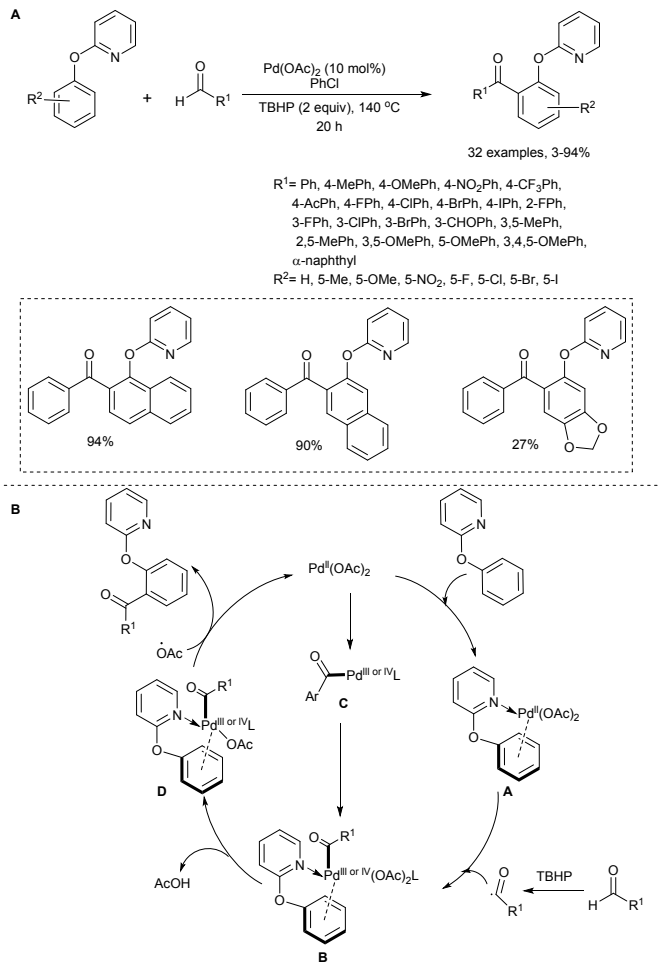
Yi's group in 2015 described the synthesis of *ortho*-acylphenols by performing an oxidative C-H coupling reaction between phenols and aldehydes using the cationic ruthenium hydride complex $[(C_6H_6)(PCy_3)(CO)\ RuH]^+BF_4^-$ as an effective catalyst in the absence of metal oxidant.[51] The reaction progressed significantly with the applied phenols and aldehydes comprising electron donating and electron withdrawing groups, and resulted in the formation of 26 *ortho*-acylphenol derivatives in 35-78% yield. Besides the cationic ruthenium hydride complex, the reaction involved the use of K_2CO_3 as base and PPh_3 as additive in chlorobenzene solvent for the smooth transformation at 110 °C (**Scheme 17**). Interestingly, the coupling of phenols with α,β-unsaturated aldehydes under the optimized reaction conditions resulted in flavonoids. The authors prepared 20 flavonoid derivatives successfully with 23-88% yield having various functional groups. The chemoselectivity of the developed protocol was explored by treating estrone with cyclohexanecarbaldehyde and 4-chlorobenzaldehdye and the corresponding coupling products were obtained in a 1:2 ratio.



Scheme 17: (A) Synthesis of 2-acylphenol via oxidative C-H coupling reaction of phenols with aldehydes; (B) Coupling between phenols and a,b-unsaturated aldehydes to give flavonoids.

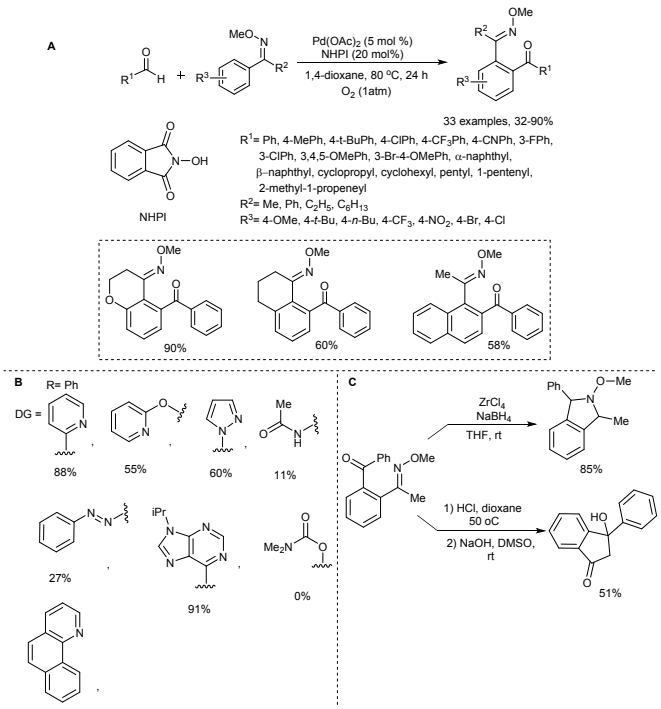
In the same year Wu *et al.* reported a study for the direct *ortho*-acylation of 2-phenoxypyridines with aldehydes to produce a series of novel aryl ketones in the presence of $Pd(OAc)_2$ as catalyst, TBHP as oxidant and chlorobenzene as solvent (**Scheme 18**).[52] In order to gain an insight into the reaction mechanism, authors performed intramolecular and intermolecular kinetic isotope effect studies. The results of experiments showed that the *ortho* C-H bond cleavage of 2-phenoxypyridines does not participate in the rate determining steps of the reaction. The binding of 2-phenoxypyridines with the palladium ion was considered as the crucial rate-determining step for the acylation. Furthermore, the effect of various radical scavengers on the reactivity was determined to probe either the reaction was following an ionic pathway or proceeding *via* a radical pathway. The results of experiments strongly supported the radical pathway. In

addition to the above studies, some other control experiments were also performed by carrying out the reaction between 2-phenoxypyridine palladacycle (**A**) with different benzaldehydes in the presence and absence of TBHP. Based on all these experiments, a plausible mechanism was proposed as shown in **Scheme 18B**. The authors also demonstrated the synthetic utility of this protocol by synthesizing (2-hydroxyphenyl)(phenyl)methanones and 1-hydroxy-9*H*-fluoren-9-ones.



Scheme 18: Direct *ortho*-acylation of 2-phenoxypyridines with aldehydes and proposed reaction mechanism.

In early 2016, Jiao and co-workers reported the *N*-hydroxyphthalimide (NHPI) and palladium co-catalyzed oxidative acylation of acetophenone *o*-methyl oxime using aldehydes *via* selective C-H functionalization. In this protocol molecular oxygen was used as terminal oxidant for C-H acylation.[53] A wide range of *o*-methyl oximes and aldehydes (alkyl/aryl) was explored and various derivatives were prepared bearing electron withdrawing and releasing groups at 80 °C within 24 h in 1,4-dioxane as solvent (**Scheme 19A**). The developed acylation reaction conditions were also applied for benzo[*h*]quinolone, 1-phenylpyrazole, 2-phenylpyridine and 2-phenoxypyridine and the corresponding targeted products were acquired in moderate to good yields (**Scheme 19B**). Unfortunately, azobenzene and acetanilide provided inferior yields of the acylated products and phenyl *N,N*-dimethylcarbamate was found to be unreactive under these reaction conditions. The removal of the directing group using HCl/dioxane and subsequent intramolecular aldolization in the presence of NaOH/DMSO converted the oxime ether into the isoindoline (**Scheme 19C**).



Scheme 19: NHPI and palladium co-catalyzed aryl C-H bond aerobic oxidative acylation in presence of various directing group with aryl/alkyl aldehydes and conversion of acylation product into isoindoline and 3-hydroxy-3-phenylindanone.

Zhao and Jiang in 2016 reported a proficient method for the selective acylation of 1,4-disubstituted 1,2,3-triazoles applying the 1,2,3-triazole moiety as directing group using aromatic aldehydes as acyl transfer agent in presence of Pd-catalyst (**Scheme 20A**).[54] The best reaction conditions were used to prepare 27 derivatives in 55-92% yield after 24 h of reaction at 120 °C. Reaction proceeded with almost equal efficacy in case of aldehydes as well as 1,4-disubstituted 1,2,3-triazoles. However, aldehydes with strong electron withdrawing groups (NO_2, MeS=O) afforded relatively lower yields. Further the authors carried out several experiments to gain insight into the reaction mechanism. The reaction between 4-phenyl-1-(*p*-tolyl)-1*H*-1,2,3-triazole and benzaldehyde in the presence of the free radical scavenger TEMPO gave only traces of the desirable compound demonstrating a radical pathway. Moreover, the intermolecular kinetic isotope effect (k_H/k_D) was also determined and was found to be 6.3, suggesting that the ~~cl~~ cleavage of the C-H bond may be the rate-limiting step (**Scheme 20B**). Based on outcomes of these experiments, a

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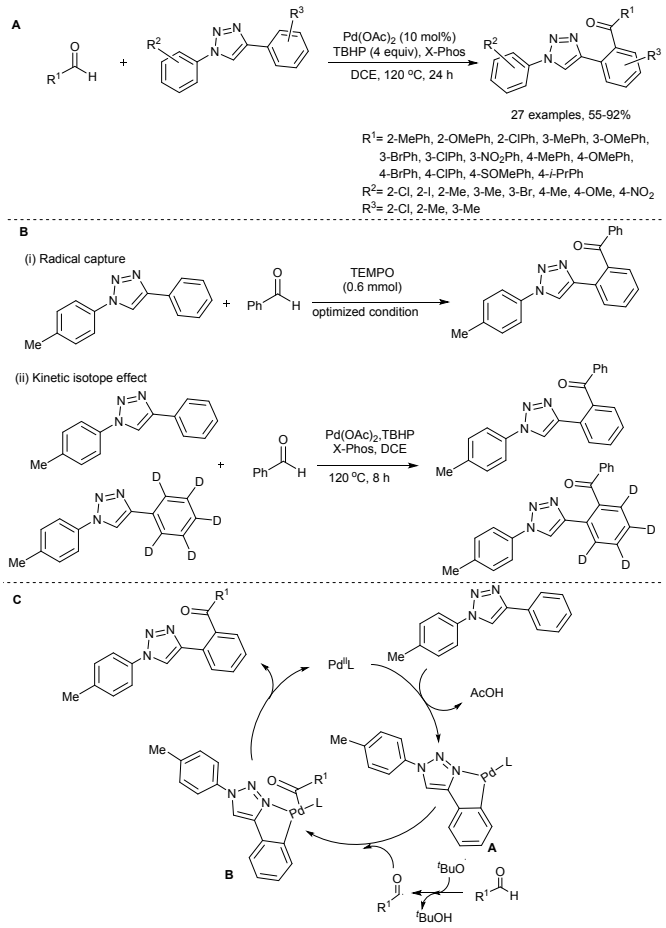
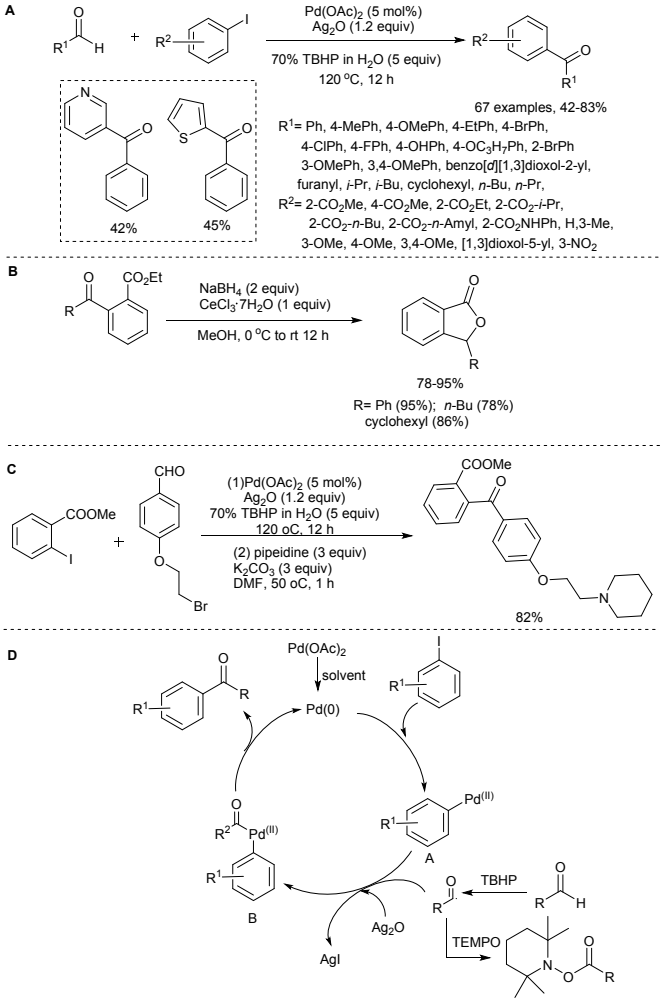
plausible reaction mechanism was proposed as outlined in **Scheme 20C**.



Scheme 20: (A) Regioselective acylation of 1,4-disubstituted 1,2,3-triazoles with aromatic aldehydes; (B) control experiments; (C) plausible reaction mechanism.

In contradiction of directing-group assisted direct acylation, in 2016, Suchand and Satyanarayan described an environmentally benign protocol for the Pd-catalysed direct acylation of an aryl system starting from simple and commercially available iodo arenes and aldehydes (alkyl/aryl), leading to the production of aryl-aryl and alkyl-aryl ketones (**Scheme 21A**).[55] In total, 69 derivatives could be prepared in 45-89 % yield using of $Pd(OAc)_2$ as catalyst, Ag_2O as additive and 70% aqueous solution of TBHP as oxidant after 12 h at 120 ^oC, revealing a broad substrate scope and generality of the developed method. However, *p*-nitrobenzaldehyde could not result in the corresponding product but reaction was found to be compatible with *m*-nitroiodobenzene. The reaction was favorable with furan-2-carboxaldehyde, but was unsuccessful with pyridinecarboxaldehyde and thiophenecarboxaldehyde. Furthermore, product formation could not be observed with bromo arene implying that the more reactive iodo arenes are necessary for the achievement of this transformation. To further demonstrate the synthetic utility of this newly developed protocol, it was extended to the synthesis of benzofuranones by selective reduction of the keto group with $NaBH_4$, followed by *in-situ* intramolecular nucleophilic attack of the hydroxyl group to the ester group of selected acylated compound to afford the corresponding benzofuranones (**Scheme 21B**). This approach was also used for the preparation of the antispasmodic pitofenone a combined drug in Spasmalon. Pitofenone was successfully prepared in just two steps using this protocol (**Scheme 21C**).



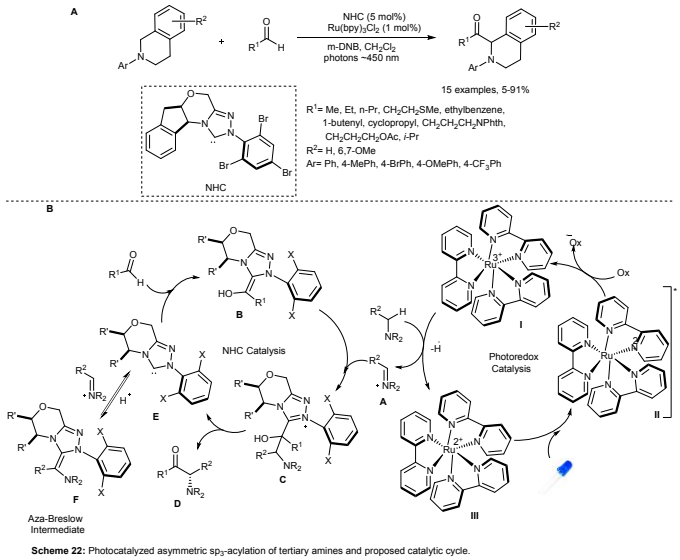
Scheme 21: (A) Pd-catalyzed direct acylation of iodo arenes with aldehydes (alkyl/aryl) leading to the aryl-aryl and alkyl-aryl ketones;(B) Conversion to benzofuranones by selective reduction of keto group; (C) conversion to pitofenone; (D) plausible reaction mechanism.

To investigate the reaction mechanism, the authors anticipated that the reaction may progress through the development of an acyl radical of aldehyde due to TBHP. This hypothesis was proven by performing the reaction in the presence of TEMPO under standard conditions, as no product formation was observed whereas the aldehyde radical-trapped ester was obtained in 95% yield. A plausible reaction pathway for this transformation is shown (**Scheme 21D**).

3.2. Acylation of alkyls

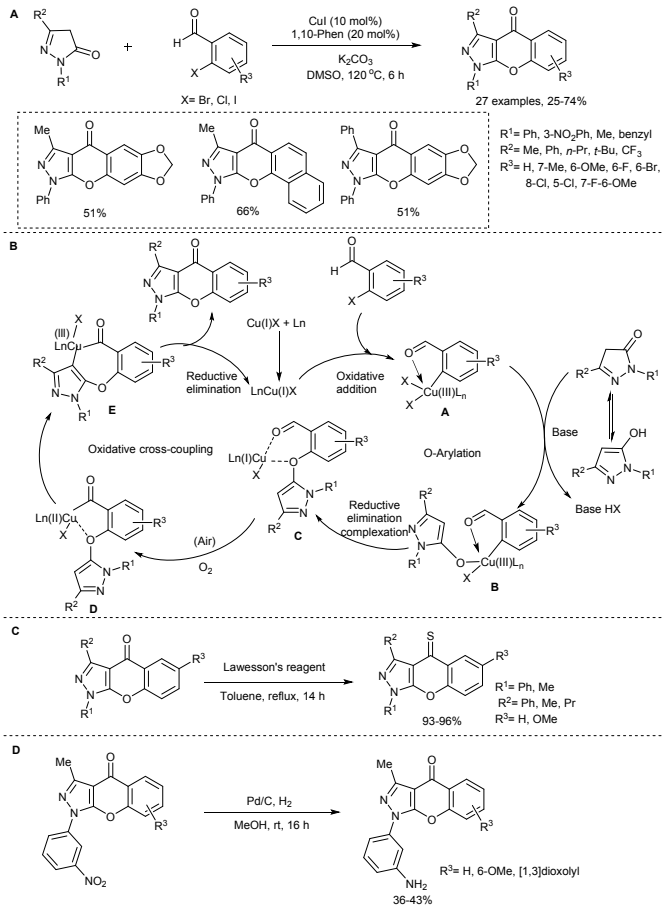
3.2.1. Acylation of sp^3 carbons

Rovis and co-workers (2012) employed a dual-catalysis strategy for the asymmetric sp^3 α-acylation of 1,2,3,4-tetrahydroisoquinoline using aldehydes as acylating agents. A chiral *N*-heterocyclic carbene (NHC) in combination with photocatalyst $[Ru(bpy)_3]^{3+}$ was used in the presence of *m*-dinitrobenzene (*m*-DNB) under blue light irradiation.[56] Various aldehydes were reacted with substituted *N*-aryl-1,2,3,4-tetrahydroisoquinolines and 16 derivatives were prepared in 51-94% yield at ambient temperature (**Scheme 22A**). Authors projected a catalytic cycle which involves irradiation of $[Ru(bpy)_3]^{2+}$ (**III**) using blue light resulting in excited $[Ru(bpy)_3]^{*2+}$ (**II**) which generated a powerful oxidant $[Ru(bpy)_3]^{3+}$ (**I**).[57] Afterwards, single electron oxidation of the tetrahydroisoquinoline followed by hydrogen abstraction resulted in iminium ion **A** and recovering of $[Ru(bpy)_3]^{2+}$ (**III**). On the other hand, interaction between NHC and aldehyde generated the nucleophilic Breslow intermediate **B**, which then captured iminium ion **A** to form a new intermediate **C**. Elimination of the NHC from intermediate **C** provided α-amino ketone **D** and allowed NHC **E** to re-enter in catalytic cycle again (**Scheme 22B**).



Scheme 22: Photocatalyzed asymmetric sp_3-acylation of tertiary amines and proposed catalytic cycle.

Suresh and co-workers developed a intermolecular tandem Cu-catalyzed *O*-arylation-oxidative acylation protocol between 2,4-dihydro-3*H*-pyrazol-3-ones and *O*-halo aryl carboxaldehydes to synthesize chromone fused pyrazoles using air as an ideal oxidant.[58] The reactions were carried out taking 0.5 mmol of 2,4-dihydro-3*H*-pyrazol-3-ones, 0.6 mmol of *o*-halo aryl carboxaldehydes in the presence of CuI as catalyst, 1,10-phenanthroline as ligand, K_2CO_3 as base at 120 ^oC in DMSO as solvent. The reaction was used to prepare 25 chromone fused pyrazoles in moderate to good yields pre-setting countable tolerance towards diverse substituents in substrate. During the initial screening of substrates 2-bromobenzaldehdye provided better results than 2-chlorobenzaldehdye and 2-iodobenzaldehdye, suggesting that bromo group as a better leaving group for this transformation. Afterwards, the scope of various differently substituted 2-bromobenzaldehydes was explored and it was found that electron donating groups on 2-bromobenzaldehdye were well accepted and provided the resultant products in good yield. However, an electron-withdrawing group such as fluorine gave the corresponding chromone fused pyrazole in moderate yield. Tetracyclic chromone fused pyrazole was obtained in 66% yield with 1-bromo-2-naphthaldehdye on the other hand the reaction of *N*-Boc pyrazolone with 2-bromobenzaldehdye failed to deliver product. Moreover, this methodology was not found suitable in the case of heteroaromatic aldehyde like 2-chloronicotinaldehdye (**Scheme 23A**).



Scheme 23: (A) Cu-catalyzed *ortho*-arylation-oxidative acylation of 2,4-dihydro-3H-pyrazol-3-ones with *ortho*-halo aryl carboxaldehydes; (B) Plausible reaction mechanism; (C) Thionation of few chromone fused pyrazoles; (D) conversion of chromone fused pyrazoles into an A_2-subtype selective adenosine receptor antagonist and its derivatives.

Based on the literature report and control experiments, a plausible mechanism was proposed for this methodology (**Scheme 23B)**. The applicability of the developed method was also checked for the gram scale and the targeted product was obtained in 68% yield. Moreover, some synthesized compounds were also treated with Lawesson's reagent and

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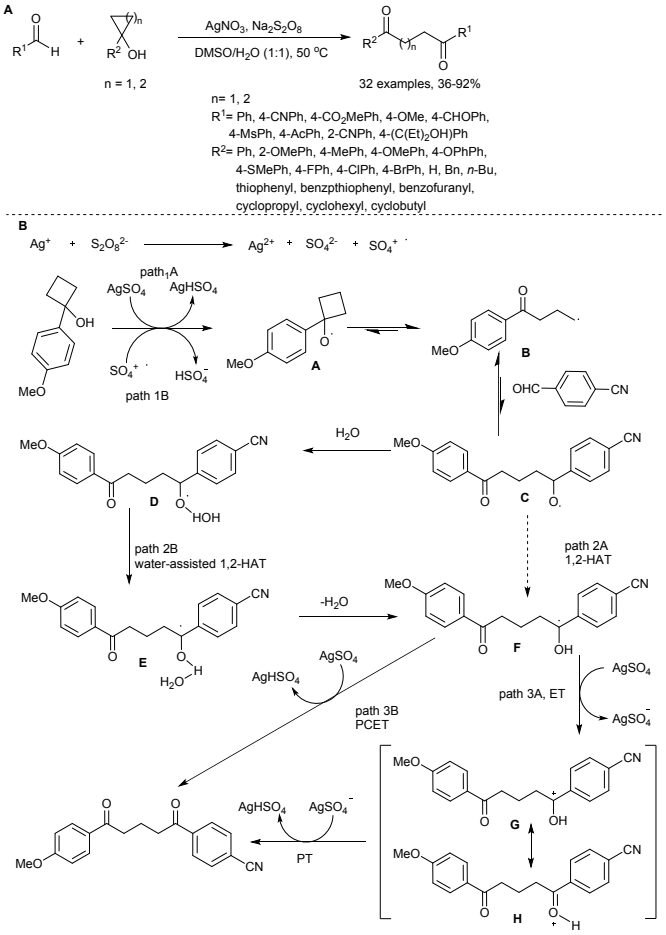
the thione derivative was obtained in 93% yield (**Scheme 23C**). The method had also been extended to synthesize an A2-subtype selective adenosine receptor antagonist and its derivatives (**Scheme 23D**).

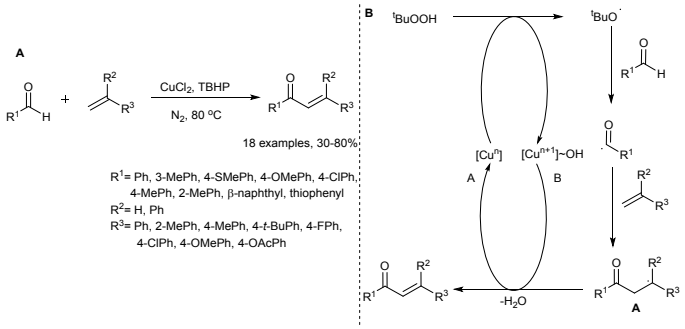


Scheme 24: Ag-catalyzed ring opening acylation of cyclopropanols and cyclobutanols using aldehydes and plausible reaction mechanism.

Che *et al.* in 2018, described Ag-catalyzed ring opening acylation of cyclopropanols and cyclobutanols through intermolecular oxidative radical addition of aromatic aldehydes using mild and neutral reaction conditions.[59] 1-(4-Methoxyphenyl)cyclobutan-1-ol and *p*-cynobenzaldehydye were chosen as model reaction substrates to evaluate the reaction parameters. Using the optimized reaction conditions, the substrate scope with respect to cyclopropanols, cyclobutanols and aromatic aldehydes was explored and 32 derivatives were prepared in 36-92% yield at 50 °C (**Scheme 24A**). The reactions proceeded smoothly with the applied substrates bearing distinct functional groups of varying electronic behaviour. To investigate the reaction mechanism, the reaction between model reaction substrates 1-(4-methoxyphenyl)cyclobutan-1-ol and *p*-cyanobenzaldehdye was carried out using TEMPO under standard reaction conditions and a mixture of products was obtained without any acylated product. The results of control experiments ruled out the formation of any possible acyl radical. Based on these outcomes and earlier reports, a probable mechanism was proposed as displayed in **scheme 24B**.

3.2.2. Acylation of sp² carbons

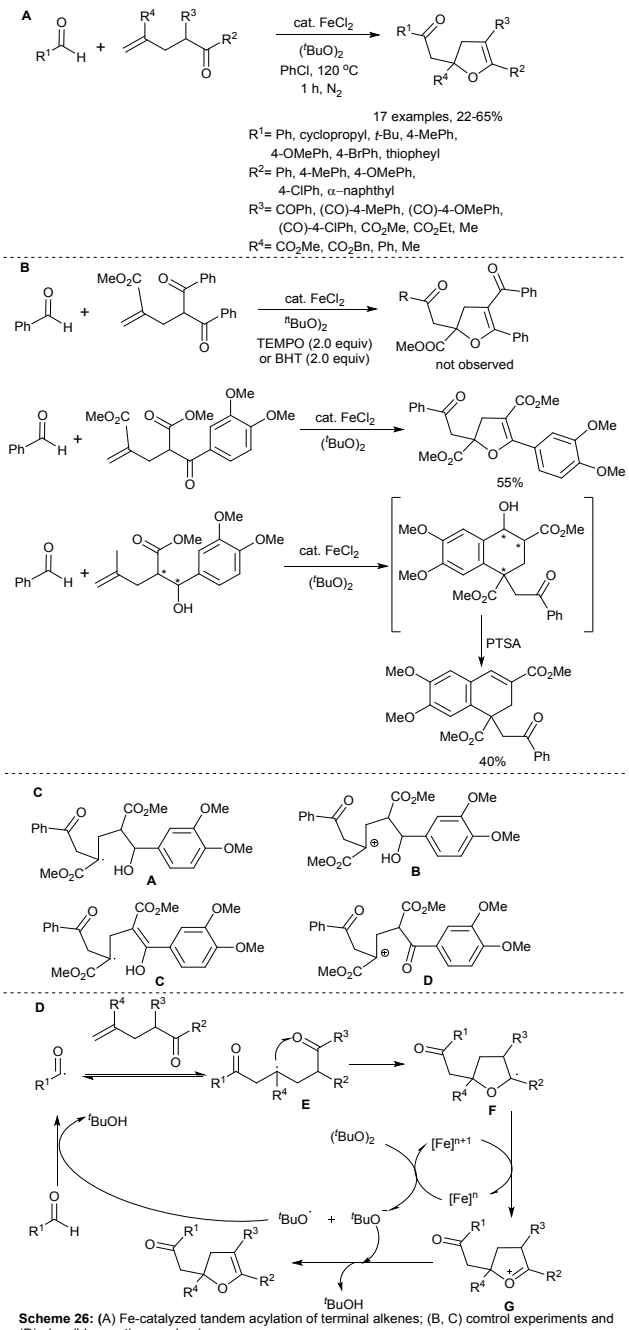
In 2013, Wang *et al.* developed an efficient and novel approach for the synthesis of α,β-unsaturated keto compounds by Cu-catalysed direct oxidative coupling reaction of alkenes and aldehydes with high atom economy.[60] For the successful transformation of alkenes and aldehydes into the desirable α,β-unsaturated keto compounds, the authors carried out the reactions using $CuCl_2$ as most suitable catalyst and TBHP as oxidant under nitrogen atmosphere. All the employed aldehydes and alkenes underwent coupling reaction effectively under the used reaction conditions irrespective of the positions and electron behaviour of substituents present either on thearomatic aldehydes or the alkenes resulting in 18 derivatives in 30-80% yield (**Scheme 25**). Authors investigated the possible mechanism by performing the reaction in the presence of radical trapping substance 2,6-di-*tert*-butyl-4-methylphenol (BHT) under standard reaction conditions, and the reaction found to follow a free radical pathway as shown in **scheme 25**.



Scheme 25: Cu-catalyzed direct oxidative coupling between alkenes and aldehydes and plausible reaction mechanism.

In 2015, Li and co-workers developed a Fe-catalysed protocol for the acylation of terminal alkenes which undergoes subsequent intramolecular oxygenation in a tandem manner to deliver functionalized 2,3-dihydrofurans having a quaternary carbon.[61] The method bears a few salient features, which include the insertion of carbonyl substituents and a quaternary carbon containing various functional groups like alkyl, aryl and esters. To check the applicability of the newly developed method several aldehydes (aromatic and aliphatic) were treated with a variety of terminal alkenes in the presence of $FeCl_2$ as catalyst, di-*tert*-butylperoxide (DTBP) as oxidant and chlorobenzene as solvent under nitrogen atmosphere. The authors prepared 17 different acylated-oxygenated products in 22-65% yield after 1h of reaction at 50 °C (**Scheme 26A**).

Olefinic β-diketones and olefinic β-ketone esters smoothly reacted with benzaldehydes to provide theresultant dihydrofurans in moderate yields. However, the presence of a SO_2Ph group on the alkene suppressed the reaction with benzaldehyde and the desired product was not observed. Moreover, the scope of aldehydes was also studied and both aromatic as well as aliphatic aldehydes reacted effectively under the optimized reaction conditions and afforded the products in moderate to good yields. However, in the case of cyclohexane carboxaldehdye and pivaldehyde, decarbonylation products were obtained.



Scheme 26: (A) Fe-catalyzed tandem acylation of terminal alkenes; (B, C) comtrol experiments and (D) plausible reaction mechanim.

To get an insight in the reaction mechanism, few control experiments were performed under standard conditions (**Scheme 26B**). The use of radical scavengers TEMPO and BHT totally suppressed product formation and the alkene was recovered quantitatively supporting the addition of an acyl radical to the C=C bond in the initial step. The reaction of benzaldehyde with the olefinic ketone resulted in the preferred dihydrofuran in 55% yield. An alkene having a hydroxyl group instead of a carbonyl group delivered a tetrahydronaphthalene as the major product, which on subsequent dehydration gave dihydronaphthalene. However, required the tetrahydrofuran product could not be obtained *via* possible intermediates **A** and **B**. Based on these results, it wasclear that the formation of the dihydrofuran was not possible through the possible intermediate **C** or **D** (**Scheme 26C**). Based on the observations of experiments and literature reports, a tentative reaction mechanism was established (**Scheme 26D)**.

Recently in 2019, Fe-catalyzed acyl-azidation of alkenes to synthesize unsymmetrical β-azido ketones has been reported by Ge *et al.* under mild reaction conditions. Aromatic and aliphatic aldehydes were used as acyl radical precursors, azidotrimethylsilane ($TMSN_3$) as azido source, and TBHP as an oxidant in this transformation (**Scheme 27**).[62] The effects of various parameters including metal catalyst, solvent, additives and temperature was studied taking styrene and benzaldehyde as model substrates and $TMSN_3$ as azido source to achieve the best reaction conditions. Interestingly, best product yield was obtained when styrene (0.5 mmol) was treated with benzaldehyde (2.5 mmol) in the presence of Fe $(OTf)_3$ (2 mol%) catalyst and TBHP (1.25 mmol) oxidant using $TMSN_3$ (1.25 mmol) after 24 h at room temperature.

Having the optimized reaction conditions in hand, initially the authors investigated the scope of alkenes, *o*-, *m*- and *p*-substituted styrenes (vinylarenes) with benzaldehyde delivering products in moderate to good yields. Styrenes having alkyl substituents performed better than those carrying halogens. Interestingly, vinylarenes containing an ester or a free carboxylic group at the *para*-position also reacted effectively under the optimized reaction conditions providing moderate yields of the products. Moreover, heterocyclic compounds, α,β-unsaturated carbonyl compounds and conjugated dienes also resulted in the corresponding azido ketones in moderate yields on treatment with benzaldehyde and $TMSN_3$. Subsequently, the scope of aromatic aldehydes, aliphatic aldehydes and α,β-unsaturated aldehydes was investigated. Aryl aldehydes having either electron-releasing or electron-withdrawing groups reacted

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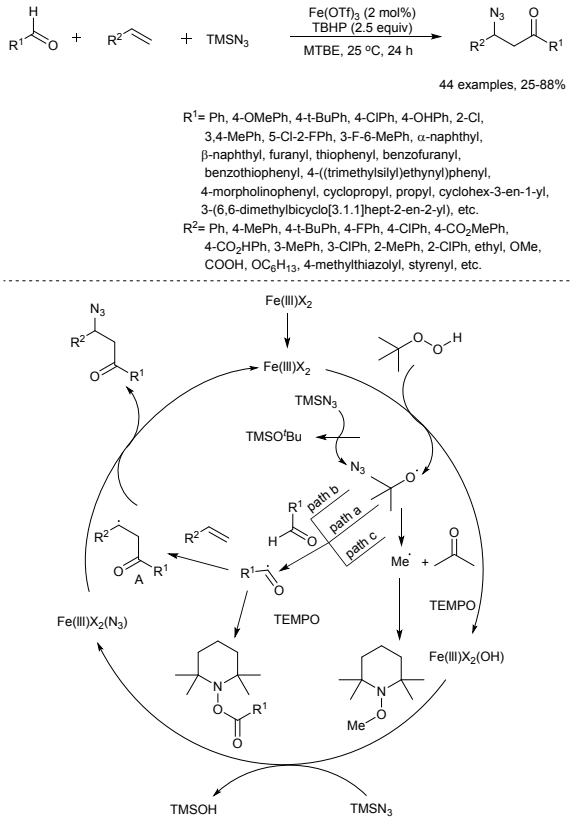
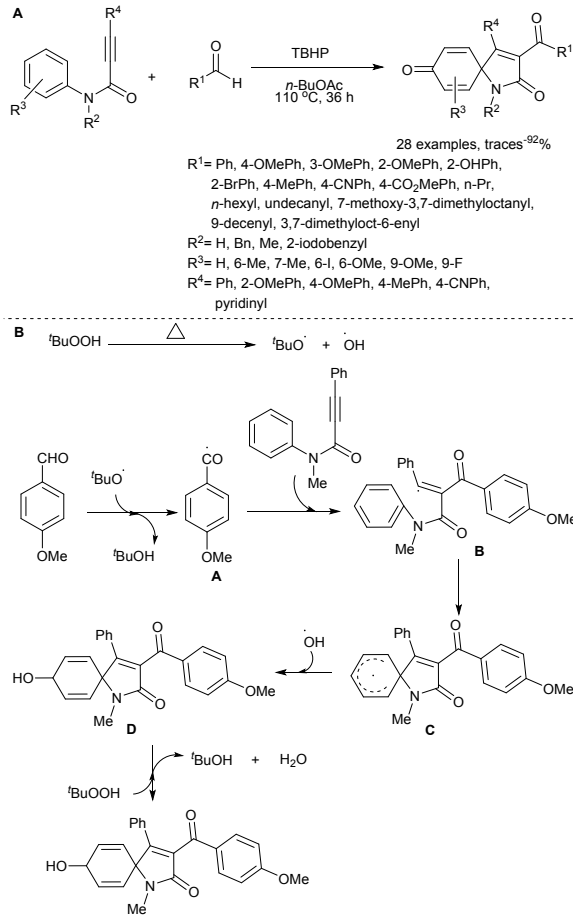
smoothly with moderate to good yields; however, electron-releasing groups were found to be more efficient than electron-withdrawing groups.Few preliminary experiments were executed to investigate the reaction pathway and, depending on these studies, a plausible reaction mechanism for this acyl-azidation reaction was proposed as outlined in **scheme 27**.



Scheme 27: Iron catalyzed acyl-azidation of alkene and plausible reaction mechanism.

3.2.3. Acylation of sp carbons

In 2014, Li and co-workers disclosed a metal-free protocol for the acylation of *N*-arylacrylamides with aldehdyes followed by an intramolecular cyclization to synthesize 3-acylspiro[4,5]trienones.[63] The flexibility of reaction was demonstrated by the synthesis of 28 3-acylspiro[4,5]trienones in good to excellent yields. Reactions were performed between several electron-rich and electron-deficient *N*-arylacrylamides and aldehydes (aromatic and aliphatic) using TBHP as optimum free-radical initiator oxidant without any catalyst under optimized reaction conditions giving the respective products in 66-94% yield. Extensive screening of *N*-arylacrylamides suggested that several groups including OMe, Me, CN on the aryl ring of the terminal alkyne were well tolerated, and electron-releasing groups showed better reactivity in comparison to electron-withdrawing groups. *N*-arylacrylamides bearing substituents like *o*-Me/I, *m*-Me on the aryl ring of nitrogen also performed well affording the good product yields. Moreover, the presence of a OMe or F group at the *para*-position of the *N*-aryl ring delivered the respective 3-acylspiro[4,5]trienone in 81% and 74% yield. The arylaldehydes bearing a Br, OH, OMe, Me, CN or CO_2Me group on the aryl ring were also found compatible with the optimal reaction conditions and the reactivity order was found to be *para>meta>ortho*. Moreover, aliphatic aldehydes could be easily reacted using the optimized reaction conditions,resulting in thecorresponding spiro[4,5]trienones in good yields (**Scheme 28A**).



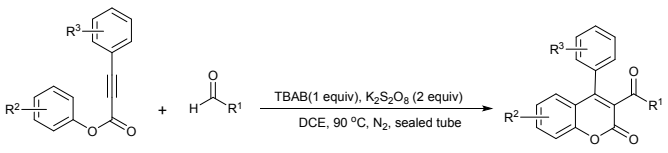
Scheme 28: Acylation of N-arylacrylamides with aldehdyes followed by an intramolecular cyclization and plausible reaction mechanism.

On the basis of control experiments and literature support, the authors designed a plausible reaction mechanism (**Scheme 28B**). The mechanism involves the formation of carbonyl radical **A** from the aldehyde through a single-electron transfer (SET) process in the presence of TBHP. Subsequent acylation of the alkyne with carbonyl radical **A** resulted in vinyl radical **B**, which on selective *ipso*-carbocyclization produced radical intermediate **C**. This intermediate **C**, after selective addition of OH radical, afforded another intermediate **D**. Lastly, intermediate **D** on the

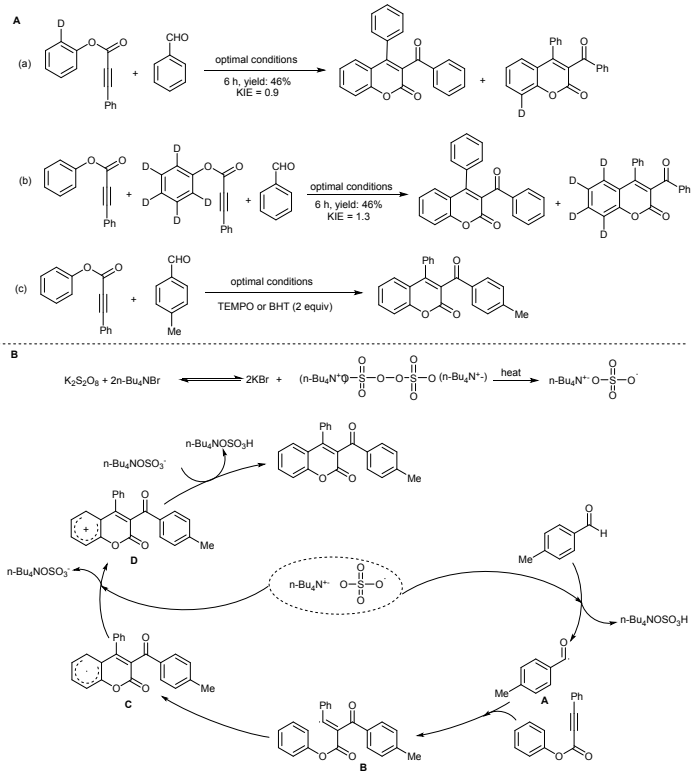
oxidation in presence of TBHP, delivered the preferred 3-acylspiro[4,5]trienone.

In 2015, Wu and co-workers also revealed a metal-free tandem acylation of alkynoates with aldehydes followed by an intramolecular cyclization resulting in 3-acyl-4-arylcoumarins. The reaction proceeded under metal-free conditions in the presence of tetrabutylammonium bromide (TBAB) as additive and $K_2S_2O_8$ as oxidant for the selective synthesis of biologically attractive 3-acylcoumarins.[64] Under the optimized reaction conditions, various differently substituted aldehydes and aryl alkynoates could be coupled in a metal-free acylation/cyclization process to obtain the 3-acylcoumarins in moderate to good yields. Aromatic aldehydes having electron-releasing groups at the *para*-position of the aromatic rings coupled more efficiently than those containing electron-withdrawing groups. Although, *ortho*- and *meta*-substituted benzaldehydes were also appropriate for this conversion but a slight decrease in yields was found. Moreover, alkyl and cyclic aldehydes also provided coumarin derivatives in moderate yields.

Similarly, the aryl alkynoates with either electron-rich substituents or electron-poor substituents at the *para*-position of the phenoxy ring reacted well and products were obtained in good yields. However, in the presence of the strong electron-withdrawing CF_3-group on the phenoxy ring, only 38% yield was obtained whereas, no product was formed for the *ortho*-substituted system. Furthermore, aryl alkynoate with a methyl group at the *meta*-position of the phenoxy ring resulted in a mixture of two regioisomers in a 1.6:1 ratio. However, the presence of a methoxy group at the *meta*-position delivered only one isomer in 76% yield (**Scheme 29**).



Scheme 29: Metal-free tandem acylation of alkynoates with aldehydes followed by an intramolecular cyclization.



Scheme 30: (A) Control experiments; (B) Plausible reaction mechanism.

To gain insight in the reaction mechanism for this newly developed protocol, the authors performed some control experiments. The intramolecular and intermolecular kinetic isotope, effects were measured using deuterium labeled substrates in competing experiments and the k_H/k_D values were found to be 0.9 and 1.3, respectively. The observed low k_H/k_D suggested that the C-H bond cleavage is not the rate-limiting step in this transformation. Moreover, when the reactions were carried out in the presence of the free radical scavengers TEMPO or BHT, no product formation was observed and the adduct of *p*-tolualdehdye with TEMPO or BHT was observed, suggesting a free radical pathway of the reaction (**Scheme 30A**). In accordance with the observations of the control experiments, a plausible mechanism following the free radical pathway was proposed (**Scheme 30B**). Initially bis(tertrabutylammonium) peroxysulfate is generated by the reaction between peroxysulfate and TBAB, which get converted into the tetrabutylammonium sulfate radical anion at high temperature. This radical reacted with *p*-methylbenzaldehyde to give an acyl radical **A**. Subsequently, the selective addition of acyl radical **A** to the α–position of the C=O bond in alkynoate **Y**, resulted in the vinyl radical **B**. This intermediate **B** then cyclized to the arene and formed another radical intermediate **C**. Next, a single-electron transfer from intermediate **C** to another sulfate radical could give cation **D**. This cation **D** upon deprotonation by the formed sulfate di-

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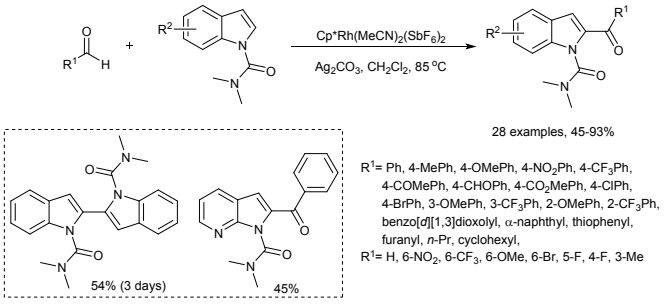
anion provided the 3-acylcoumarin derivative and another bisulfate anion.

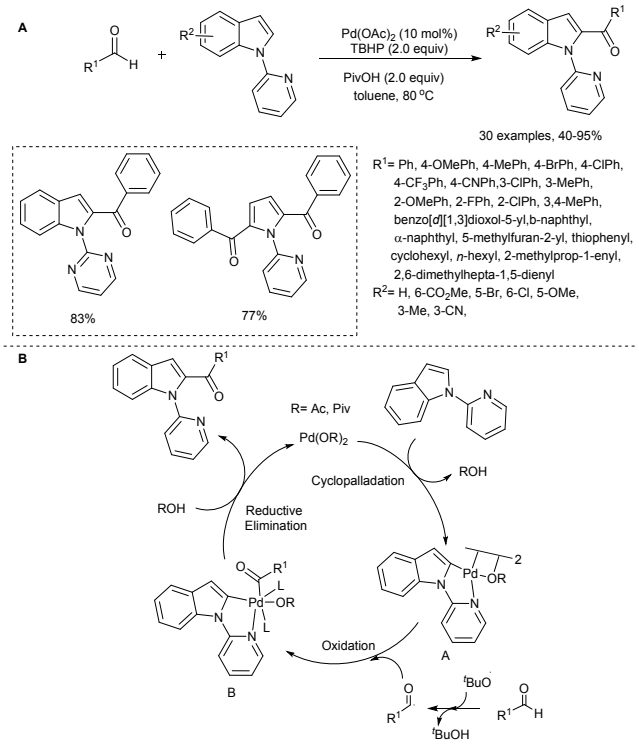
3.3. Acylation of heteroarenes/heteroaryls

Heterocyclic compounds represent the largest and one of the most vital classes of organic compounds used in many biological fields due to their importance for the treatment of multiple illnesses and building blocks for industries. Presently, several heterocyclic compounds are known and due to the enormous synthetic research as well as their synthetic utility the number of heterocyclic molecules is increasing rapidly day-by-day. Heterocyclic compounds play a significant role in almost all fields of science such as medicinal chemistry, biochemistry and synthetic chemistry, and are widely distributed in natural products, biomolecules and other bioactive molecules. Heterocyclic scaffolds are major constituents of biological molecules such as DNA, RNA, vitamins, enzymes, chlorophyll, haemoglobin and many more. Therefore, pharmacists and organic chemists have been making extensive efforts for the formation and functionalization of heterocyclic molecules through developing versatile, atom- and step-economical efficient synthetic strategies. In this direction, Zhou and co-workers (2012) explored the first Rh-catalysed regioselective oxidative C2-acylation of the ubiquitous indole (*N,N*-dimethyl-1*H*-indole-1-carboxamide) by coupling with aryl/alkyl aldehydes involving direct sp^2 C-H bond cleavage and C-C bond formation strategy.[65] The scope of *N*-protected indoles was explored with various aldehydes using $Cp^*Rh(MeCN)_3(SbF_6)_2$ as optimum catalyst and Ag_2CO_3 as oxidant. The presence of electron-releasing and electron-withdrawing groups at the aryl ring of the benzaldehyde did not affect the outcome of the reactions and good reactivity was demonstrated with *N*-protected indoles irrespective of the position of the substituents. Benzaldehydes having Me, OMe, NO_2, CF_3, $COCH_3$, CHO and COOMe, etc. at the *para*-position gave the corresponding products in 50-92% yields. Notably, 2-furaldehyde, thiopene-2-carbaldehyde and 2-naphthaldehdye underwent sp^2-sp^2 coupling efficiently and delivered the respective products in 73%, 85% and 90% yield, respectively. Interestingly, coupling between *N,N*-dimethyl-1*H*-indole-1-carboxamide and paraformaldehdye resulted in the formation of dimeric 2,2'-biindolyl product with complete regiocontrol in 54% yield. Moreover, *N*-protected indoles having both electron-donating (OMe) and electron-withdrawing (CF_3, NO_2, Br etc.) groups at the C6-position were readily converted into the targeted products in good to excellent yield (**Scheme 31**).



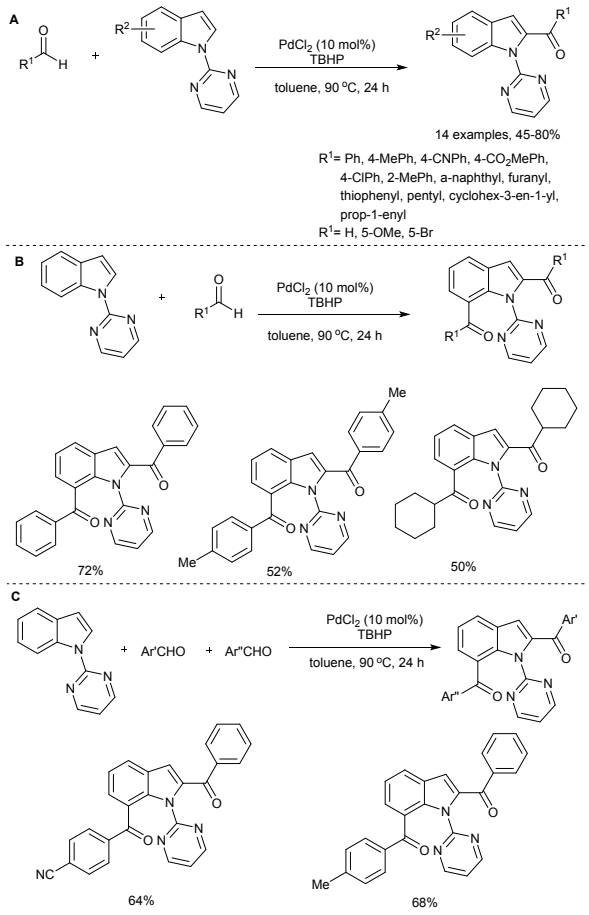
Scheme 31: Rh-catalyzed regioseletive oxidative C_2-acylation of indole by coupling wit aryl/alkyl aldehydes.

Later in 2014, Yan *et al.* described a Pd-catalyzed C-2 acylation of *N*-pyridinyl indoline with aliphatic and aromatic aldehydes by direct C-H functionalization.[66] Various *N*-protected indoles were coupled with various aliphatic and aromatic aldehydes in the presence of $Pd(OAc)_2$ as catalyst, TBHP as oxidant and PivOH as additive. Benzaldehydes having electron-withdrawing groups or electron-releasing groups at the *para*-position provided the corresponding products in good yields. However, relatively lower yield were observed in case of *ortho*-substituted benzaldehydes, because of steric hindrance. α-naphthaldehdyde and β-naphthaldehdyde also underwent the acylation reaction smoothly to afford the products in good yields. Interestingly, 5-methylfuran-2-carbaldehyde and thiophene-2-carbaldehyde also participated in this oxidative coupling to give the products in 64% and 74% yields, respectively. The reaction scope was not found to be limited to aryl aldehydes as several aliphatic as well as conjugated aldehydes also effectively participated in the reaction to give the products in good yields (**Scheme 32A**). Likewise aldehydes, several indoles containing functional groups such as methoxy, chloro, bromo, ester, etc. reacted smoothly to give products in moderate to good yields. However, 3-substituted indole afforded a lower yield of the acylated product due to steric crowding. The proposed mechanism for this protocol is depicted in **scheme 32B**.



Scheme 32: Pd-catalyzed C-2 acylation of *N*-pyridinyl indoline with aliphatic and aromatic aldehydes and plausible reaction mechanism.

A method describing the selective C-2 monoacylation and C-2, C-7 diacylation through C-H bond functionalization of 1-(pyrimidin-2-yl)-1*H*-indole using aldehydes was disclosed by Govindasamy Sekar and his group in 2015.[67] The authors synthesized fourteen C-2 monoacylated products, three C-2, C-7 symmetric diacylated products and two C-2, C-7 unsymmetric diacylated products in moderate to good yields using $PdCl_2$ catalyst and TBHP (70 % aqueous solution in toluene) as oxidant in toluene. For monoacylation, 3 equivalents of TBHP were used, whereas, for diacylation, 5 equivalents of TBHP were required. Aromatic aldehydes containing both electron-releasing and electron-withdrawing groups yielded 2-acylated products of 1-(pyrimidin-2-yl)-1*H*-indole in moderate to good yields. Sterically hindered α–naphthaldehyde and heteroaromatic aldehydes like 2-furaldehyde and thiophene-2-carbaldehyde provided the corresponding C-2 acylated products in 79 %, 58 % and 54 % yield, respectively. Indoles with electron-releasing and electron-withdrawing groups at the C-5 position coupled effectively and yielded C2-acylated products in moderate yields. Moreover, aliphatic and α,β-unsaturated aldehydes, when subjected to these reaction conditions, resulted in the expected products in good yield (**Scheme 33**). The use of 3 equiv of aldehyde and 5 equiv. of TBHP under the same reaction conditions provided the symmetric C2, C7-diacylated products through dual C-H bond functionalization with good yields **(Scheme 33B)**. Whereas using two different aldehydes (1.5 equiv. each) one after another resulted in the formation of unsymmetrical diacylated products **(Scheme 33C)**.



Scheme 33: (A) Selective C-2 monoacylation of 1-(pyrimidin-2-yl)-1*H*-indole with aldehydes; (B) Symmetric and (C) Unsymmetric C-2, C-7 diacylation of 1-(pyrimidin-2-yl)-1*H*-indole with aldehydes.

In 2017, Van der Eycken and his group established a mild and versatile method for C2 C-H acylation of *N*-pyrimidylindoles with aldehydes through dual photoredox/transition-metal catalysis in batch and flow at room temperature.[68] Initially the authors explored various reaction parameters including solvent, catalysts, photocatalysts and ligands to achieve optimal reaction conditions. Finally, the use of 10 mol% $Pd(OAc)_2$ catalyst, 2 mol% of photocatalyst fac-$[Ir(ppy)_3]$, 20 mol% Boc-Val-OH ligand and 4 equiv. of 0.1 M TBHP in acetonitrile delivered the best outcome after 20 h of blue LED irradiation in a batch process. Whereas in a flow process only 0.5 mol% of photocatalyst fac-$[Ir(ppy)_3]$ with slight excess of oxidant (6 equiv. of 0.2 M TBHP in acetonitrile) along with the rest of the other reagents was found to be enough to give good product yields in just 2 h. With these optimized reaction conditions in hand, the scope of the reaction was determined by exploring various substituted benzaldehydes as coupling partners of *N*-protected indoles. C2-Acylation of indole derivatives with benzaldehyde bearing alkyl/aryl groups or a methoxy group smoothly proceeded with good product

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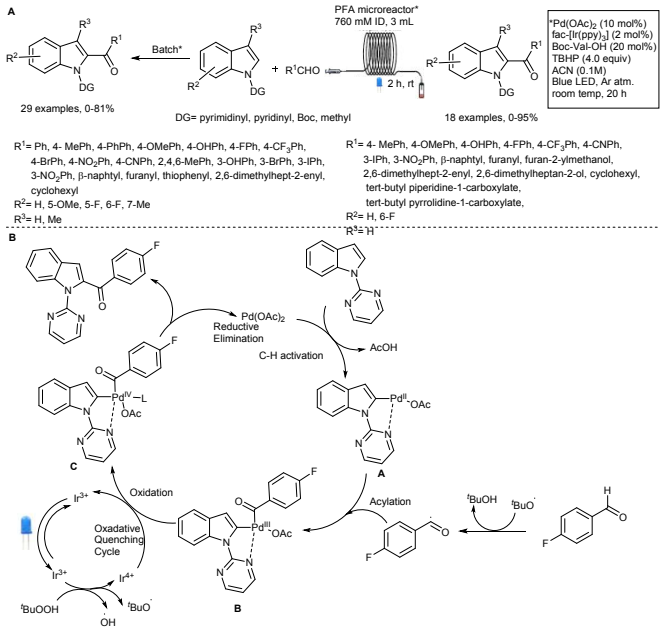
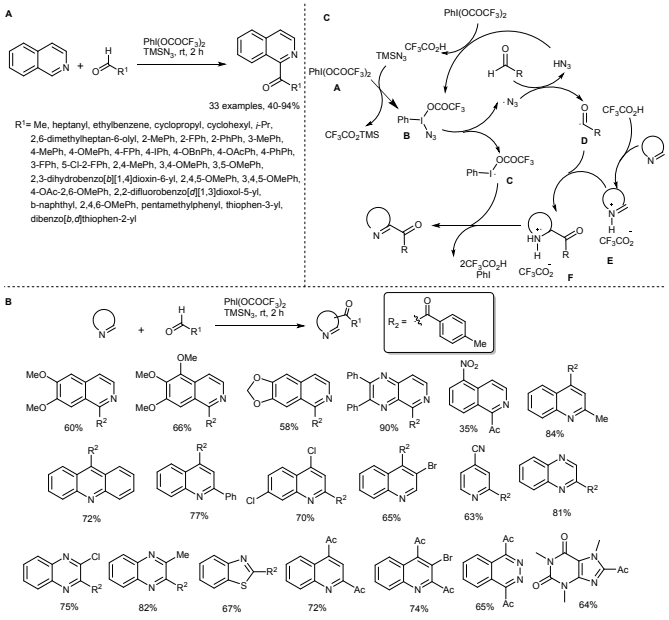
yields. However, hydroxylated benzaldehydes delivered inferior yields. Furthermore, the acylated products were obtained in good yields (54-89%) when benzaldehyde contained electron withdrawing groups such as Br, CN, NO_2 and CF_3. Interestingly, heterocyclic aromatic aldehydes, aliphatic acyclic and cyclic/heterocyclic aldehydes reacted efficiently to afford C2-acylated *N*-pyrimidylindoles in good to excellent yields (**Scheme 34**). Based on observations of control experiments performed by authors and available literature reports, a plausible SET (single electron transfer) mechanism was designed as described in **Scheme 34B** which initiates by the formation of a five membered palladacycle **A** *via* interaction between *N*-pyrimidylindole and $Pd(OAc)_2$ catalyst. In the meantime, the photocatalytic process generated an acyl radical. The photo-excitation of the photocatalyst produced an excited state (Ir^{3+*}) which get oxidatively quenched by TBHP to generate a key radical intermediate *t*-$BuO^{\cdot}$. This radical abstracts a proton from the aldehyde to produce an acyl free radical, which on reaction with intermediate **A** resulted in intermediate **B**. This undergoes a single electron oxidation to Pd^{IV}, which closes the photocatalytic cycle *via* a back-electron donation process. Finally, reductive elimination resulted in the targeted product and regenerated the Pd^{II} catalyst.



Scheme 34: Acylation of N-pyrimidylindoles with aldehdyes via dual photoredox/transition-metal catalysis in batch and flow and plausible reaction mechanism.

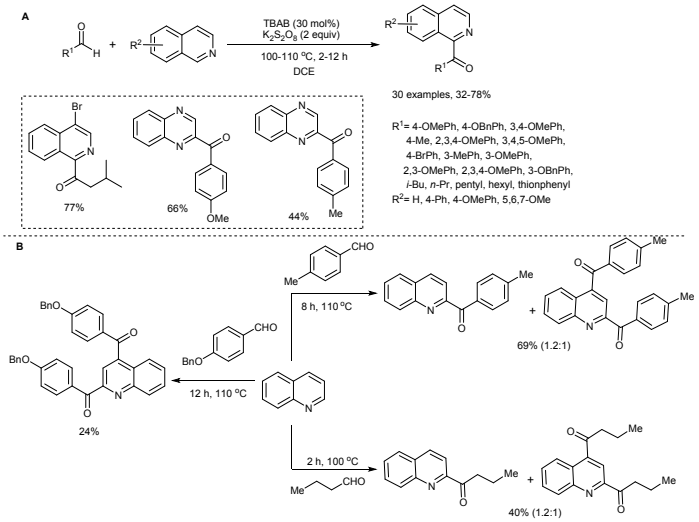
In early 2013, Antonchick and Matcha developed a metal-free cross-dehydrogenative coupling reaction between various heterocyclic compounds and aldehydes for selective sp^2 C-H bond acylation (**Scheme 35**). The reaction proceeded efficiently with all the applied heterocyclic compounds and aldehydes giving a library of 62 compounds in the presence of $PhI(OCOCF_3)_2$ as oxidant and $TMsN_3$ as additive.[69] Employing the best reaction conditions, the scope of the isoquinoline synthesis with various aldehydes was explored.. The reaction provided a broad substrate scope and aromatic aldehydes having electron-releasing and electron-withdrawing groups at the aryl ring were selectively coupled to isoquinolines under metal-free conditions at ambient temperature. Polysubstituted benzaldehydes also provided the desiredcoupling products efficiently under the developed reaction conditions. Moreover, aliphatic aldehydes could be reacted competently with isoquinoline using smaller amount of iodide and $TMSN_3$. Aromatic aldehydes with electron-releasing groups at the *ortho*, *para* and *meta*-position delivered comparable yields. Whereas, the benzaldehydes with electron-withdrawing groups at the *para*-position gave better yields of the corresponding products in comparison of their *ortho*- and *meta*-substituted derivatives. Moreover, polymethoxy substituted benzaldehydes were also tolerated and provided products in good to excellent yield. Notably, sulphur containing heterocyclic aldehydes provided cross-coupled products in good yields without over-oxidation to sulfoxides and sulfones (**Scheme 35A**). After exploring the effect of aldehydes, the scope of various heterocyclic molecules such as isoquinoline, quinoline, quinaxaline, acridine, benzothiazole and caffeine was also explored and all the heterocyclic compounds coupled smoothly under the optimized reaction conditions to yield the targeted molecules in good yields (**Scheme 35B**).

Through the observations of control experiments, a plausible mechanism has been proposed for this transformation (**Scheme 35C**). The mechanism starts with a ligand exchange between $PhI(OCOCF_3)$ and $TMSN_3$, which provides the intermediate **B**. A double exchange of trifluoracetyl groups in **A** by azide ions give $PhI(N_3)_2$. Intermediate **B**, on thermal homolytic cleavage, generates an azide radical and a radical intermediate **C**. Reaction between azide radical and aldehyde generates nucleophilic acyl radical intermediate **D**. Subsequent attack of generated acyl radical onto protonated heterocyclic **E** delivers intermediate **F**. Finally, re-aromatization of the intermediate **F** results the anticipated products.

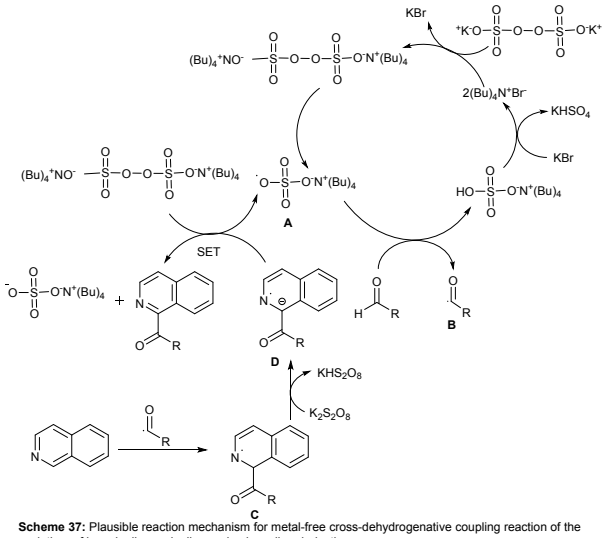


Scheme 35: Metal-free cross-dehydrogenative coupling reaction between isoquinoline, isoquinoline, quinoline,quinaxaline, acridine, benzothiazole and caffeine with aldehydes for the sp^2 C-H bond acylation and plausible reaction mechanims.

A similar transition metal-free cross-dehydrogenative coupling reaction for acylation of isoquinoline, quinoline and quinoxalines - using aldehydes as acylating agents was reported by Prabhu and his group in 2014.[70] This method involved the use of a substoichiometric amount of tetrabutylammonium bromide (TBAB) as an additive and $K_2S_2O_8$ as an oxidant. With optimized reaction conditions, several isoquinolines were acylated using aromatic and aliphatic aldehydes to give the respective acylated products with 32-78% yields. Notably, thiophene-2-carbaldehyde also underwent a facile coupling with 4-(*p*-methoxyphenyl)-isoquinoline to afford the product in 41% yield. Moreover, quinoxaline, when coupled with 4-methoxybenzaldehdye and 4-methylbenzaldehdye delivered the acylated products were in 66% and 44% yield (**Scheme 36A**). To explore the further scope of the developed acylation method, quinoline was also subjected to this CDC strategy. Coupling of the quinoline with 4-methylbenzaldehyde and butanal furnished the mixture of 2-acylated and 2,4-diacylated products in 1.2:1 ratio. On the other hand, 4-benzyloxybenzaldehyde provided only 2,4-diacylated product in just 24% yield (**Scheme 36B**).



Scheme 36: Metal-free cross-dehydrogenative coupling reaction for the acylation of isoquinoline, quinoxaline and quinoline derivatives using aldehydes.



Scheme 37: Plausible reaction mechanism for metal-free cross-dehydrogenative coupling reaction of the acylation of isoquinoline, quinoline and quinoxaline derivatives.

Based on the literature, the authors proposed a free radical mechanism (**Scheme 37**). The mechanism starts with the reaction between $K_2S_2O_8$ and TBAB resulting in sulfate radical **A**, which abstracts hydrogen from the aldehyde to form the acyl radical **B**. Further, the acyl radical reacts with the heteroarene resulting in the formation of the corresponding amidyl radical **C**. The formed amidyl radical gets deprotonated with the sulfate anion and forms radical anion **D**. This radical anion **D** transfers an electron to the persulfate resulting in the desired product.

Benzofurans and benzothiophenes are highly privileged structural moieties, which are present in several natural products and exhibit a broad spectrum of biological properties.[71] Moreover, benzofuran and benzothiopene scaffolds containing an acyl group at the C-3 position are of great interest for medicinal chemistry due to their antibacterial, anti-tumor, anti-arhythmic activities.[72] Therefore, the development of new efficient protocols for the synthesis of 3-acylbenzofurans and 3-acylbenzotionphenes is highly desirable.

In 2013, Zhao *et al.* published a pyridinyl group-assisted Pd-catalyzed cross-dehydrogenative coupling reaction for the C-3 acylation of benzofuran and benzothiophene derivatives using TBHP as an oxidant under air.[73] Several derivatives of aldehyde were coupled with benzofuran and benzothiophene in the presence of $Pd(OAc)_2$ as catalyst, TBHP as oxidant in chlorobenzene at 120 °C. The reaction exhibited a broad scope and high compatibility with the functional groups such

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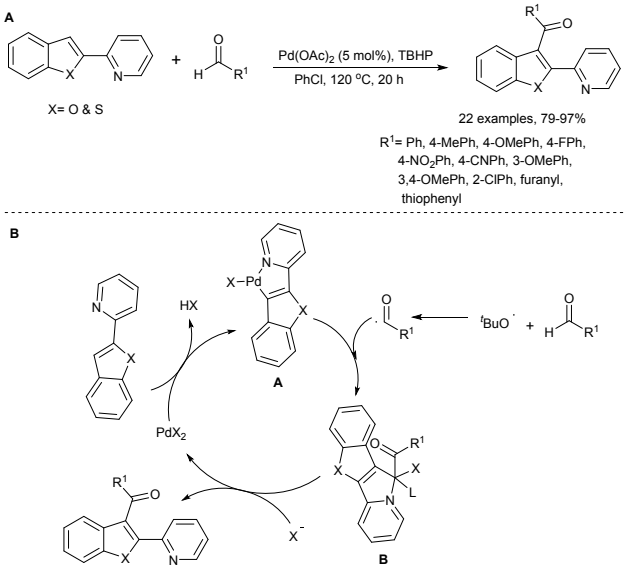
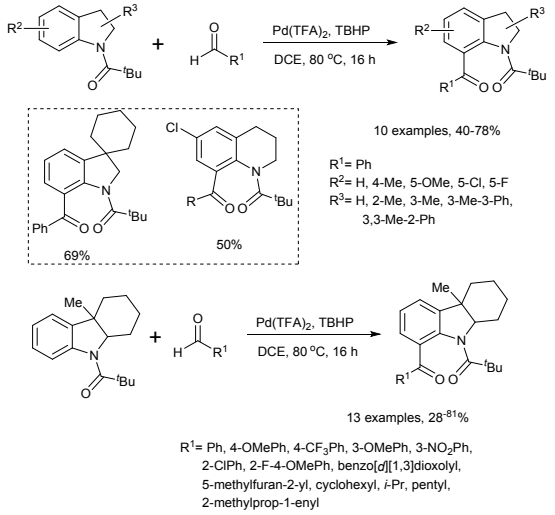
as OMe, Me, NO_2, CN and halogens, etc. and provided excellent yields (89-97%) of the desired products regardless the position of the substituents on the benzene ring of benzaldehydes. However, dimethoxy-substituted benzaldehyde provided a slightly lower yield of acylated products of benzofuran and benzothiophene. Moreover, heterocyclic aldehydes such as thiopehen-2-carbaldehyde and 2-furaldehyde also reacted smoothly and the corresponding products were obtained in good to excellent yields. Unfortunately, no product was formed in case of aliphatic aldehyde (**Scheme 38A**). As per previous reports, the authors designed a plausible mechanism to rationalize this methodology as presented in **scheme 38B**.



Scheme 38: Pd-catalyzed cross-dehydrogenative coupling reaction for the C-3 acylation of benzofuran and benzothiophene derivatives and plausible reaction mechanism.

Kim and co-workers in 2014 disclosed a Pd-catalyzed oxidative coupling reaction for the selective C-7 acylation of substituted indolines using aldehydes *via* a C-H activation approach.[74] The reactions were carried out between various *N*-pivaloyl indolines/*N*-pivaloyl carbazoles and aromatic/aliphatic aldehydes using $Pd(TFA)_2$ as catalyst, TBHP as oxidant in DCE as solvent at 80 °C to prepare 24 derivatives. The coupling reaction of C-2 or C-3 unsubstituted indolines with benzaldehyde afforded the corresponding acylated products in moderate yields. C-2 and C-3 alkyl/aryl substituted indolines also underwent the oxidative acylation reaction to provide products in moderate to good yields under the developed reaction conditions. Electron-rich as well as electron-deficient benzaldehydes were found to favor the acylation reaction irrespective the position of the substituents on the phenyl ring and afforded the products in good to high yields. Isobutyraldehyde, cyclohexanecarbaldehyde and 1-hexanal provided moderate yields. However, 5-methylfuran-2-carbaldehyde and 3-methylbut-2-enal delivered the products in poor yields (**Scheme 39**). Two parallel reactions of *N*-protected carbazole derivatives and their deuterated analogues with benzaldehyde were performed in order to gain mechanistic insight. The kinetic isotope effect (k_H/k_D = 2.79) revealed that C-H cleavage might be involved in the rate limiting step.

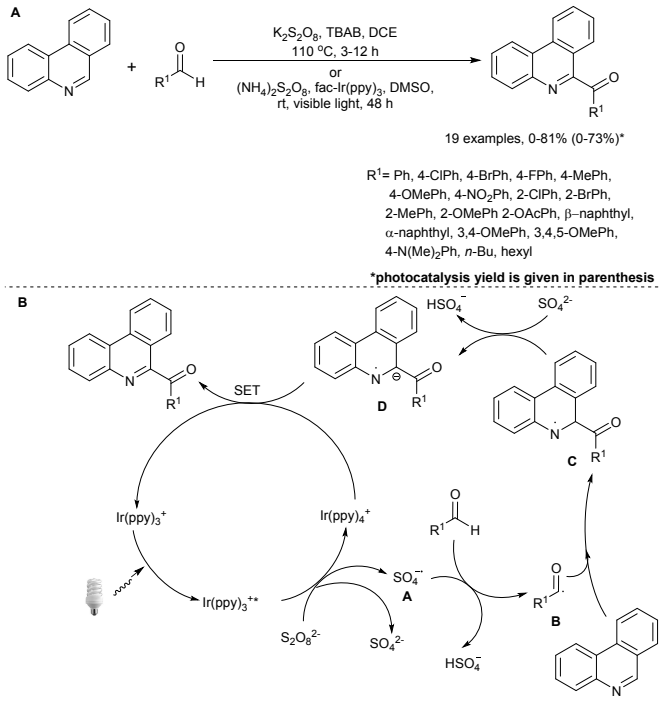


Scheme 39: Pd-catalyzed oxidative C-7 acylation of indolines and carbazoles with aldehydes.

Later, in 2014 Cheng *et al.* reported a regiospecific Minisci acylation of phenanthridine based on a cross-dehydrogenative coupling strategy *via* thermolysis or photolysis.[75] Under thermal conditions (100 °C) the acylation of phenanthridine with aldehydes was carried out using a substoichiometric amount of the phase transfer catalyst tetrabutylammonium bromide (TBAB, 30 mol%) and $K_2S_2O_8$ as oxidant. Interestingly, a preliminary research based on literature reports indicated that phenanthridine could be acylated selectively at room temperature replacing the TBAB/$K_2S_2O_8$ system with $(NH_4)_2S_2O_8$ and using 5 mol% of *fac*-$Ir(ppy)_3$ as photocatalyst under visible light irradiation. However, the reaction proceeded slowly (48 h) under photocatalytic reaction conditions in comparison to thermal reaction conditions (12 h). Several aromatic aldehydes with electron-releasing (Me, OMe) and electron-withdrawing (F, Cl, Br, OAc etc.) groups at the aromatic ring were coupled with phenanthridine under the optimized thermal conditions as well as photo-catalytic conditions and targeted products could be obtained in moderate to good yields. Benzaldehydes with di- and tri-methoxy substituents triggered good results in both conditions. Interestingly, 4-fluorobenzaldehyde provided the maximum yield of 80% under thermal conditions. Unfortunately, no product was obtained with 4-nitrobenzaldehdye and 4-*N,N*-dimethylbenzaldehydes in

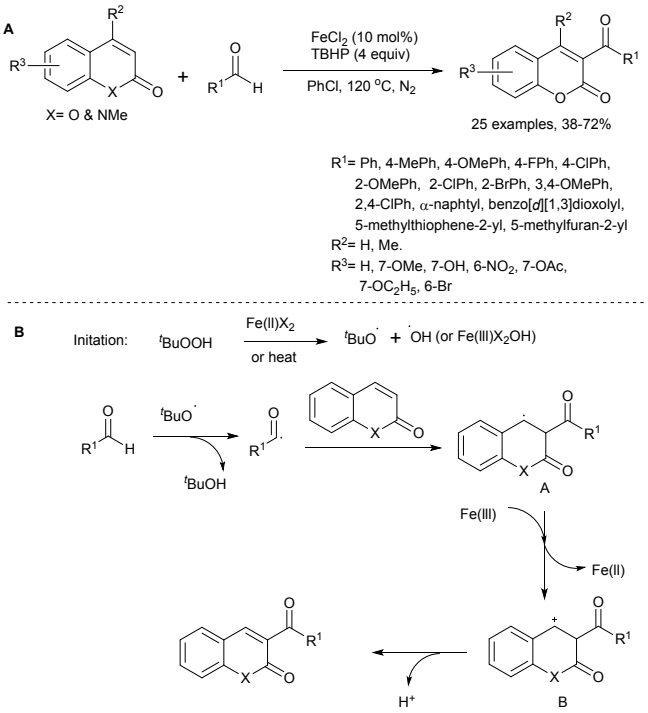
either of the conditions. Aliphatic aldehydes provided inferior product yields (**Scheme 40**).

Based on the literature and experiments, a possible photocatalytic pathway was proposed (**Scheme 40**). The persulfate anion can be reduced by visible light excited $[Ir(ppy)_3]^{3+*}$ to give sulfate and the sulfate radical anion **A** along with $[Ir(ppy)_3]^{4+}$. H-Atom abstraction from the aldehyde by radical **A** gives acyl radical **B** which on addition to phenanthridine afforded amidyl radical **C**. Deprotonation of the α-proton in the amidyl radical **C** by the sulfate anion generates radical anion **D**. Reductive quenching of $[Ir(ppy)_3]^{4+}$ by radical anion **D** through SET generates $[Ir(ppy)_3]^{3+}$ sustaining the photocatalytic chain.



Scheme 40: Acylation of phenanthridine with aldehydes via thermolysis or photolysis and proposed reaction mechanism.

In a span of four years (2015-2018), four individual studies[76] on the application of aldehydes as acylating agents were published for the selective direct C3-acylation of coumarins. In 2015, Fe-catalyzed cross-coupling of coumarins was carried out with aromatic aldehydes in the presence of TBHP oxidant under N_2-atmosphere by the team of Ling-Bo Qu.[76a] Initially, several aromatic aldehydes (1.0 mmol) were coupled with coumarin (0.25 mmol) under the optimized reaction conditions using $FeCl_2$ as catalyst, TBHP as oxidant in toluene at 120 °C under nitrogen atmosphere. The targeted molecules were achieved in moderate to good yields after 12 h. Aromatic aldehydes with electron-releasing (CH_3, OCH_3, OCH_2O) and mild electron-withdrawing (F, Cl, Br) groups on the benzene ring smoothly favored the selective C3-acylation of coumarin in moderate to good yields. However, aromatic aldehydes with electron-withdrawing groups afforded inferior product yields in comparison to aldehydes bearing electron-releasing groups at the aryl ring. The steric hindrance on aromatic aldehydes did not affect this transformation since *ortho*-substituted aldehydes and α-naphthaldehyde smoothly generate the corresponding products in moderate yields. Unfortunately, aliphatic aldehydes failed to deliver the targeted products. Furthermore, coumarin substituted with electron-rich (OCH_3, OCH_2CH_3, etc.) and electron-poor (OH, $OCOCH_3$, NO_2, etc.) groups at the C6 or C7-position were found to give the corresponding products in moderate yields (**Scheme 41A**). A series of *N*-methyl quinolinone derivatives was also examined successfully using the optimized reaction conditions and acyl groups were exclusively attached to the C3-position of 2-quinolinones delivering 55-77% yield of the products. On the bases of control experiments and previous reports, a plausible reaction mechanism was proposed by authors as depicted in **scheme 41B**.



Scheme 41: Fe(II)-catalyzed cross-coupling of coumarins for the selective direct C3-acylation and plausible reaction mechanism.

Later in 2016, Aihua Zhou and co-workers developed a new coupling reaction for the selective C3-acylation of coumarins by a sp^2 C-H functionalization process involving aldehydes in the presence of a Cu-catalyst and TBHP as oxidant (**Scheme 42**). [76b] Various coumarin derivatives were acylated regioselectively at the C3 position by aldehydes and all substrates reacted proficiently to produce the respective products in moderate to good yields in the presence of CuO as

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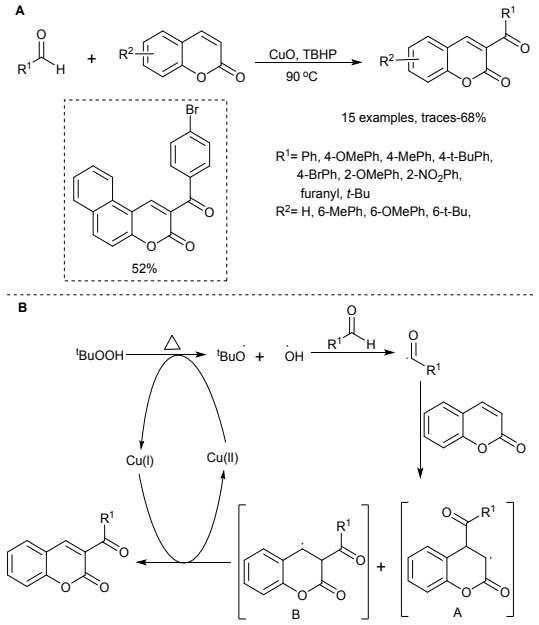
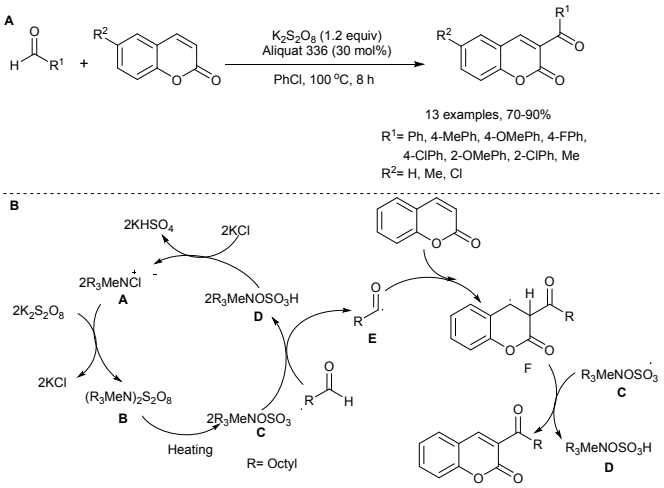
catalyst and TBHP as oxidant at 90 °C after 24 h. Aromatic aldehydes with electron-releasing groups (OMe, Me, ^{t}Bu, etc.) and the electron-withdrawing bromine group were found suitable for this transformation. Nevertheless, in case of nitrobenzaldehyde no expected product could be observed, whereas *iso*-butyraldehdye delivered the C3-acylated product in 48% yield. Noticeably, 2-furaldehyde also afforded the product upon coupling with coumarin, and 6-methyl coumarin in 65% and 63% yield, respectively. Moreover, the presence of substituents on the coumarin did not alter the reaction outcome and good yields were obtained. The proposed mechanism for this protocol is presented in **scheme 42B**.



Scheme 42: Cu-catalyzed C3-acylation of coumarin and its plausible reaction mechanism.

Subsequently in 2016, Peiman Mirzaei and his team worked on a transition metal-free cross-dehydrogenative coupling reaction for the synthesis of 3-acylcoumarins. Reactions were carried out by heating a mixture of coumarins and aldehydes in the presence of $K_2S_2O_8$/Aliquat-336 system in chlorobenzene. Various substituted coumarin and aldehyde derivatives were coupled at 100 °C for 8 h to synthesize 14 derivatives of 3-acylcoumarins in good to excellent yields (**Scheme 43A**).[76c] The electronic behaviour of the substituents present on the benzene ring of the aromatic aldehydes played a key role for the yields irrespective of their positions. Aromatic aldehydes having either electron-releasing (Me, OMe) groups or mild electron-withdrawing groups (F, Cl) reacted proficiently and delivered the products in high yields. The scope of substituted coumarins was also explored using 6-methyl-coumarin and 6-chlorocoumarin and the expected products could be obtained in good yields. Moreover, treatment of acetaldehyde with coumarin afforded 88% of the desired product. The control experiments revealed that the reaction followed a free-radical mechanism since the addition of free radical scavenger TEMPO to the reaction mixture inhibits the formation of the product completely. The proposed mechanism is depicted in **scheme 43B**. This starts with the reaction between Aliquat-336 (tricaprylmethylammonium chloride) **A** and $K_2S_2O_8$ resulting in the formation of tricaprylmethylammonium persulfate **B**, which generates tricaprylmethylammonium sulfate radical **C** on heating. Then, acyl radical **E** is generated*via* the reaction between benzaldehyde and the sulfate radical **B** and this process is accompanied by the removal of tricaprylmethylammonium hydrogensulfate **D**. Radical addition of **E** to the 3-position of coumarin forms resonance stabilized benzyl radical **F**. Finally, removal of a hydrogen atom from **F** by another sulfate radical **C** afforded the desired product together with **D**. Tricaprylmethylammonium chloride gets regenerated by the reaction between tricaprylmethylammonium hydrogensulfate **D** and KCl.



Scheme 43: Metal-free cross-dehydrogenative coupling for C_3-acylation of coumarin and proposed reaction mechanism.

Recently, our group has developed a highly proficient, metal-free approach for the regioselective C3-acylation of coumarins with aromatic aldehydes using *tert*-butyl peroxybenoate (TBPB) as free radical initiator (**Scheme 44**).[76d] Various differently substituted aromatic aldehydes having electron-releasing and electron-donating groups were reacted with 7-methoxy coumarin under the optimized reaction conditions. All applied aromatic aldehydes delivered the anticipated products in moderate to good yields at 90 °C after 24 h. Also, other derivatives of coumarin produced the desired products in good yields upon treatment with benzaldehyde. Unfortunately, neither aromatic aldehyde nor coumarin having strong electron-withdrawing NO_2-group furnished the corresponding acylated compound. Moreover, *iso*-

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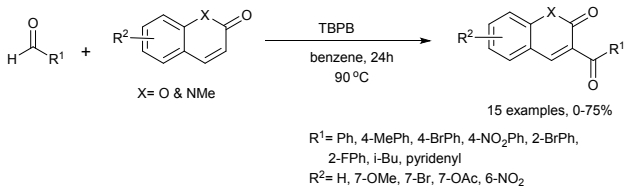
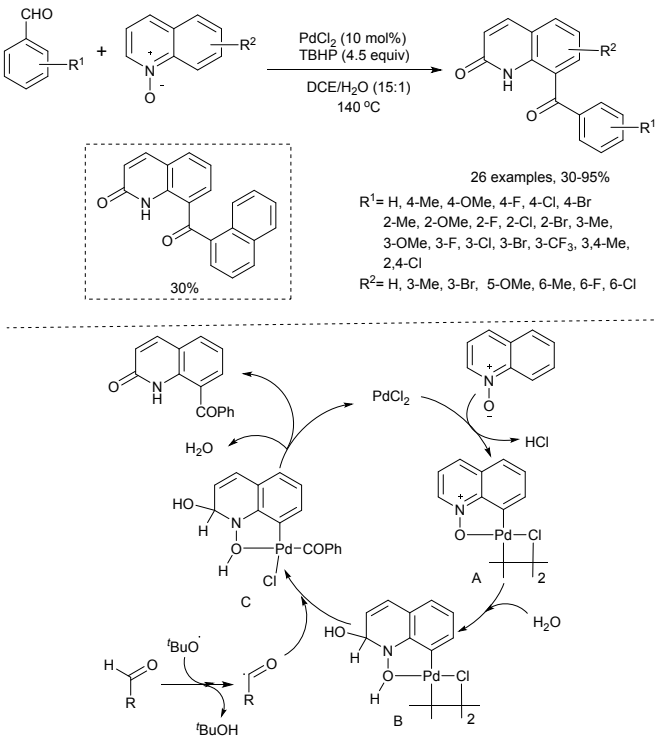
butyraldehyde and pyridine-2-carbaldehyde also resulted in the acylation of coumarin at C3-position in 41% and 60% yield, respectively. Furthermore, *N*-methylquinolone also delivered the individual C3-acylated product upon treatment with simple benzaldehyde under the optimized reaction conditions.



Scheme 44: Regioselective C3-acylation of coumarin with aldehydes.

In 2016 Wu and his team described a one-pot process for the selective formation of 8-acylated-2-quinolinones starting from quinilone-*N*-oxides and aldehydes using a Pd-catalyst and TBHP as oxidant *via* the formation of *N*-oxide-chelated palladacycle.[77] A total of 26 8-acylated-2-quinolinones were synthesized in good to excellent yields starting from various quinoline-*N*-oxides and benzaldehydes in the presence of $PdCl_2$ catalyst, TBHP (5-6 M in decane) as oxidant, water as additive and DCE as solvent at 140 °C for 24 h. (**Scheme 45A**). Benzaldehydes having electron-releasing (Me and OMe) and weak electron-withdrawing (F, Cl and Br) groups at the *para*-position of the aryl ring gave the corresponding products in good to excellent yields. However, proficiency of acylation was slightly affected by steric hindrance as *p*-methylbenzaldehyde gave a higher yield than *o*- and *m*-methylbenzaldehyde and a similar pattern was observed for methoxy and halogen-substituted benzadehydes. 3-(trifluoromethyl)benzaldehyde provided the acylated product in just 43% yield. Furthermore, disubstituted aromatic aldehydes also provided good yields of the desired products. Substituted quinoline-*N*-oxides were also coupled smoothly with benzaldehyde and the positions of the substituents did not interfere with reaction outcomes significantly improving the synthetic effectiveness of this protocol.

Based on several control experiments such as free radical trapping and kinetic isotope effect, a plausible mechanism was proposed by the authors as presented in **scheme 45B**. The mechanism starts with the formation of a palladacycle dimer intermediate **A** *via* co-ordination of the palladium with the *O*-atom of quinoline-*N*-oxide and subsequent electrophilic attack at the C8-position. Subsequently, complex **A** gets converted into another intermediate **B** through nucleophilic addition of H_2O at the C2-position of the quinoline. In the meantime, an acyl radical was generated from the aldehyde in the presence of TBHP. The reaction between intermediate **B** and the acyl radical afforded the oxidative addition intermediate **C** as a Pd(III) or Pd(IV) complex. Finally, intermediate **C** gave the desired product through reductive elimination and regenerated Pd(II).



Scheme 45: Pd-catalyzed selective C-8 acylation of quinilone-*N*-oxides using aldehydes and plausible reaction mechanism.

4. Miscellaneous

In 2012, Zhang and Hong reported the direct *N*-acylation of lactams, oxazolidinones and imidzolidinones using aldehydes in the presence of Shvo's catalyst in toluene as solvent.[78] The best reaction conditions were defined as stirring a mixture of lactam/oxazolidinone/imidzolidinone (0.25 mmol, 1 equiv.), aldehyde (3.0 equiv.) in the presence of Shvo's catalyst (2.5 mol%) in toluene (0.5 mL) as solvent at 100 °C for 24 h. In total 33 *N*-acylated derivatives of lactams, oxazolidinones and imidzolidinones were synthesized in moderate to excellent yields using several aromatic, aliphatic, heterocyclic and α,β-unsaturated aldehydes as acylating agents (**Scheme 46A**). Based on the mechanism of Shvo's catalyst, the authors proposed a plausible mechanism for this method as presented in **scheme 46B**. This involves nucleophilic attack of lactam **A** to the carbonyl carbon of the activated aldehyde to form a hemiaminal **B**, which further oxidizes *via* β-hydride elimination and undergoes proton transfer to produce the acylation product and ruthenium species **C3**.

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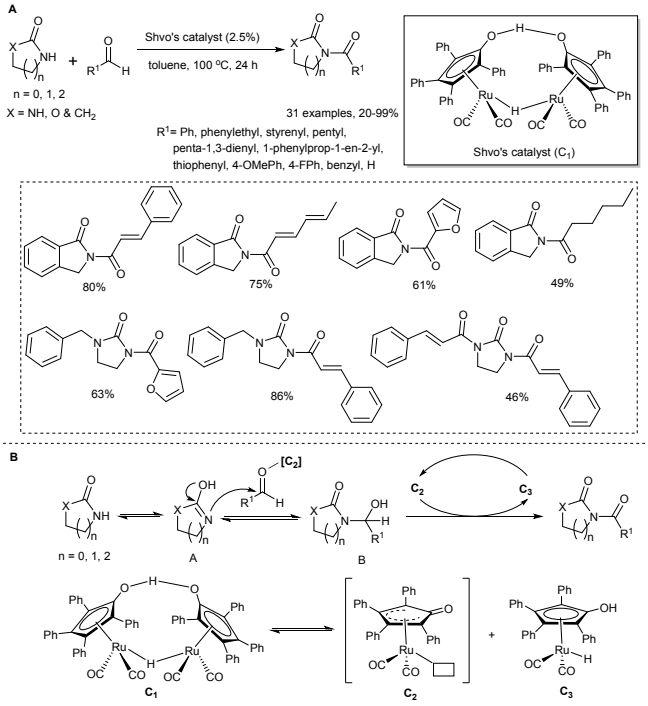
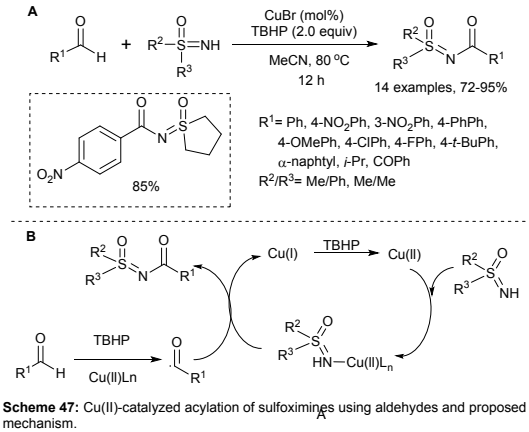


Scheme 46: Direct N-acylation of lactams, oxazolidinones and imidzolidinones with aldehdyesusing Shvo's catalyst and proposed mechanism.

A copper catalyzed oxidative cross-coupling involving dual C-N/N-H functionalization for *N*-acylation of sulfoximines was disclosed by Wang *et al.* in 2013 by treating aldehydes with sulfoximines in the presence of TBHP as oxidant under mild reaction conditions (**Scheme 47A**).[79] A set of 14 derivatives of *N*-acylsulfoximines was prepared with good functional group tolerance. In addition to *S,S*-methylphenyl sulfoximine, the reaction proceeded smoothly with *S,S*-dimethyl and *S,S*-tetramethylenesulfoximines also and afforded their respective products in excellent yields. Also, benzaldehyde bearing a nitro group at the *para*- and *meta*-position furnished the targeted compounds in excellent yields. Not only a nitro group but also other electron-withdrawing groups such as F, Cl and electron-releasing groups such as methoxy, alkyl, etc. were well tolerated, delivering various *N*-benzoylsulfoximines in good to excellent yields. A redox process based plausible pathway for this protocol is described in **scheme 47B**. The proposed pathway involves the interaction of a Cu(II) catalyst with sulfoximine to give intermediate **A**. This intermediate **A** reacts with an acyl radical generated from the aldehyde in the presence of TBHP. Subsequently, an electron transfer processes results in the construction of *N*-acylsulfoximine and a Cu(I) species. The later re-oxidizes to Cu(II) in the presence of TBHP.



Scheme 47: Cu(II)-catalyzed acylation of sulfoximines using aldehydes and proposed mechanism.

In 2014, Luo and Liang developed a metal-free one-pot cascade cyclization of 1,6-enynes with aldehydes involving simultaneous one C(sp^2)-C(sp^2) and two C(sp^2)-C(sp^3) bond formation for the synthesis of carbonylated tricyclic fluorene derivatives by using PivOH and TBHP.[80] The reaction conditions were optimized as the reaction of a 1,6-enyne (0.2 mmol) with an aldehyde (1.0 mmol) in the presence of the oxidant TBHP (0.4 mmol, 70% aqueous solution), the additive PivOH (0.4 mmol) in acetonitrile as solvent (1 mL) at 120 °C for 48 h under argon atmosphere. The developed reaction conditions were initially examined for exploitation of aldehydes in this cascade oxidative cyclization process. Various aromatic aldehydes containing electron-releasing and electron-withdrawing groups participated in this reaction to give the targeted fluorene derivatives in good yields regardless the positions of substituents on the aryl ring of the benzaldehydes (**Scheme 48A**). Aliphatic aldehydes were not suited in this transformation and only traces of the products could be obtained. Remarkably, benzo[*d*][1,3]dioxole-5-carbaldehyde and thiophene-2-carboxyaldehyde could also undergo the reaction giving the products in 45% and 35% yields, respectively. Delighted by these promising results, the scope of 1,6-enyne substrates was examined with benzaldehyde and the reaction progressed efficiently in most cases to give the desired products in moderate to good yields (**Scheme 48A**). 1,6-Enynes substituted with electron-releasing alkyl or alkoxy groups at the *ortho*, *meta* or *para*-position or containing either halogen or an electron-withdrawing COOMe or CN group at the *para*-position were suitable for this reaction affording the corresponding carbonylated fluorenes. Tosylamides also react with benzaldehyde to give products in moderate yield, whereas only trace amounts of the product (9,9-dimethyl-1,3,9,9a-tetrahydroindeno[2,1-*c*]pyran-4 yl)(phenyl)methanonewas obtained from the corresponding enyne substrate.

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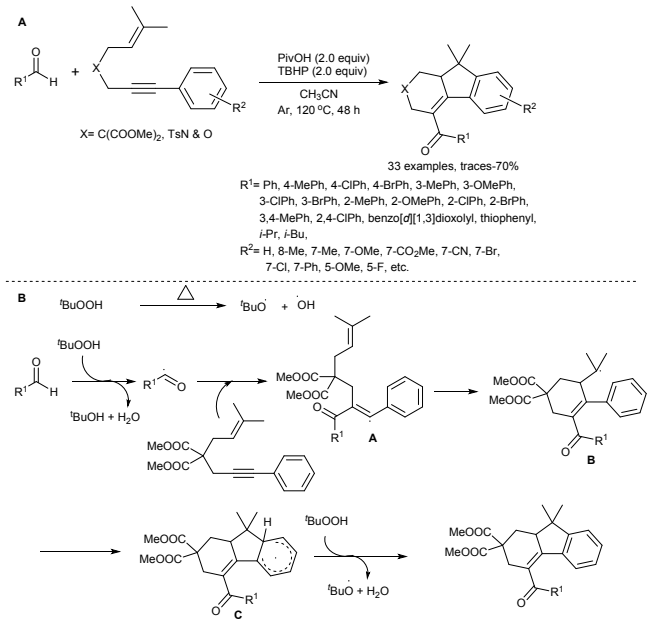

Scheme 48: Metal-free one-pot cascade cyclization of 1,6-enynes with aldehydes and plausible reaction mechanism.

To understand the mechanism, kinetic isotope effect and free-radical quenching experiments were examined. No kinetic isotope effect ($k_H/_{kD}$ = 1.0) was found by the outcome of intramolecular and intermolecular reactions under standard reaction conditions. This ultimately revealed a free-radical or SEAR route for this reaction. Also, inhibition of the reaction in the presence of 4 equiv of TEMPO clearly indicated that the reaction proceeds via a free-radical route. A large kinetic isotope effect (KIE, $k_H/_{kD}$ = 9.1) value for the 1:1 mixture of benzaldehyde and [D_6]-benzaldehyde implied that cleavage of the carbonyl C-H bond is the rate-determining step for this conversion. Depending on these observations and previous reports in this field,[81] a plausible mechanism was proposed (**Scheme 48B**). Initially, homolytic cleavage of TBHP under heating conditions generated alkyloxy and hydroxyl radicals. These radicals capture a hydrogen atom from benzaldehyde to form an acyl radical, and successive attack of this acyl radical at the C≡C bond of the enyne afford the radical intermediate **A**. Next, an intramolecular cyclization process generates a tertiary carbon radical **B**, which subsequently by another intramolecular cyclization with an aryl ring give rise to radical intermediate **C**. Lastly, direct oxidation and deprotonation of intermediate **C** by TBHP furnishes the final product.

Fuwei Li and his team in 2014 demonstrated a KI-catalyzed oxidative cross-coupling of C-N and N-H bonds between azoles and aromatic aldehydes for the direct *N*-acylation of azoles in the presence of TBHP as oxidant.[82] Various derivatives of azole (0.3 mmol) were reacted with aldehydes (0.45 mmol) in the presence of KI (0.06 mmol) as standard catalyst using TBHP (0.9 mmol) as ideal oxidant in dichloroethane (DCE) as solvent at 100 °C for 12 h. A total 28 derivatives were prepared in moderate to excellent yields irrespective of the positions and nature of the substituents on the azoles as well as on the aldehydes (**Scheme 49A**). When the scope of aldehydes was examined with pyrazoles, *para*-substituted benzaldehydes containing electron-donating (OMe, ^{t}Bu) groups and electron-withdrawing (Cl, Br, CN) groups reacted effectively with 3-phenyl pyrazole and delivered the products in 57% to 95% yield. *Ortho*-methoxybenzaldehydes resulted inferior yield in comparison to *para*-methoxybenzaldehydes. β-naphthaldehdyde and thiophene-2-carbaldehdydes were also found suitable for this transformation leading to 90% and 72% yield of the products, respectively. Encouraged by these findings, the authors further explored the scope of other azoles such as benzimidazole, benzotriazole and indazole with various substituted aromatic aldehydes. Benzaldehydes with electron-releasing groups provided products in 85% to 98% yield whereas electron-withdrawing substituents afforded yields of 24% to 78% upon reaction with benzimidazole. Surprisingly, benzotriazole reacted only with *ortho*-substituted benzaldehydes and no product formation was observed with *para*-substituted benzaldehydes. Furthermore, indazole upon treatment with *para*-bromobenzaldehyde gave 44% yield.

To investigate the reaction mechanism, control experiments were performed in the presence of free-radical scavengers like TEMPO and 1,1-diphenylethylene. These experiments suggested the formation of an acyl radical and a free-radical pathway for this conversion. Based on these results, two possible pathways were proposed as shown in **scheme 49C**. It was hypothesized that the *tert*-butoxyl and *tert*-butylperoxy radicals are generated initially in the catalytic system, which could abstract a hydrogen atom from the aldehyde to generate the acyl radical. This acyl radical on reaction with the azole give the acyl azole radical anion **A**. Subsequently, radical anion **A** by losing an electron *via* a SET process in the presence of the *tert*-butoxyl or *tert*-butylperoxy radical afforded the desired *N*-acyl azoles (**Path A**). In **path B**, it is represented that the *tert*-butoxyl and *tert*-butylperoxy could capture a single electron from the azoles leading to an azole cation species **B**, which upon deprotonation with the help of tert-bytoxyl anion could convert to azole radical **C**. Finally, the coupling between acyl radical and azole radical cation **B** or azole radical **C** provided the desired product.

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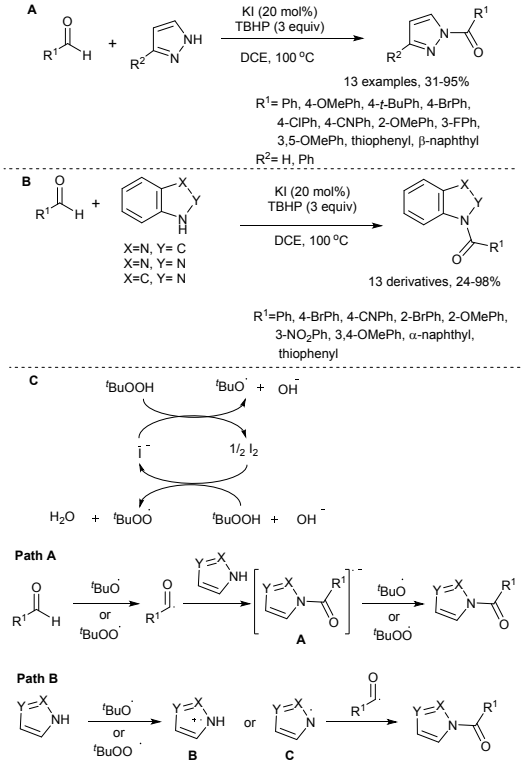
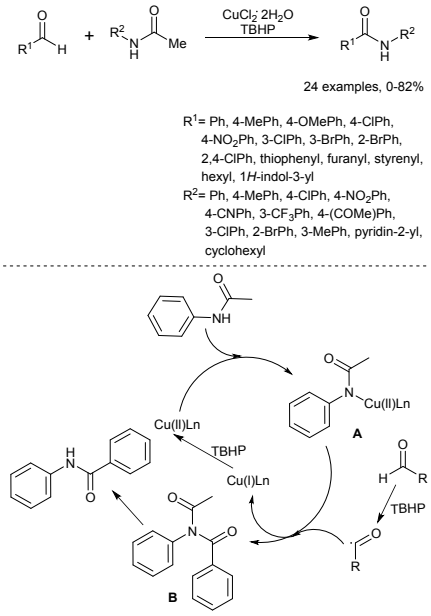


Scheme 49: KI-catalyzed oxidative cross-coupling of C-N and N-H bonds for *N*-acylation of azoles using aromatic aldehydes and Plausible reaction mechanism.

In 2015, Singh and co-workers for the first time developed a mild oxidative amidation process of aldehydes using acetanilide as amine component in the presence of copper catalyst and TBHP as oxidant.[83] Acetanilide and benzaldehyde were taken as model reactants and the reaction was carried out using NBS catalyst and TBHP as oxidant in acetonitrile at 100°C, and 55% yield of benzanilide was obtained. To improve the product yield, several other catalysts, oxidants and solvents were screened. Finally, by several combinations and permutations, the reaction conditions were optimized by stirring of a mixture of acetanilide (0.5 mmol), benzaldehyde (1 mmol) in the presence of $CuCl_2.2H_2O$ (10 mol%) catalyst using TBHP (2 equivalents) as oxidant in DCE as solvent at 100 °C for 24 h. With these optimized reaction conditions, the scope and versatility of the reaction was examined using various substituted acetanilides and aldehydes, and finally a library of 24 benzanilide derivatives was prepared (**Scheme 50A**). Acetanilides as well as benzaldehydes containing electron-releasing and electron-withdrawing groups such as Me, OMe, Cl, Br, NO_2, CN, etc. underwent the reaction smoothly delivering the products in moderate to good yields. Thiopene-2-carbaldehyde gave the product in 52% yield. However other heterocyclic aldehydes such as furfural and indole-3-carboxyaldehyde showed no product formation because of their decomposition in the presence of TBHP. Aliphatic aldehydes such as heptanal and cinnamaldehyde afforded the corresponding products in 64% and 76% yield, respectively. Based on literature reports and experiments, a plausible reaction mechanism was proposed as shown in **scheme 50B**.



Scheme 50: Cu-catalyzed oxidative amidation of aldehydes using acetanilide and plausible reaction mechanism.

In the same year (2015), Achar *et al.* executed a metal-free oxidative cross-coupling for the amidation of aldehydes with *N*-chloramines in the presence of TBAI (tetrabutylammonium iodide) in combination with TBHP under neat conditions at 50°C or ball-milling conditions at room temperature (**Scheme 51A**).[84] Using this protocol, 19 amide derivatives were obtained in good yields by treating aromatic aldehydes, heteroaromatic aldehydes and aliphatic aldehydes with primary and secondary *N*-chloramines. Aryl aldehydes having electron-donating Me and OMe substituents give 84% and 82% yield of the respective amides. Furthermore, the presence of electron-withdrawing substituents such as F, Cl, Br, CF_3, NO_2, etc. on the aryl system of aromatic aldehydes was found to be competent for this amidation reaction. Thiophene-2-carbaldehyde provided 76% yield of the product, whereas in case of aliphatic aldehydes, inferior yields (53%-64%) were obtained. Similarly, various *N*-chloramine derivatives such as *N*-chloro-1-phenylmethanamine, *N*-chloro-*N*-methyl-1-phenylmethanamine, *N*-benzyl-*N*-chloro-1-phenylmethanamine etc. also reacted smoothly and enabled good product yields. To get insight into the reaction mechanism, control experiments were performed under neat conditions (**Scheme 51B**). Based on the results of these experiments, a plausible reaction mechanism was proposed as shown in **Scheme 51C**.

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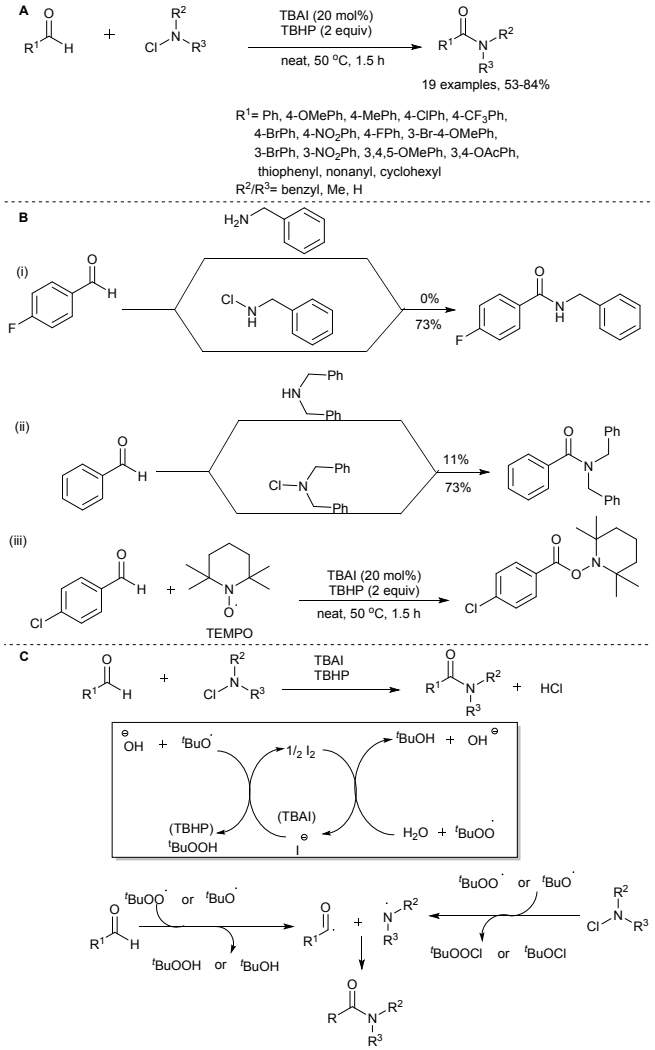
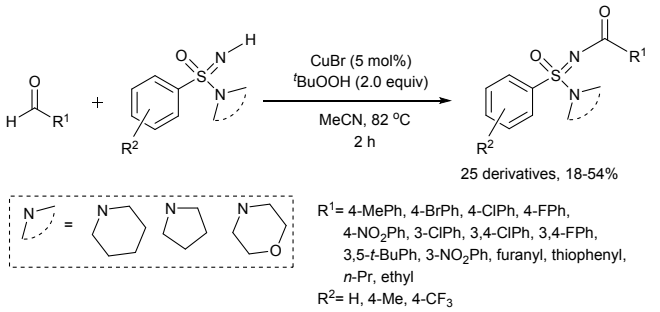


Scheme 51: Metal-free oxidative cross-coupling for the amidation of aldehydes using N-chloramines, control experiments and plausible reaction mechanism.

In 2017, Cijil Raju and co-workers reported a Cu-catalyzed double C-H/N-H activation protocol between sulfonimidamides and aldehydes affording a diversity of *N*-acyl sulfonimidamides in low to moderate yields (**Scheme 52**).[85] In this typical procedure, a mixture of sulfonimidamides (4.0 equiv.), aldehydes (1.0 equiv.) in the presence of CuBr (5 mol%) as catalyst and TBHP (2.0 equivalent) as oxidant in acetonitrile was stirred at 82 °C for 2 h. Employing these optimal conditions, 26 different *N*-acyl sulfonimidamides were prepared in 18-56% yields, starting from aromatic, heterocyclic and aliphatic aldehydes and various sulfonimidamides. Various benzaldehydes with electron-donating and electron-withdrawing substituents in different positions display identical ease towards the N-acylation of sulfonimidamides. Both mono- and di-substituted aromatic aldehydes worked well under these developed reaction conditions. Interestingly, the presence of the bulky ^{t}Bu group at the C-3 and C-5 position of the aryl aldehyde does not inhibit the product formation and 47% yield was obtained. The scope of the reaction was not limited only to aryl aldehydes as hetero-aromatic and aliphatic aldehydes were also found feasible for this transformation. The modifications in the aryl system of the sulfonimidamide moiety were well tolerated and replacement of the piperidine part with morpholine and pyrrolidine was also found to be compatible and yielded the corresponding products smoothly.



Scheme 52: Cu-catalyzed double C-H/N-H activation between sulfonimidamides and aldehydes for the synthesis of N-acyl sulfonimidamides.

Later in 2017, Zheng and Ma published a direct oxidative *N*-acylation reaction of primary amines with aryl/α,β–unsaturated aldehydes in the presence of the azolium salt of an *N*-heterocyclic carbene and base such as ^{t}BuOK or NaH using 3,3′,5,5′-*tetra*-*tert*-butyldiphenoquinone (DPQ) as oxidant at 25 °C (**Scheme 53**).[86] This methodology provided a proficient approach for the synthesis of *N*-sulfonylcarboxamides, *N*-sulfinylcarboxamides and dicarboxyimides in good yields. The reactions were carried out by reacting a mixture of the corresponding amine (0.4 mmol) and aldehyde (0.6 mmol) in the presence of NHC (10 mol%) catalyst, *t*-BuOK (0.8 mmol)/NaH (1.2 mmol) base in THF as solvent under N_2 atmosphere at 25 °C followed by quenching using 1M HCl aqueous solution. The scope of the primary amines with aldehydes was investigated by synthesizing 24 *N*-acylated derivatives of amines in high yields. Aryl aldehydes bearing substituents such as F, Cl, OMe and NO_2 at different positions (*ortho*-, *meta*- and *para*-) of the aryl ring participated in the reaction with tosylamide to give the respective *N*-tosylcarboxamindes in high yields. Interestingly, thiophene-2-carbaldehyde and 2-naphthaldehyde provided the respective imides in 87% and 91% yields with these newly developed conditions. Moreover, α,β–unsaturated aldehydes including enals and ynals were well suited for this direct *N*-acylation protocol of tosylamide and conjugated ynals having aliphatic or aromatic substituents exhibited a wide scope resulting in 71-87% yields of the products. Unfortunately, alkylated aldehydes were found inactive under the current reaction conditions and could not afford the imide products probable due to competing enolization of the aldehyde substrate.

To expand the synthetic utility of this methodology, other amide substrates were examined. Electron-rich

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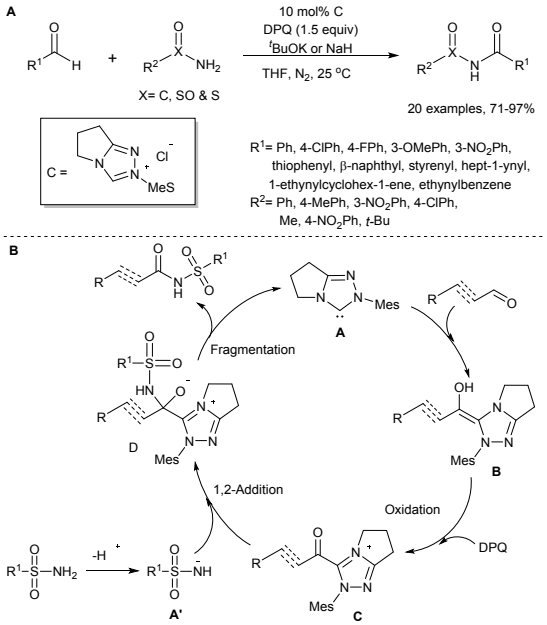
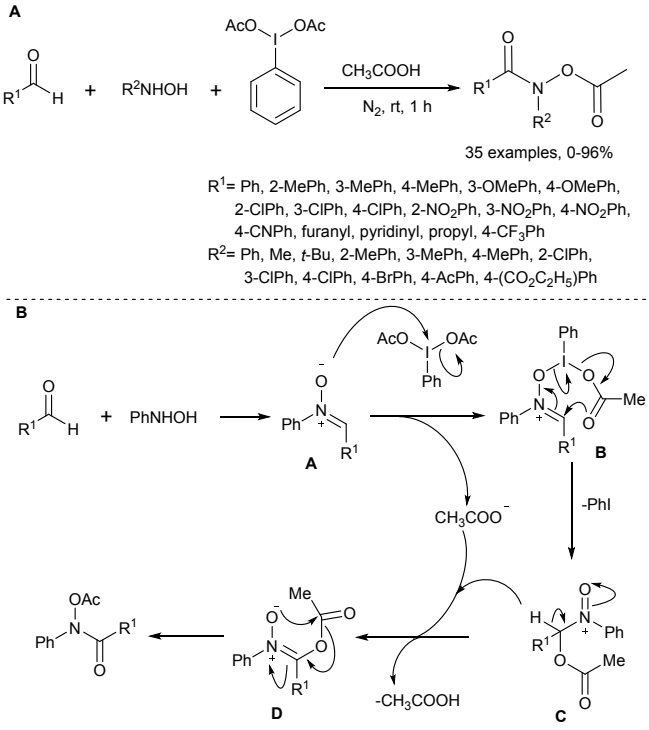
(unsubstituted) as well as electron-poor (*p*-NO_2 and *p*-Cl substituted) aryl sulfonamides upon reaction with 4-chlorobenzaldehyde delivered the corresponding products in 93-96% yields. Besides, methanesulfonamide was also witnessed as a competent reaction partner given that 92% yield of the product was obtained. Additionally, benzamide and its *p*-chloro and *p*-nitro derivatives could also be employed for the formation of dicarboxyamides using a stronger base NaH (3.0 equiv.) instead of ^{t}BuOK, due to the inferior acidity of carboxamides compared with sulfonamides. (*S*)-*tert*-butylsulfinamide (99% ee) suited efficiently in this protocol and yielded the (*S*)-*tert*-butylsulfinamide-4-chlorobenzamide in 81% yield with almost complete retention (98% ee) of configuration (**Scheme 53A**).

The postulated catalytic cycle for this transformation is presented in **Scheme 53B**. The pathway initially involved the formation of Breslow intermediate **B** through nucleophilic addition of *in situ* generated carbene **A** to aldehyde. The intermediate **B** oxidized to form acylazolium species **C** upon treatment with DPQ. Then attack of the deprotonated amide compound **A'** probably *via* 1,2-adduct **D**, on azolium intermediate **C**, followed by a fragmentation sequence gave the final compound along with the carbene catalyst **A**.



Scheme 53: *N*-acylation reaction of primary amines with aryl/a,b-unsaturated aldehydes using azolium salt of an N-heterocyclic carbene and plausible reaction mechanism.

In the meantime, Hu and co-workers developed an efficient $PhI(OAc)_2$-promoted double acylation (*N*- and *O*-acylation) of hydroxylamines with aldehydes at room temperature in acetic acid for the synthesis of *N*-acetoxy-*N*-arylamides in good to excellent yields.[87] The acylation of *N*-atoms in hydroxylamines are due to the acyl group of aldehydes whereas the *O*-atoms get acylated by the acetyl group of $PhI(OAc)_2$. This transformation exhibited great substrate scope under the optimized reaction conditions. Initially, the effect of aromatic aldehydes was explored with *N*-phenylhydroxylamine and all the selected aryl aldehydes could give the desired products regardless of the nature (electron-releasing or electron-donating) of the substituents present on the aromatic ring. However, in some cases, the positions of the substituents on the aryl ring of the benzaldehydes were found to influence the reaction yield. For example, *m*-nitrobenzaldehyde delivered 85% yield whereas *p*-nitrobenzaldehyde resulted in 73% yield but unfortunately no product formation took place with *o*-nitrobenzaldehyde. The 2-furaldehyde and pyridine-2-carboxaldehdye offered their respective products in good yields; on the other hand, no product formation was observed with aliphatic aldehydes (**Scheme 54**).

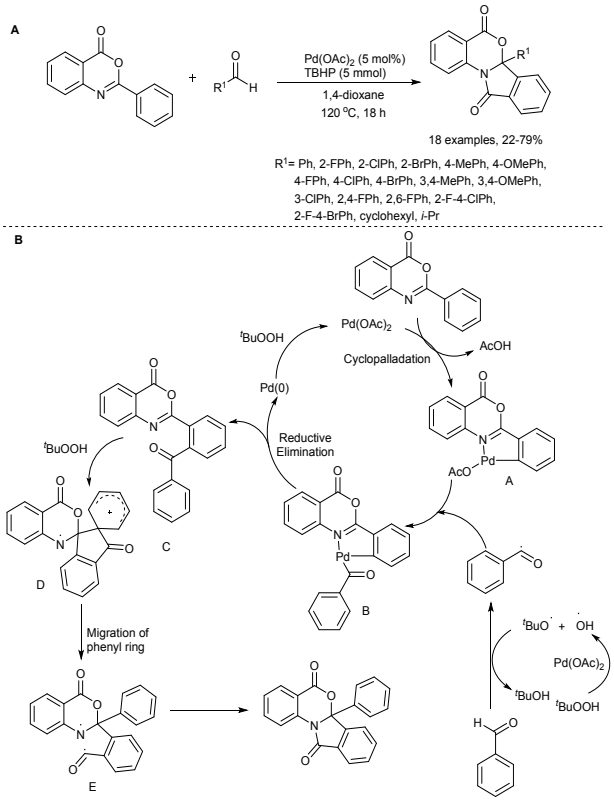


Scheme 54: $PhI(OAc)_2$-promoted double acylation (*N*- and *O*-acylation) of hydroxylamines with aldehydes and plausible reactioN mechanism.

Similarly, the applicability of various *N*-aromatic hydroxylamines bearing an electron-rich methyl group or electron-poor chloro, bromo, acetyl or ester group reacted with benzaldehyde, and the corresponding products were obtained in 45-75% yields. However, no product could be obtained with aliphatic hydroxylamines such as *N*-methylhydroxylamine and *N*-(*t*-butyl) hydroxylamine. The compatibility of the simultaneous in present substituents on aromatic aldehydes and aromatic hydroxylamine was also exploited. The aromatic aldehydes delivered a higher product

yield when electron-withdrawing groups were present as substituents, compared to aromatic aldehydes having electron-withdrawing groups. On the other hand, aromatic hydroxylamines with electron-donating groups on their phenyl rings resulted in higher product yields than those with electron-withdrawing groups with the same aldehydes (**Scheme 54A**). A plausible mechanism for this reaction is shown in **scheme 54B**. At the beginning, the aldehyde reacted with hydroxylamine to form a nitrone intermediate **A**. Then a ligand exchange process took place between nitrone **A** and $PhI(OAc)_2$ to produce intermediate **B**, which on intramolecular rearrangement produced another intermediate **C**. The deprotonation of intermediate **C** by an acetate resulted in intermediate **D**, which on subsequent migration of the acyl group and isomerization gave the final product.

In 2018, our lab disclosed a radical-induced Pd-catalysed approach for the direct functionalization of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones with aldehydes. The reaction proceeded through the formation of the *o*-acylated 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one intermediate to give 6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones in the presence of the TBHP oxidant.[88] Various aryl aldehydes with electron-releasing groups (Me, OMe) and electron-withdrawing groups (F, Cl, Br, etc.) reacted smoothly with 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one in the presence of $Pd(OAc)_2$ (5 mol%) as catalyst using TBHP (5 mmol) oxidant in 1,4-dioxane as solvent at 120 °C for 18 h to afford 19 derivatives in 21-79% yields (**Scheme 55**). Aliphatic aldehydes such as cyclohexanecarboxaldehyde and isobutyraldehyde delivered the corresponding products in 48% and 33% yields, respectively. A plausible reaction mechanism was proposed based on control experiments and previous literature reports (**Scheme 55**). Initially, 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one underwent the *ortho*-palladation reaction with $Pd(OAc)_2$ to form complex **A** and by-product AcOH. At the same time, an acyl radical is formed from the aldehyde by action of TBHP. A subsequent reaction between complex **A** and acyl radical promoted the formation of complex **B**, which goes through a reductive elimination process to give *o*-acylated intermediate **C**. In the next step, the *o*-acylated intermediate underwent an aryl ring migration in the presence of TBHP and gave intermediate **D** followed by biradical intermediate **E**. Biradical **E** undertook C-N bond formation and provided the final compound.



Scheme 55: Pd-catalyzed direct functionalization of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones with aldehydes and plausible reaction mechanism.

Conclusions and Future Perspectives

Over the past decades, aldehydes have emerged as excellent acylation surrogates for the direct forging of acylated compounds containing keto motifs. Consequently, there has been a profitable interplay of acylation and C-H activation for gaining a ready access to these bioactive molecules with enhanced selectivity and improved atom economy under ambient reaction conditions. Also, considerable attention has been devoted by researchers to the exploration of the mechanisms behind these fascinating transformations, opening new horizons for further research in this area. There have been massive breakthroughs with more than 100 research articles published in high impact factor journals involving the selective acylation of arenes, heteroarenes and alkyls (sp^3, sp^2 and sp) C-H bonds. Interestingly, this strategy is witnessing expanded applications in the fields of photocatalysis as well as flow chemistry. The pivotal findings from various studies clearly delineate prospects of large-scale industrial synthesis for obtaining diverse heterocyclic compounds.

Although tremendous accomplishments in this field have been achieved to change the landscape of organic synthesis, yet a lot of work remains to be accomplished. Particularly, future directions in this research area should focus on the

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post-functionalization of drug molecules and natural products and transient directing group mediated acylations. Research in the fields of visible light mediated synthesis and continuous flow synthesis are still in their infancy. There is a room for further improvements via the use of alternative energy sources like ultrasound and microwaves that have also played a crucial role in achieving the green chemistry objectives in organic synthesis via enhancing the efficiency and rapidity of organic reactions.

Nevertheless, we anticipate that in the upcoming years, the limitations and scope of these protocols shall be duly addressed, fuelling more interest in this area. This review has been an attempt to propagate the key findings on the use of less toxic and stable aldehyde motifs for the construction of a plethora of keto compounds; few examples discussed herein are quite motivating from the viewpoint of armouring the organic chemists with sustainable synthetic methodologies which is the pre-requisite of the hour.

Conflicts of interest

There are no conflicts to declare.

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To
The Editor
Organic & Biomolecular Chemistry

Subject: Submission of review article entitled "Aldehydes: magnificent acyl equivalents for direct acylation."

Dear Editor,

Thank you very much for your kind consideration of our review entitled "Aldehydes: magnificent acyl equivalents for direct acylation" for publication in Organic and Biomolecular Chemistry. We are enclosing the final full review along with other relevant files for your perusal. With the submission of the manuscript we ensure that it is original and all the authors are well aware of the contents and concurred with its submission.

In this review, we have comprehensively highlighted and discussed the recent and complete development on the use of aldehydes as magnificent acylation surrogates in the acylation of arenes, heteroarenes and alkyls (sp^3, sp^2 and sp C-H bond), leading to the synthesis of valuable C-C, C-O and C-N bonds *via* the proficient use of C-H activation. Although a diversity of acylation reactions using the title compound-aldehydes as a key starting material, have been described in recent years, yet there is no single review that compiles the utilization of aldehydes in the selective acylation of all these functionalities. We have presented some of the impressive breakthroughs achieved in the past decade in the development of new catalytic reactions for direct acylation and there is a special highlight on some of the latest synthetic tools including flow chemistry and photochemical technologies that have been integrated with these approaches for deriving utmost benefits. There is a comprehensive discussion on the mechanistic aspects that will enable the researchers to think creatively and work in this area.

We truly believe that such a comprehensive review related to this burgeoning field will be of benefit to a broad readership of the journal and stimulate further investigations.

Sincerely,

Dr. Prashant Kumar (On the behalf of all authors)