



HAL
open science

Recent advances in metal-catalyzed C-H functionalization of pyrimidinones, quinazolinones and fused quinazolinones

Corinne Fruit, Thierry Besson

► **To cite this version:**

Corinne Fruit, Thierry Besson. Recent advances in metal-catalyzed C-H functionalization of pyrimidinones, quinazolinones and fused quinazolinones. *Targets in heterocyclic systems: chemistry and properties*, 22, pp.56, 2018, 10.17374/targets.2019.22.56 . hal-02359918

HAL Id: hal-02359918

<https://normandie-univ.hal.science/hal-02359918v1>

Submitted on 12 Nov 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

RECENT ADVANCES IN METAL-CATALYZED C-H FUNCTIONALIZATION OF PYRIMIDINONES, QUINAZOLINONES AND FUSED QUINAZOLINONES

DOI: <http://dx.medra.org/10.17374/targets.2019.22.56>

Corinne Fruit*, Thierry Besson

Normandie University, UNIROUEN, INSA Rouen, CNRS, COBRA UMR 6014, 76000 Rouen, France

(e-mail: corinne.fruit@univ-rouen.fr)

Abstract. This review emphasises the recent developments in metal-catalyzed functionalization using direct C-H bond activation of pyrimidinones (uracils), quinazolinones and quinazolinone-based fused poly-N-heterocycles as well as metal-catalyzed C-H functionalization of high valuable 2-arylquinazolinones.

Contents

1. Introduction
 2. Metal-catalyzed C-H functionalization of pyrimidinones
 - 2.1. Intramolecular palladium-catalyzed C-H arylation of protected uracils using aryl halides
 - 2.2. Intermolecular metal-catalyzed C-H arylation of protected uracils
 - 2.3. Metal-catalyzed dehydrogenative cross-coupling of pyrimidinones with (hetero)-arenes
 - 2.4. Palladium-catalyzed dehydrogenative alkenylation of uracils
 - 2.5. Miscellaneous functionalization of uracils and pyrimidinone
 3. Metal-catalyzed C-H functionalization of quinazolinones
 4. Metal-catalyzed C-H functionalization of 2-arylquinazolinones
 5. Metal-catalyzed C-H functionalization of fused quinazolinones
 6. Conclusion
- Acknowledgments
Abbreviations
References

1. Introduction

Pyrimidinones as well as fused pyrimidinones are an important class of nitrogen-containing heterocycles and are considered as privileged cores in medicinal chemistry.¹ The pyrimidinones scaffold, including uracil derivatives, represents a relevant substructure for a vast array of drug molecules, exhibiting a broad spectrum of both biological and pharmacological activities.² Furthermore, various drugs containing a pyrimidinone nucleus are in clinical use as anticancer agents (5-fluorouracil and tegafur)³ or as anti-schizophrenia⁴ (Figure 1).

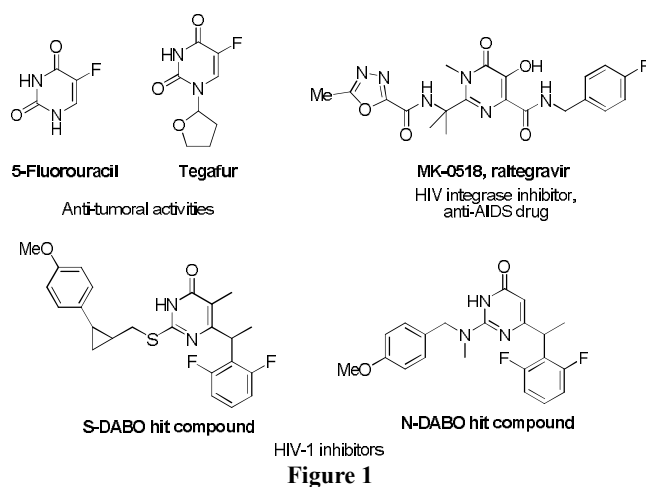


Figure 1

The pyrimidin-4-one core is also used as an inhibitor of the enzyme reverse transcriptase to develop anti-HIV drugs such as raltegravir (MK0518)⁵ and dihydro-benzyl-oxopyrimidinones⁶ (N-DABOs and S-DABOs) (Figure 1). Six-member aromatic ring such as pyrimidinone-5-carbonitrile derivatives were also reported as anticancer and antimicrobial agents (Figure 2).

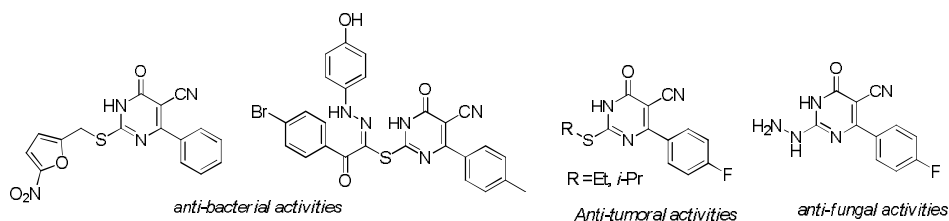
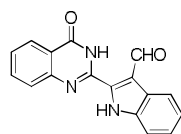


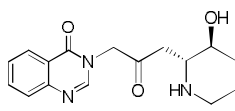
Figure 2

Besides pyrimidinones, a recent survey of quinazolinones revealed their occurrence in many bioactive alkaloids, isolated from various natural sources, and pharmaceuticals products (Figure 3).⁸ Quinazolin-4(3*H*)-ones are an important class of fused heterocyclic compounds with a wide range of therapeutic activities such as anticancer,⁹ antimicrobial,¹⁰ antibacterial,¹¹ antifungal,¹² hypotensive, antiviral, anti-inflammatory, protein kinase inhibitory activities.¹³ For example, febrifugine,¹⁴ isolated from the plant *Dichroa febrifuga* used as a traditional Chinese herbal remedy, is effective against malaria and raltitrexed¹⁵ (Tomudex), which developed by Astra-Zeneca, is an antimetabolite drug used in cancer chemotherapy (Figure 3). Based on the aforementioned activities, numerous synthetic strategies for the construction of the fused pyrimidinones such as quinazolin-4(3*H*)-ones have been developed in the recent decade.¹⁶

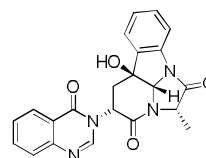
Natural products:



Bouchardatine
Adipogenesis inhibitors
Treatment of obesity

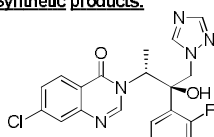


(+)-Febrifugine
Antimalarial activity

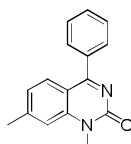


(-)-Chaetominine
Anticancer activity

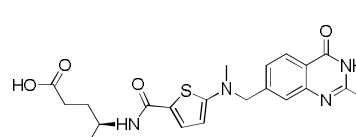
Synthetic products:



Albicanazole
Antifungal activity



Proquazone
Anti-inflammatory activity



Raltitrexed
Anticancer activity

Figure 3

In addition, quinazolinone-based fused poly-*N*-heterocycles are widely found in natural products.¹⁷ They have been shown to be an important class of alkaloids isolated from plant sources, including pyrroloquinazolinone derivatives such as luotonin (isolated in 1997 from the plant *Peganum nigellastrum*)¹⁸ and vasicinone (isolated from *Adhatoda vasica*),¹⁹ indoloquinazolinones such as cruciferane (extracted from *Isatis indigotica* a Chinese biennial herbaceous plant)²⁰ and tryptantrin,²¹ and the indolopyridoquinazolinone rutaecarpine (isolated from *Evodia rutaecarpa*)²² (Figure 4). The natural quinazolinobenzodiazepine alkaloids benzomalvin, sclerotigenin²³ and circumdatins²⁴ derivatives isolated from *Penicillium* sp have also

received considerable attention during the lead discovery for neurokinin receptor antagonists. All these natural alkaloids have emerged as privileged structures due to their wide-ranging biological activities such as antibacterial, antifungal, analgesic, antiobesity, antiviral, anticonvulsant, anti-inflammatory, anti-tumor, anti-microbial, antimalarial and antihyperlipidemic activities.²⁵

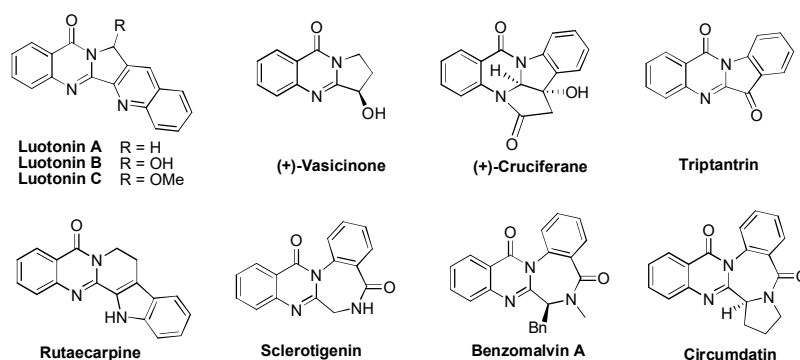


Figure 4

Both synthetic (Figure 5) and natural fused-quinazolinone derivatives (Figure 4) having biological properties are already in clinical trials as potential therapeutic agents. For example, new indazolo[3,2-*b*]quinazolinone derivatives are potent inhibitors of phosphodiesterase for the treatment of asthma and chronic obstructive pulmonary disease²⁶ and synthetic thiazoloquinazolin-9(8*H*)-ones²⁷ have also received considerable attention because of their wide range of biological activities including anticancer activity, anti-inflammatory, antifungal, antimicrobial and protein tyrosine kinase inhibitory.

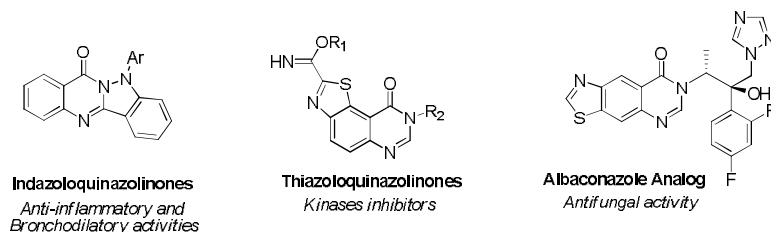


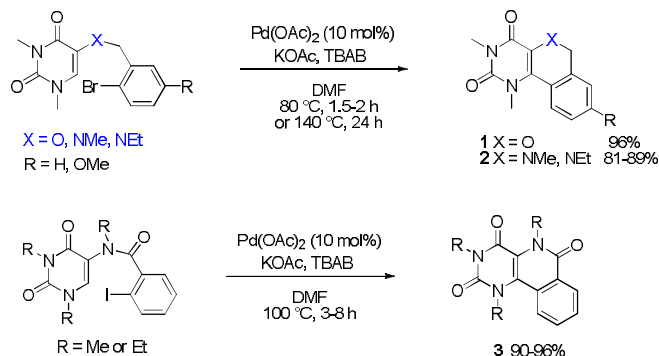
Figure 5

Due to their pharmacology and potential therapeutic applications, the development of straightforward and innovative synthesis and functionalization of pyrimidinones, quinazolinones and fused quinazolinones is still required for organic and medicinal chemists. The direct C-H functionalization of heterocycles has become an increasingly valuable tool in complex molecule synthesis without the need for pre-functionalized synthetic handles.²⁸ In this context, metal-catalyzed C-H activation has emerged as an important strategy for contemporary drug discovery due to the challenges encountered in functionalization of *N*-bearing ubiquitous cyclic framework.²⁹ This late-stage functionalization of drug candidates allow a streamlined route to compounds with increased novelty, essential in drug discovery.³⁰ Methods that enable direct modification of heterocycles core are among the most efficient to synthetic chemists. This paper presents a review of recent metal-catalyzed C-H functionalization of pyrimidinones, quinazolinones and fused quinazolinones highlighting these catalytic methodologies offering numerous synthetic benefits.³¹

2. Metal-catalyzed C-H functionalization of pyrimidinones

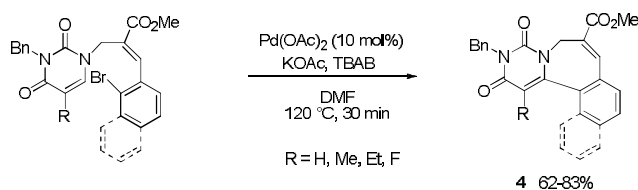
2.1. Intramolecular palladium-catalyzed C-H arylation of protected uracils using aryl halides

Compared with conventional methods, C-H arylation represents a potentially more efficient, atom economic and environmentally friendly method. Over the past decade, the direct arylation of unreactive C-H bonds of pyrimidinones has emerged as an efficient method for the C(sp²)-C(sp²) bond formation. The pioneering example was reported in 2008 by Majumdar³² and described the intramolecular C-H arylation of 1,3-dialkyluracils, discarding the site-selectivity problem to be feared with these compounds (Scheme 1). This palladium-catalyzed intramolecular vinyl C-H arylation strategy gave an easy access to benzopyrano[4,3-*d*]pyrimidine-2,4-diones **1** and benzannulated pyridopyrimidines **2** respectively. The methodology was also applied to the synthesis of pyrimido[5,4-*c*]isoquinolinone-2,4,6-triones **3**.



Scheme 1

The authors proposed a Heck-type carbopalladation process suggesting that the fairly stabilized σ -alkylpalladium intermediate, obtained from the addition of the arylpalladium intermediate to the double bond, gave the expected tricyclic products through a β -hydrogen elimination. Following this pioneering studies, Kim and co-authors³³ reported in 2012 the intramolecular C6-H arylation of *N*-prefunctionalized uracils leading to novel benzo[*c*]pyrimido[1,6-*a*]azepine scaffold synthesis (Scheme 2).



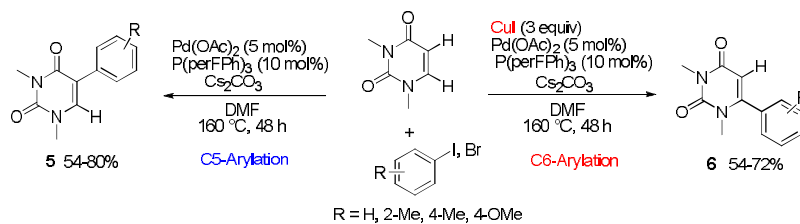
Scheme 2

The authors suggested that a 7-exo-carbopalladation of the arylpalladium intermediate took place before an epimerization at C-5 position, through the corresponding *O*-palladium intermediate, which results in the formation of the cyclized product by a syn β -H elimination process. Further experiments, including a palladium-catalyzed Fujiwara-Moritani reaction (see section 2.4.) were conducted on the obtained C5-H benzo[*c*]pyrimido[1,6-*a*]azepine **4** (R=H) in order to obtain an array of functionalized benzoazepine derivatives.

2.2. Intermolecular metal-catalyzed C-H arylation of protected uracils

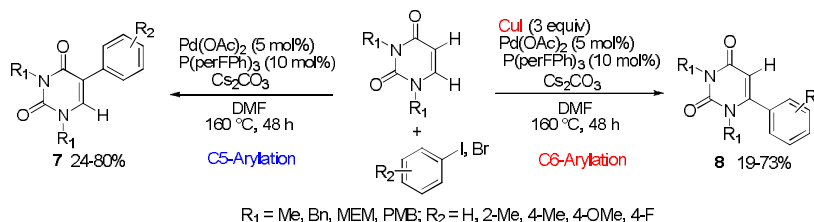
The first challenge to be overcome was a regioselective activation of the C5-H or C6-H bond of the uracil scaffold. Hocek and co-workers have first reported the intermolecular version using

1,3-dimethyluracil as model substrate for the regioselective C-H arylation.³⁴ The authors' attention turned to investigating how they might steer the reaction to produce exclusively one isomer. The C5/C6 regioselectivity was controlled by a judicious choice of the catalyst (Scheme 3).³⁵ Thus, the C5-arylated uracils **5** were mainly obtained using a palladium-catalyzed C-H activation in the presence of Cs₂CO₃ as base in DMF with aryl iodides or bromides (C5:C6 selectivity >5:1) whilst the C6 selectivity was reached when employing CuI as additive.



Scheme 3

The same authors further improved the site-selectivity and the scope of the substrate was extended to diverse *N*-protected uracils.³⁶ Among the tested protective groups, benzyl-type substituents such as Bn and PMB were found to be the most stable protective groups and led to the corresponding arylated compounds in moderate yields whereas the MEM-protected uracil derivatives were obtained in moderate yield. As previously reported, the direct C5-H arylation is selectively reached under Cs₂CO₃-assisted concerted metalation-deprotonation (CMD)-based process whereas the direct arylation occurred selectively at C6-H site under copper-assisted catalysis (Scheme 4). It was noted that the Copper-mediated reactions in the absence of the Pd(II) catalyst gave the expected C6-tolyated uracils in lower yields.



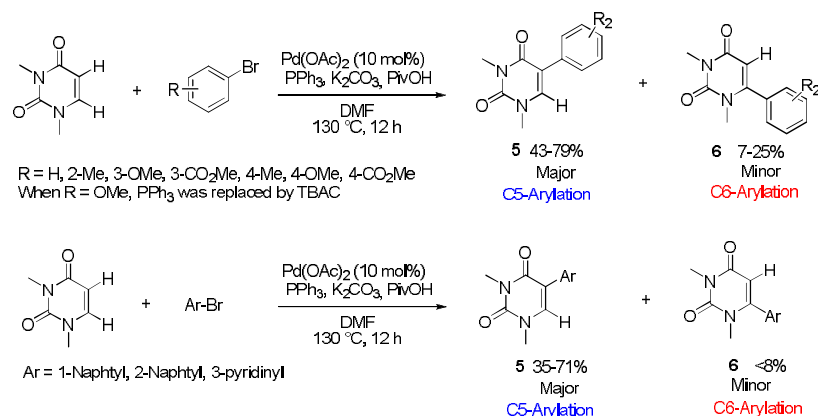
Scheme 4

The palladium-catalyzed favored C5-arylation protocols was improved by Kim and co-workers with aryl bromides allowing facile installation of diversities into 1,3-dimethyluracil.³⁷ This more efficient protocol involved the use of pivalic acid as proton shuttle. 5-Aryluracil derivatives were formed in moderate to good yields most likely via an electrophilic metalation-deprotonation (EMD) process while the 6-aryl isomers via a Heck-type mechanism as minor products (Scheme 5). Aryl bromides bearing electron-withdrawing group and 3-bromopyridine could be introduced but in lower yield than described by Hocek³⁶. A slight modification was done when bromoanisole derivatives were used as coupling partners. In this case, a ligand-less condition was applied in the presence of TBAC in order to make the arylpalladium intermediate more electrophilic.

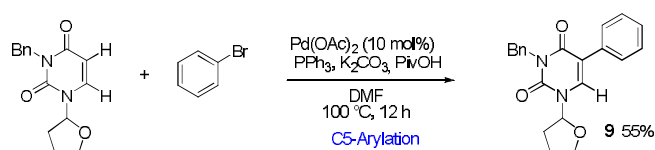
The C-H arylation reaction was applied to the more sensitive substrate 1-(tetrahydrofuran-2-yl)-3-benzyluracil, at 100 °C instead of 130 °C to avoid the degradation of the starting material, and the C5-phenylated product was isolated in 55% yield as the sole compound (Scheme 6).

More recently, Wnuk³⁸ disclosed one example of this strategy under milder conditions reaction. The authors carried out direct C-H arylation of 1-*N*-benzyluracil with aryl halides in the presence of TBAB. Thus, treatment of 1-*N*-benzyluracil with 4-iodoanisole (3 equiv) and TBAB/Pd(OAc)₂/AgCl at lower

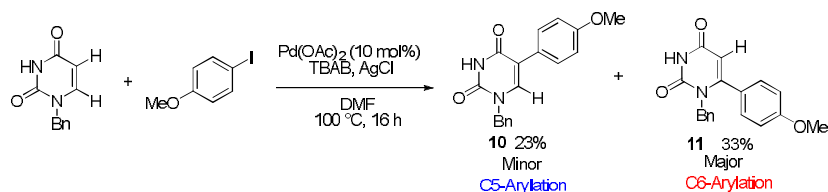
temperature than previously reported by Hocek and Kim gave a mixture of the C5 (23%) and C6-arylated (33%) uracil products with recovered *l*-*N*-benzyluracil (Scheme 7). The moderate overall yield (56%) and the low selectivity must be assigned to the poor electrophilicity of the resulting arylpalladium intermediate, even with the presence of silver salt.



Scheme 5



Scheme 6

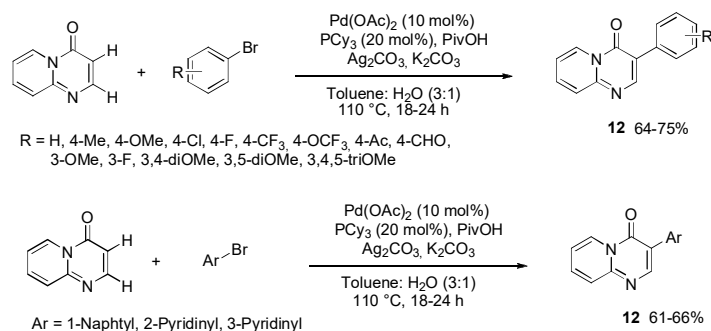


Scheme 7

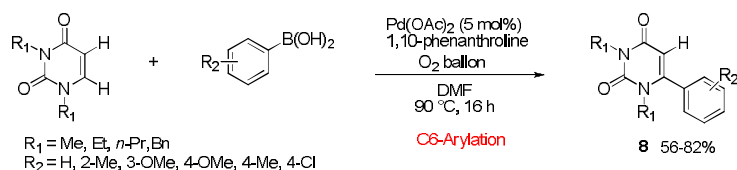
A palladium-catalyzed silver-promoted arylation of fused pyrimidinone under aqueous conditions was also reported by Guchhait.³⁹ Under these step-economic process, 4*H*-pyrido[1,2-*a*]pyrimidin-4-one was C3-arylated using aryl iodides or bromides as coupling partners (Scheme 8) leading to target-based discovery of potent anticancer agents.⁴⁰ Several synthesized arylated compounds were found to exhibit pronounced human topoisomerase II α (hTopoII α) inhibitory activities. As demonstrated by relevant mechanistic studies, the C-3 arylation undergoes via a concerted metalation deprotonation (CMD) pathway triggered by an unusual feature involving the formation of cationic arylpalladium species promoted by halo-sequestering silver salts.

The palladium catalyzed C-H arylation of uracils was also reported by Roy in 2014 using arylboronic acids instead of aryl halides as coupling partners.⁴¹ The authors have developed a regioselective and base-free protocol for the efficient synthesis of C6-arylated *N*-protected uracils via oxidative Heck reaction.⁴²

Various 6-aryluracil derivatives were exclusively obtained in good yields by a combination of Pd(OAc)₂ and 1,10-phenanthroline as the ligand under oxygen atmosphere in DMF (Scheme 9).

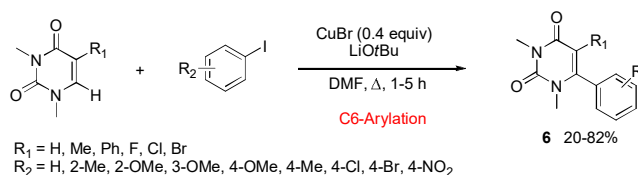


Scheme 8



Scheme 9

The copper-catalyzed C-H arylation was then investigated by Chien and co-authors to design a streamlined and rapid synthetic route to an arylated 1,3-dimethyluracils at C6 position library (Scheme 10).⁴³ The site-selectivity was obtained using the inexpensive CuBr catalyst in the presence of LiOtBu as the base in DMF. These optimized conditions minimized the formation of C5-arylated product as much as the 5,6-diarylated one. Evaluation of both the steric and electronic effects of a substituent at the C5 position revealed a slight decrease in yields for the resulted 5-substituted-6-arylated uracil derivatives.



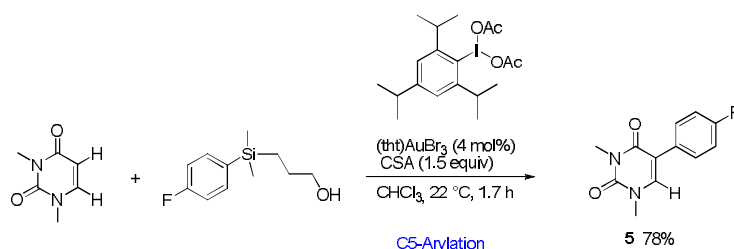
Scheme 10

The sole example of gold-catalyzed C-H arylation of 1,3-dimethyluracil was recently reported by Lloyd-Jones.⁴⁴ The authors have first established a rapid and efficient arylation process for a C-H arylation of indole using arylsilane bearing a hydroxypropyldimethylsilyl (HPDMS) group. The undesired oxidation of the starting materials with the hypervalent iodine(III) compound was avoided by sterically encumbering this oxidant. Applying the optimized conditions to 1,3-dimethyluracil, the C5-arylated compound was exclusively obtained using (tht)AuBr₃ as catalyst in 78% yield after 1.7h at room temperature (Scheme 11).

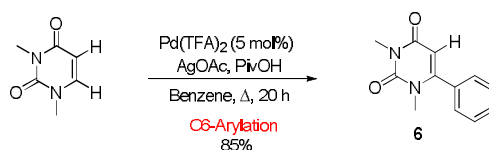
2.3. Metal-catalyzed dehydrogenative cross-coupling of pyrimidinones with (hetero)-arenes

The second approach involves cross-couplings between two inactivated substrates. The earliest report containing an example of a modest yielding intermolecular arylation of pyrimidinone appeared in 1989.⁴⁵ Since then, this cross-dehydrogenative coupling (CDC) reaction⁴⁶ has been recently developed and new

types of direct intra- and intermolecular C-H activation leading to (hetero)-arylation and vinylation have been studied. An example of palladium-catalyzed cross-dehydrogenative coupling (CDC) reactions was first reported by Kim and co-authors in 2011. In this study, 1,3-dimethyl-6-phenyluracil was exclusively obtained in high yield by oxidative phenylation via a CMD mechanism in the presence of AgOAc (3 equiv) and pivalic acid (6 equiv) at reflux in benzene (Scheme 12).³⁶ This C6-phenylation proceeded through a regioselective palladation, most likely via a CMD process involving the deprotonation of the more acidic hydrogen atom, followed by an arylation of the uracil palladium intermediate with benzene and the reductive elimination of Pd(0).

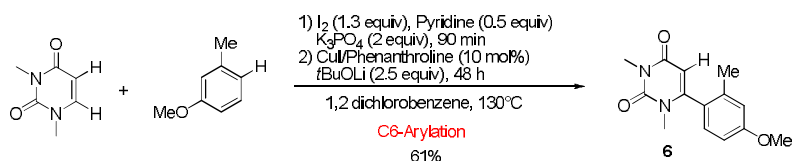


Scheme 11



Scheme 12

The C6-arylated compound was also obtained using copper-catalyzed C-H bond activation.⁴⁷ CuI/phenanthroline-catalyzed cross-dehydrogenative coupling of *N,N*-dimethyluracil with 3-methylanisole led selectively to C6-arylated uracil in 61% yield using iodine as a terminal oxidant (Scheme 13). The process was supposed to proceed by *in situ* iodination of one of the coupling partners followed by Cu-catalyzed arylation at the most acidic bond (C6-H).



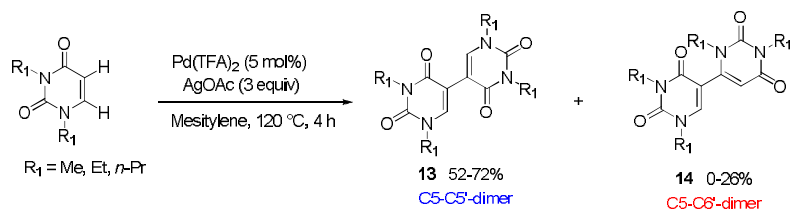
Scheme 13

A palladium-catalyzed oxidative homo-coupling of 1,3-dimethyluracil derivatives was reported by Kim in 2012.⁴⁸ A solvent screening was done in order to favor the formation of a dimer, needing the competitive aforementioned cross-dehydrogenative coupling³⁶ (CDC) reaction discarded. In almost cases, a C5-C5' dimer was mainly obtained along with a small amount of C5-C6' dimer (Scheme 14).

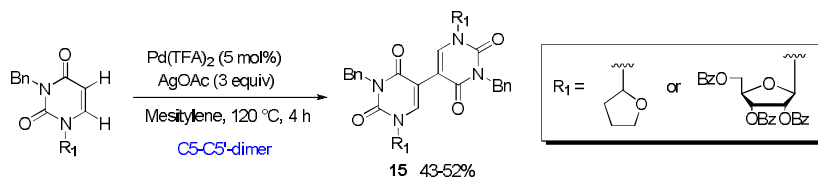
The scope of the oxidative CH/CH homo-coupling was extended to *N*³-benzyl *N*⁷-tetrahydrofuranyl derivative and *N*⁷-2',3',5'-tri-*O*-benzoyluridine (Scheme 15) to afford exclusively the C5-C5' isomer in moderate yield.

A palladium-catalyzed regioselective dehydrogenative cross-coupling of *N*-protected uracils and heteroarenes was further reported by Kianmehr. An efficient process for coupling pyridine-*N*-oxide and uracils using Pd(OAc)₂ as catalyst in the presence of Ag₂CO₃ as oxidant was developed (Scheme 16).⁴⁹ The

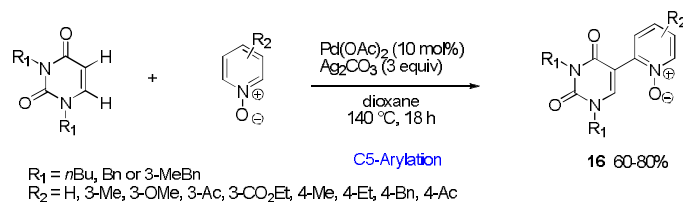
reaction took place exclusively at the C-5 position of the uracil and gave access to high valuable heteroarylated derivatives. In addition, 3-substitued pyridine-*N*-oxides are readily introduced with a complete selectivity at the C6 position that is the less bulky site in yield ranging from 60% to 85%.



Scheme 14

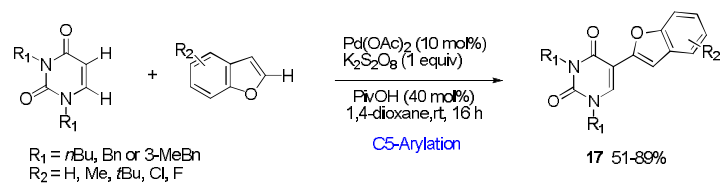


Scheme 15



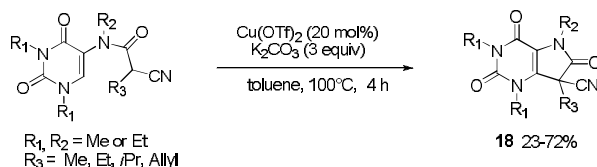
Scheme 16

On the basis of the high regioselectivity and in the presence of silver salt, the authors suggested a Pd(0)/Pd(II) mechanism for this cross-coupling reaction. Uracil undergoes also a palladium-catalyzed direct hetero-arylation with a range of benzofuran derivatives in the presence of $\text{K}_2\text{S}_2\text{O}_8$ as the oxidant in 1,4-dioxane at room temperature to give the corresponding 5-arylated uracil analogues (Scheme 17).⁵⁰ Nevertheless, the reaction was limited to benzofuran derivatives as coupling partners. In addition, it could be noted that the reactions depicted in both schemes 15 and 16 failed with unprotected uracil.



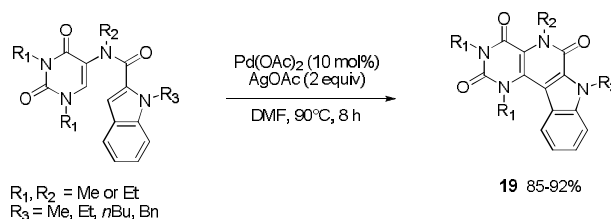
Scheme 17

Two examples of intramolecular metal-catalyzed dehydrogenative coupling were described by Roy and co-authors. The first one is dealing with a copper-catalyzed dehydrogenative C-H activation/cyclization sequence of the 5-amidouracils via the selective activation of uracil C6-H bond under atmospheric oxygen and led to various potentially bioactive pyrrolo[3,2-*d*]pyrimidines (Scheme 18).⁵¹



Scheme 18

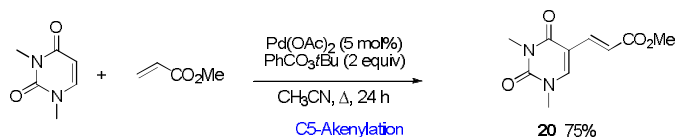
In the presence of silver acetate as oxidant, a palladium-catalyzed cross-dehydrogenative coupling reaction allowed the straightforward synthesis of uracil-annulated β -carbolinones (Scheme 19).⁵² Unprotected indole precursor led to no reaction. A classical electrophilic palladation at the C3 position of the indole was envisioned by the authors following by a σ -bond methathesis reaction to produce a palladacycle intermediate which affords the expected tetracyclic compound after reductive elimination.



Scheme 19

2.4. Palladium-catalyzed dehydrogenative alkenylation of uracils

One of the earliest examples highlighting the potential of C-H bond activation by the alkenylation of uracil derivatives in an intermolecular fashion with isomerisable alkenes, under palladium-catalysed conditions, was reported thirty years ago by Hirota.⁵³ Treatment of *N,N*-dimethyluracil with methyl acrylate and a catalytic amount of palladium acetate using *tert*-butyl perbenzoate as the reoxidant afforded the corresponding 5-alkenyluracil in 75% yield (Scheme 20). This coupling reaction proceeded stereoselectively to give exclusively the *trans* isomer product.



Scheme 20

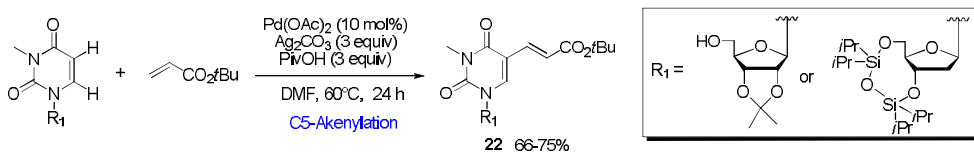
The second example of dehydrogenative alkenylation of *N*-protected uracils was reported more recently by Georg.⁵⁴ The authors developed an efficient regioselective palladium-catalyzed cross-dehydrogenative coupling between uracils and a wide range of alkenes (Scheme 21).



Scheme 21

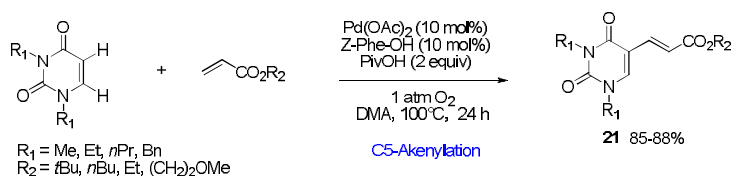
The expected 5-alkenyluracils were obtained with absolute stereoselectivity (*E*-isomers) and various functional groups were tolerated. These described protocols provide a synthetically useful route for alkenylation of this valuable scaffold, required in drug discovery.

The reaction was successfully extended to uracil-based nucleosides leading to alkenylated uridine and 2'-deoxyuridine derivatives in 66% and 75% yields respectively (Scheme 22).



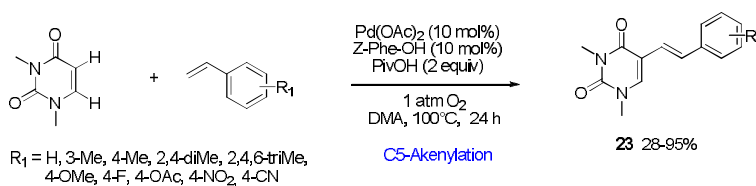
Scheme 22

Huang and co-workers recently developed a modified eco-friendly process by using the atmospheric molecular oxygen as an ecological oxidant instead of an excess of metal oxidant such as silver carbonate (Schemes 23 and 24).⁵⁵



Scheme 23

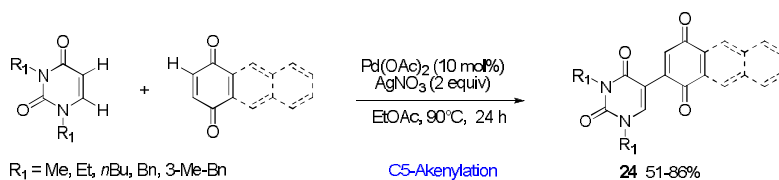
To further examine the versatility of this methodology, the alkenylation was applied to a large number of styrene derivatives as coupling partners (Scheme 24). The expected compounds were isolated in yield ranging from 28 to 95%. In this case, steric hindrance and electronic effects strongly affected the course of the dehydrogenative cross-coupling. According to the aforementioned reported C-H olefination, the free NH-uracil was also found to be inefficient for the reaction.



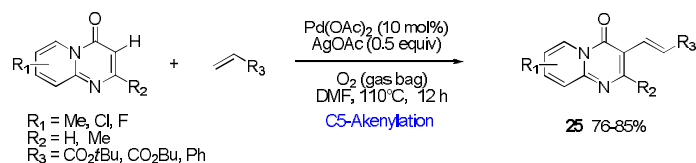
Scheme 24

The scope of the coupling partners for the alkenylation was extended to 1,4-quinone by Kianmehr (Scheme 25).⁵⁶ AgNO_3 was found to be the most efficient oxidant in this reaction. *N,N'*-dialkyl and *N,N'*-dibenzyluracils were successfully functionalized with benzoquinone, naphthoquinone and anthraquinone whereas *N,N'*-dibenzoyluracil failed to produce the corresponding alkenylated product.

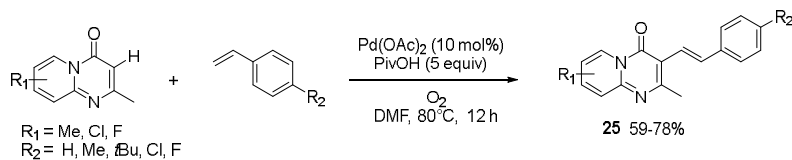
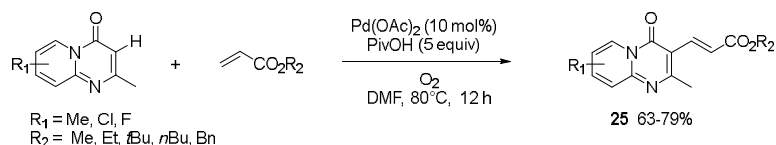
The first direct alkenylation of fused pyrimidinone at the C3 position was reported in 2014 by Wang and Cao (Scheme 26).⁵⁷ This strategy involved a synergistic effect of pure oxygen with silver acetate as co-oxidant and proceeds with high region- and stereoselectivity. In 2015 a slight modification of the protocol described by Liang⁵⁸ using oxygen as sole oxidant resulted in lower yields (Scheme 27). These strategies provide an efficient access to functionalized new 2-methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one derivatives.



Scheme 25

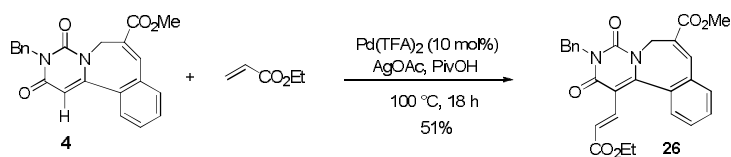


Scheme 26



Scheme 27

A palladium-catalyzed Fujiwara-Moritani reaction was also reported on the C5-H benzo[*c*]pyrimido[1,6-*a*]azepine **4** (depicted in Scheme 2) derivatives with a large excess of ethyl acrylate (30 equiv) in the presence of AgOAc and pivalic acid (Scheme 28).³³

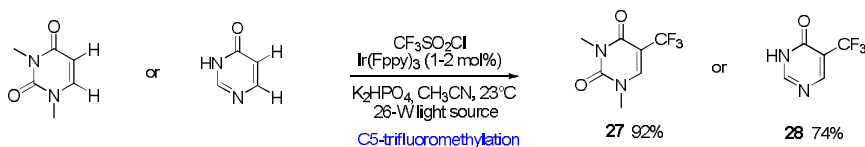


Scheme 28

2.5. Miscellaneous functionalization of uracils and pyrimidinone

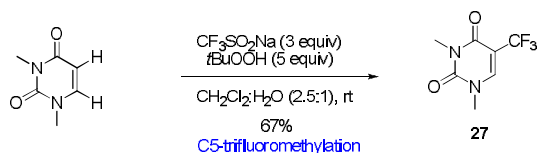
The recent developments in regioselective catalyzed direct C-H functionalization reactions have further enabled streamlined incorporation of a wide range of chemical functionalities that previously were difficult to accomplish. For example, the selective catalytic trifluoromethylation of uracil was reported in 2008 by Yamakawa and co-workers for large scale production.⁵⁹ 5-Trifluoromethyluracils, important intermediates in the field of medicinal chemistry, were obtained using FeSO_4 , H_2O_2 and H_2SO_4 as catalytic system and CF_3I as source of trifluoromethyl radical in DMSO. The incorporation of a trifluoromethyl group on heteroarenes such as pyrimidin-4-one and *N,N*-dimethyluracil was described by MacMillan in 2011 through a radical-mediated mechanism using commercial photocatalyst and a household light bulb (Scheme

29).⁶⁰ The photoredox protocol led to selective trifluoromethylation at the C5 position using $\text{CF}_3\text{SO}_2\text{Cl}$ as a cheap and easy to handle CF_3 radical source.



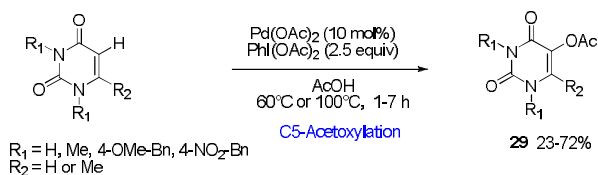
Scheme 29

The reaction of *N,N*-dimethyluracil with Langlois reagent ($\text{CF}_3\text{SO}_2\text{Na}$) under radical conditions in the presence of *t*BuOOH at room temperature was also reported by Hocek and led selectively to 5-trifluoromethylated uracil **27** in a lower yield (67%) (Scheme 30).⁶¹



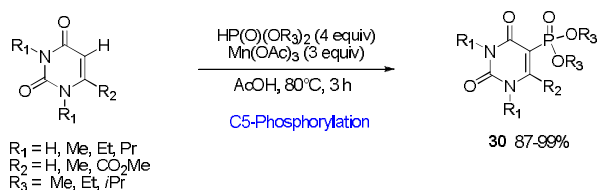
Scheme 30

Among the trifluoromethylation, a palladium-catalyzed oxidative functionalization such as acetoxylation⁶² and phosphorylation⁶³ were described by Kim and co-workers (Scheme 31 and 32). Owing to the nucleophilic nature of the carbon atom at the C5 position, 5-acetoxy and 5-phosphorylated uracil derivatives are selectively synthesized. It could be noted that both reactions are successfully applied to unprotected uracils. The acetoxylation reaction was performed on various uracil derivatives using $\text{Pd}(\text{OAc})_2$ as catalyst and an excess of iodobenzene diacetate as oxidant in acetic acid (Scheme 31). In the case of *N*-benzyl uracil derivatives, the expected 5-acetoxy products were isolated in moderate yields along with triacetoxy compounds.



Scheme 31

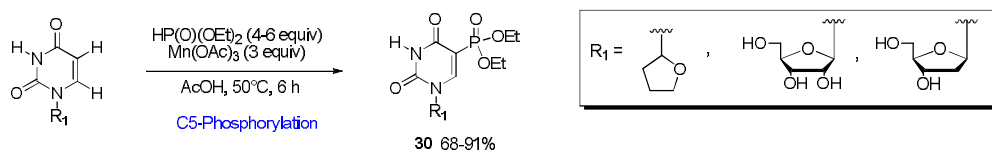
The oxidative cross-coupling between uracil and dialkyl phosphites proceeds in the presence of $\text{Mn}(\text{OAc})_3$ as oxidant in acetic acid at room temperature (Scheme 32).



Scheme 32

The plausible mechanism involved the formation of an electrophilic dialkyl phosphonyl radical generated by an oxidation of the dialkyl phosphite which reacted with uracil.

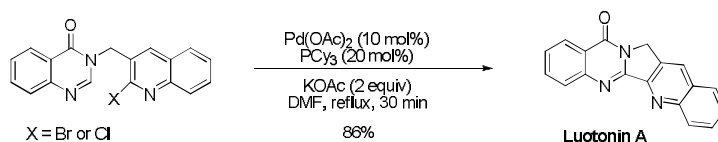
The versatility of this methodology was proved by successfully extending the reaction to 2'-deoxyuridine and uridine derivatives (Scheme 33).



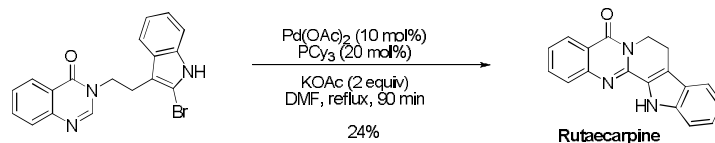
Scheme 33

3. Metal-catalyzed C-H functionalization of quinazolinones

Beside pyrimidinone such as uracil, the direct functionalization of quinazolinone scaffold through a C-H bond activation was recently developed. The widespread methodologies used in the synthesis of functionalized quinazolinones rely mainly upon condensation pathways from anthranilic acid derivatives. Indeed, C2-arylquinazolin-4(3*H*)-ones are highly valuable compounds that are widely found in bioactive molecules, pharmaceuticals and natural products. Reflecting this, their syntheses have attracted much attention. A literature survey revealed that examples of C-H arylation on quinazolinone scaffold are really sparse. However, this methodology is now recognized as an appealing alternative to traditional cross-coupling reactions regarding the generation of heteroaryl-metals intermediates, often instable and air moisture sensitive. The first examples of palladium-catalyzed C-H arylation of quinazolinone were reported as an intramolecular version.⁶⁴ This reaction was applied to a convenient synthesis of naturally occurring alkaloid Luotonins A (Scheme 34) and rutaecarpine (Scheme 35). The palladium-catalyzed intramolecular coupling reaction of 3-[2-(2-bromoindol-3-yl)ethyl]-4(3*H*)-quinazolinone using potassium acetate as base in DMF under reflux gave a direct access to rutaecarpine in modest yield.



Scheme 34



Scheme 35

More recently, Kaliappan described a new route to *N*-arylbenzimidazoquinazolinones using copper-catalyzed cascade amination (Scheme 36).⁶⁵ This strategy involves a multi-fold C-N bond formation between *N*-anilinoquinazolinones and aryl/heteroaryl halides followed by acetate ligand-assisted intramolecular C-H amination.

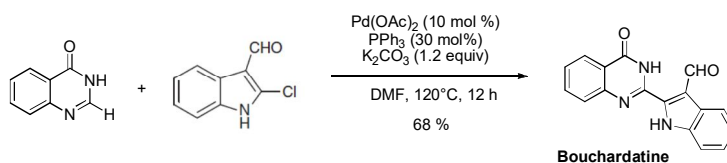
The first example of intermolecular palladium-catalyzed C-H arylation of NH-quinazolin-4(3*H*)-ones with aryl chlorides was reported by Kusurkar, in 2013 for the synthesis of Bouchardatine, a cytotoxic alkaloid (Scheme 37).⁶⁶

The palladium-catalyzed and copper-assisted arylation of C-H bond of quinazolinone derivatives on their reaction with various aryl iodides was reported under microwave irradiation⁶⁷ by Fruit and Besson in

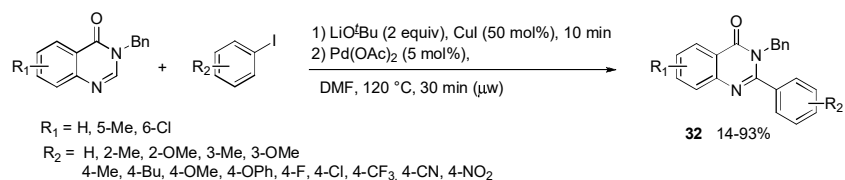
2015 (Scheme 38).⁶⁸ The screened conditions revealed that the choice of the solvent drastically affected the yields of desired product. Moderate to good conversions were only observed with DMA and DMF as solvent. In addition, the reaction was effective only in the presence of both metal. This ligandless protocol was also easily scaled up without a decrease in yield.



Scheme 36

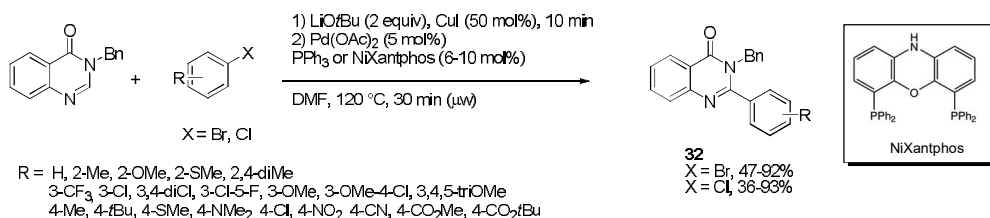


Scheme 37



Scheme 38

The scope of the C2-H arylation was examined with sterically hindered, electron-rich and electron-poor aryl iodides. The present strategy was tolerant to various functional groups. The procedure was enhanced by extending the coupling partners to bromo and chloro derivatives with adapted phosphine ligands (Scheme 39).⁶⁹

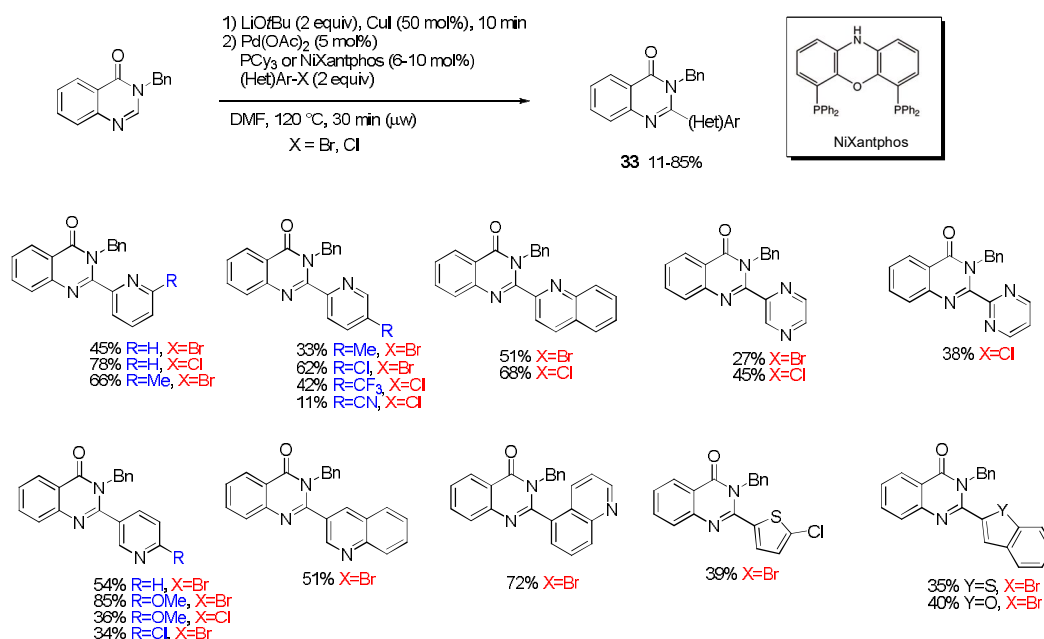


Scheme 39

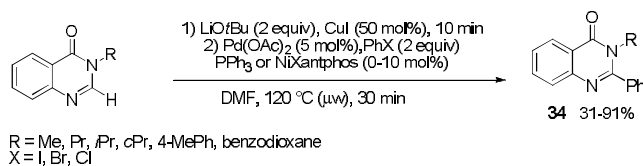
Heteroarenes are also readily introduced under optimized conditions (Scheme 40). Notably, 2-bromo- and 2-chloropyridine derivatives were efficient coupling partners, whereas 2-iodopyridine failed to produce the corresponding arylated compound.

To prove the versatility of this methodology, the scope of the model substrate was studied with various *N*-protected quinazolin-4-ones (Scheme 41) and the phenylation was also extended to pyridopyrimidinones

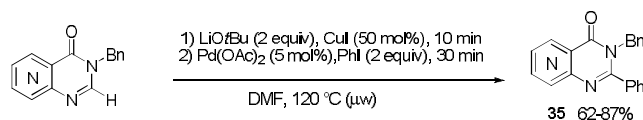
(Scheme 42). *N*-alkyl and *N*-aryl quinazolin-4-ones were found to be suitable substrate for the phenylation reaction. Nevertheless, one equivalent of CuI was required for a complete conversion in the case of *N*-alkyl derivatives. The reaction could be applied to the four isomers of pyrido-pyrimidinones, affording the expected compounds in good yields ranging from 62 to 87%.



Scheme 40



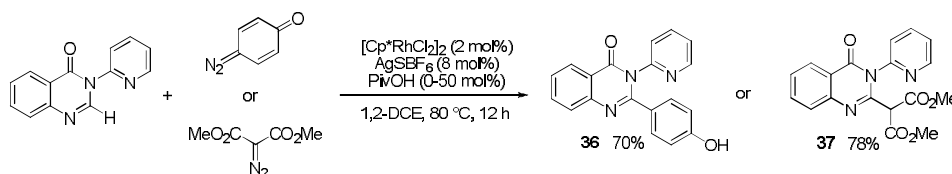
Scheme 41



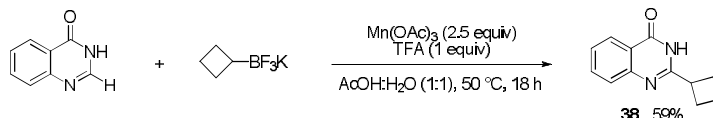
Scheme 42

Rhodium(III)-catalyzed selective alkylation and arylation (Scheme 43) of *N*-pyridinyl-quinazolin-4-one was recently reported by Samanta, using diazocompounds as coupling partners.⁷⁰ The author described one example of each reaction using the diazomalonate and quinone diazide respectively under Rh(III)-catalyzed redox-neutral conditions. The regioselectivity was achieved thanks to the pyridine directing group. This process represents an attractive strategy for late-stage functionalization of quinazolin-4-one scaffold.

One example of direct C-H alkylation of quinazolinones using manganese acetate and potassium cyclobutyltrifluoroborate as a radical precursor was previously reported by Molander in the presence of trifluoroacetic acid in a 1:1 mixture of acetic acid/water (Scheme 44).⁷¹ The alkylated compound was isolated in 59% yield.



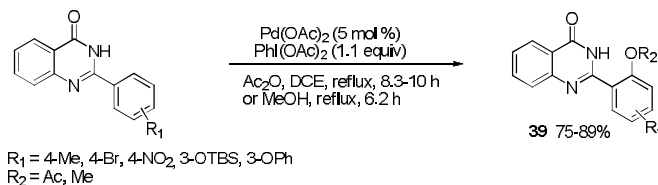
Scheme 43



Scheme 44

4. Metal-catalyzed C-H functionalization of 2-arylquinazolinones

The first example of oxidative functionalization of 2-aryl-4(3*H*)-quinazolinones through a C-H activation was reported by Yadav in 2012.⁷² Using the quinazolinone part as a directed group, both electron-rich and electron-deficient 2-aryl-4-quinazolinones undergo acetoxylation and methoxylation in the presence of Pd(OAc)₂ and a stoichiometric amount of PhI(OAc)₂ as oxidant (Scheme 45).

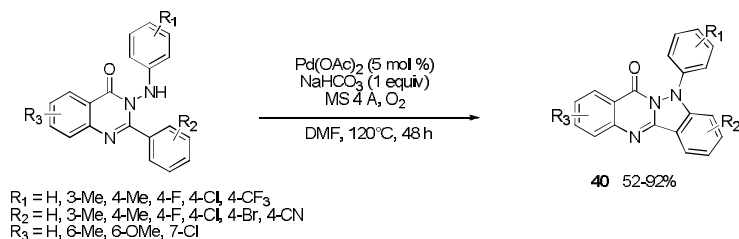


Scheme 45

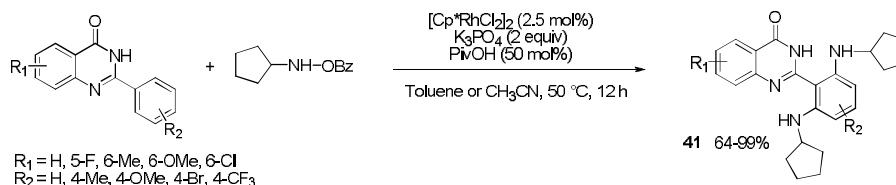
Over the last five years, the transition metal-catalyzed direct C-H bond activation of 2-arylquinazolinones has extended the frontiers in the functionalization of this heterocycle and notably in the building of fused systems. Wu and Chen have developed an alternative synthetic pathway to access indazolo[3,2-*b*]quinazolinones by a palladium-catalyzed C-H bond cleavage and C-N bond formation reaction of 2-aryl-3-(aryl-amino)quinazolinones (Scheme 46).⁷³ This strategy gave a streamlined approach for the synthesis of a new class of small-molecule fluorophores by intramolecular oxidative C-H amination.

Rhodium(III)-catalyzed intermolecular C-H amination of 2-arylquinazolin-4(3*H*)-ones derivatives using *N*-alkyl-hydroxylamine derivatives was recently described by Peng (Scheme 47).⁷⁴ K₃PO₄ as base in toluene or acetonitrile was found to give the best conversion. The scope of the amination shown that the reaction is tolerant to electron-donating and electron-withdrawing substituents leading to exclusively the 2,6-diaminated products.

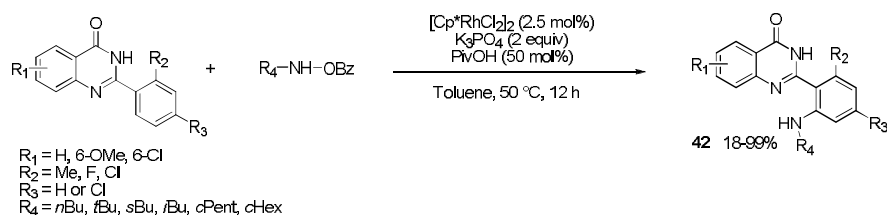
The reaction was extended to *ortho*-substituted 2-arylquinazolinones in order to achieve monoamidation products (Scheme 48). When the *ortho* position is blocked with a methyl group or halogen atom, the desired products are obtained in good yield whereas the reaction with a methoxy group completely failed to produce the mono-amidated compound. Various *N*-alkyl-hydroxylamine derivatives reacted smoothly to give the corresponding products in yields ranging from 18 to 99%.



Scheme 46

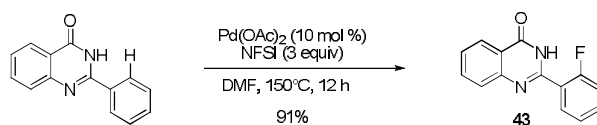


Scheme 47



Scheme 48

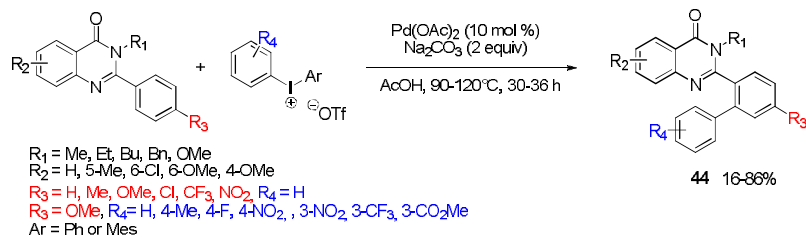
One example of palladium-catalyzed C-H fluorination of 2-phenylquinazolinone was reported by Park and Hong using NFSI as mild electrophilic fluorinating reagent under aerobic conditions (Scheme 49).⁷⁵ Using the quinazolinone part as inherent directing group, this optimal condition led to the 2-fluorinated compound in 91% yield.



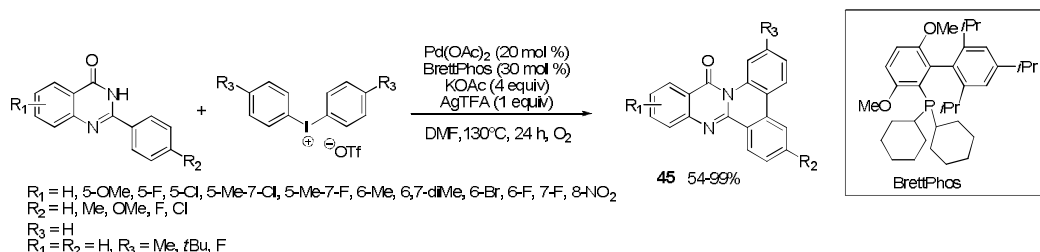
Scheme 49

Using the quinazolinone core as directing group for the palladium-catalyzed regioselective monoarylation, novel quinazolinones, useful for further structure-activity relationship (SAR) studies, were synthesized by Mhaske and co-workers (Scheme 50).⁷⁶ Diaryliodoniums have been used as coupling partners to provide a wide range of potential bioactive compounds.

Hong and Park⁷⁵ reported the reaction of diaryliodonium salts as arylating reagent with free NH-(2-aryl)-quinazolin-4(3*H*)-ones for the efficient tandem synthesis of quinazolinone-fused phenanthridinones. Based on the regioselectivity observed, the palladium-catalyzed protocol comprises a sequential combination of intermolecular C-H arylation and intramolecular C-H amidation, discarding competitive *ortho* di-arylation of the 2-aryl-quinazolin-4(3*H*)-one scaffold. The quinazolinone-fused phenanthridinone derivatives were obtained in excellent yields (Scheme 51).

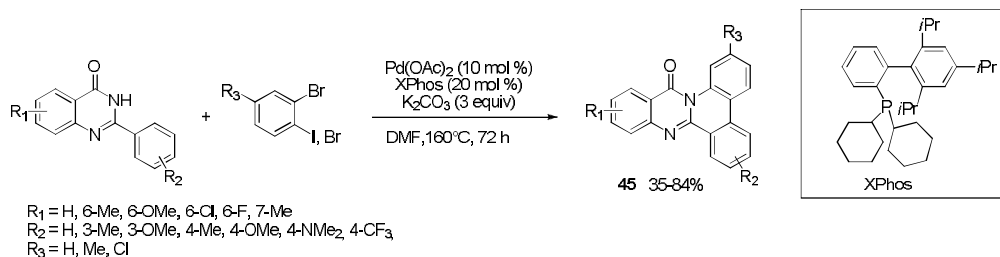


Scheme 50



Scheme 51

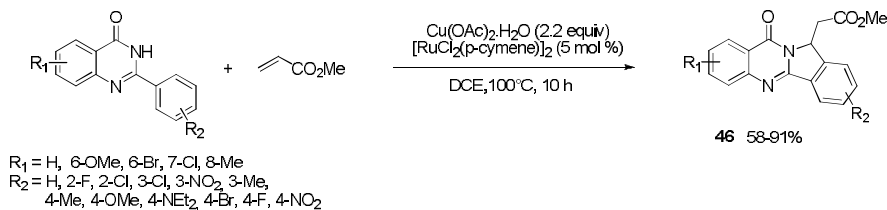
Hajela⁷⁷ and Peng⁷⁸ have also independently reported methods for the preparation of phenanthridine-fused quinazolinone derivatives by palladium-catalyzed CH and/or N-H bond activation. Whereas the first study described an intramolecular bi-aryl coupling reaction starting from 2,3-diaryl-2,3-dihydroquinazolin-4(1*H*)-one derivatives, the last one involved a tandem C-H/N-H arylation using 1,2-dihalogenobenzene as coupling partner with free NH-(2-aryl)-quinazolin-4(3*H*)-ones (Scheme 52).



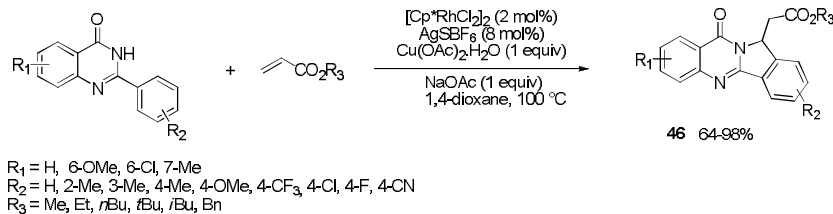
Scheme 52

Ruthenium and Rhodium-catalyzed tandem oxidative coupling and intramolecular aza-Michael addition of 2-phenylquinazolin-4-ones were respectively developed by Xuan⁷⁹ (Scheme 53) and Peng⁸⁰ (Scheme 54). These strategies allow an efficient route for the synthesis of highly valuable pyrrolo[2,1-*b*]quinazolin-9(1*H*)-one motifs, that are widely found in bioactive molecules, pharmaceuticals and natural products such as Luotonin. Reflecting this, their syntheses have attracted much attention.

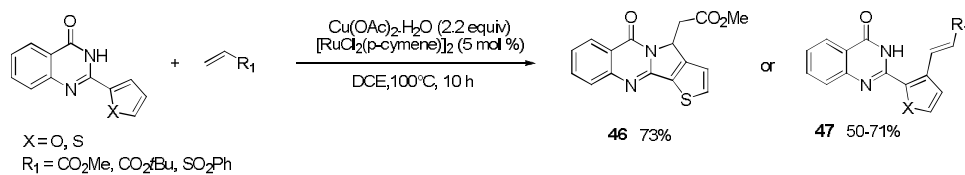
The ruthenium-catalyzed C-H functionalization was extended to 2-heteroarylquinazolin-4-ones as suitable substrates. The reaction of 2-thienyl or 2-furylquinazolin-4-ones with acrylate derivatives and vinyl sulfone gave access to the corresponding vinylation products (Scheme 55). Only 2-thienylquinazolinone led to the pyrrolo[2,1-*b*]quinazolin-9(1*H*)-one scaffold with methyl acrylate as coupling partner.



Scheme 53

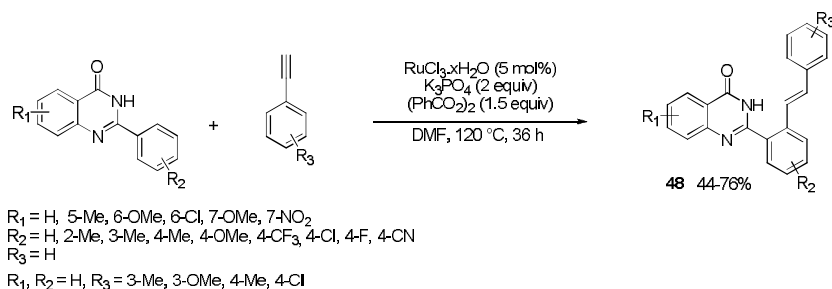


Scheme 54



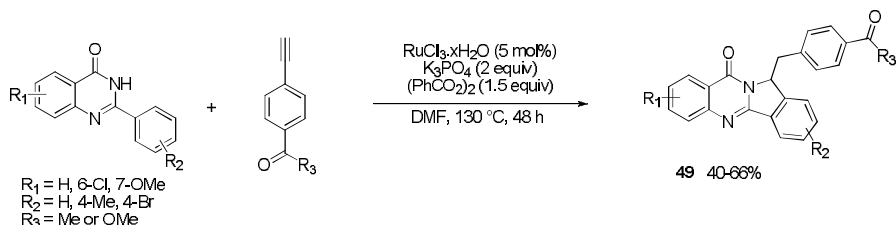
Scheme 55

More recently, Mhaske described a ruthenium-catalyzed alkenylation using quinazolinone moiety as directing group and alkynes as coupling partners. The scope of the mono C-H alkenylation was examined with various terminal alkynes using dibenzoyl peroxide as oxidant (Scheme 56).⁸¹



Scheme 56

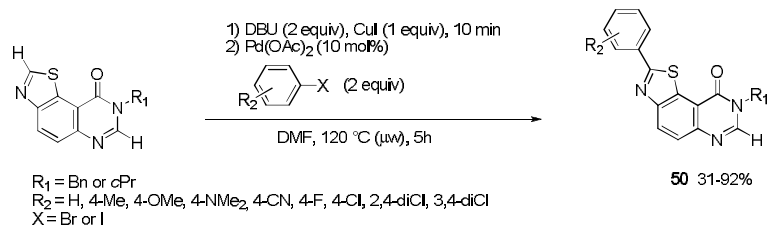
To further examine the versatility of this methodology, the reaction was attempted with alkynes bearing withdrawing groups and substituted quinazolin-4-ones. When the reaction temperature and time were increased, pyrrolo[2,1-*b*]quinazolin-9(1*H*)-one derivatives were obtained in up to 66% yield (Scheme 57).



Scheme 57

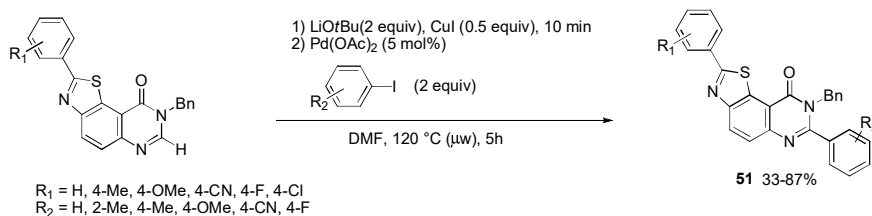
5. Metal-catalyzed C-H functionalization of fused quinazolines

Despite the recent advances that have been made in functionalization of ubiquitous pyrimidinone scaffold, the development of an attractive challenging orthogonal direct C-H arylation of fused quinazolines remained sparse. Recently, our group reported a palladium-catalyzed and copper assisted regioselective C-H arylation and alkenylation of *N*⁸-benzyl- and *N*⁸-cyclopropyl-thiazolo[5,4-*f*]quinazolin-9(8*H*)-ones (Scheme 58).⁸² Using DBU as base in DMF, the selective arylation took place exclusively at the most acidic C-H site. Under these conditions, both phenyl iodides and bromides are effective as coupling partners. π -deficient heteroarenes are also readily introduced, a notable feature with respect to medicinal agent synthesis.



Scheme 58

The C2-arylated *N*⁸-benzylthiazolo[5,4-*f*]quinazolin-9(8*H*)-ones were further successfully arylated at the C7 position to afford the corresponding di-arylated products in moderate to good yields after 5 h at 120 °C under microwave irradiation (Scheme 59). This rewarding stepwise C-H arylation of thiazoloquinazolinone gave access to valuable compounds with broad tolerance to substituents on the coupling partners. The methodology was enhanced by the development of the challenging one-pot reaction, allowing the chromatographic purification step to be discarded.



Scheme 59

6. Conclusion

Within the impressive developments that have been made in metal-catalyzed direct C-H arylation of nitrogen containing heterocycles, the development of selective challenging direct C-H functionalization methodologies of pyrimidinones and fused pyrimidinones remained still of interest. These reported strategies

provide a synthetically useful route for late-stage structural diversification of various high valuable scaffold, required in drug discovery. Even if palladium-catalyzed arylation with aryl halides is an overwhelming type of C-H functionalization of these heteroarenes, this review highlighted the versatility of the metal-catalyzed C-H activation and its appealing application in the streamlined synthesis of array of potential bioactive compounds.

Acknowledgements

This research was supported by the Normandie Universtiy and Institut Carnot I2C. The authors are gratefully acknowledged the MESR (Ministère de l'Enseignement Supérieur et de la Recherche) and the LABEX SynOrg (ANR-11-LABX-0029) for financial support. We also acknowledge Antan Paar France SAS for providing the mono-mode and multi-mode microwave reactors (Monowave 300 and Masterwave BTR) and for technical support.

Abbreviations

Bn	Benzyl
Bz	Benzoyl
CDC	Cross-dehydrogenative coupling
CMD	Concerted metalation-deprotonation
CSA	Camphorsulfonic acid
DCE	1,2-dichloroethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EMD	Electrophilic metalation–deprotonation
Fppy	2-(2,4-difluorophenyl)pyridine
MEM	Methoxyethoxymethyl
NFSI	<i>N</i> -Fluorobenzenesulfonimide
PMB	<i>p</i> -methoxybenzyl
TBAB	Tetrabutylammonium bromide
TBAC	Tetrabutylammonium chloride

References

- Li, Y.; Sun, L.; Yang, T.; Jiao, W.; Tang, J.; Huang, X.; Huang, Z.; Meng, Y.; Luo, L.; Wang, X.; Bian, X.; Zhang, F.; Wang, K. W.; Sun, Q. *J. Med. Chem.* **2018**, ASAP. DOI: 10.1021/acs.jmedchem.7b01492.
 - Gavory, G.; O'Dowd, C. R.; Helm, M. D.; Flasz, J.; Arkoudis, E.; Dossang, A.; Hughes, C.; Cassidy, E.; McClelland, K.; Odrzywol, E.; Page, N.; Barker, O.; Miel, H.; Harrison, T. *Nat. Chem. Biol.* **2018**, *14*, 118.
 - O'Dowd, C. R.; Helm, M. D.; Rountree, J. S. S.; Flasz, J. T.; Arkoudis, E.; Miel, H.; Hewitt, P. R.; Jordan, L.; Barker, O.; Hughes, C.; Rozycka, E.; Cassidy, E.; McClelland, K.; Odrzywol, E.; Page, N.; Feutren-Burton, S.; Dvorkin, S.; Gavory, G.; Harrison, T. *ACS Med. Chem. Lett.* **2018**, *9*, 238.
 - Gómez-SanJuan, A.; Gamo, A.-M.; Delang, L.; Pérez-Sánchez, A.; Amrun, S. N.; Abdelnabi, R.; Jacobs, S.; Priego, E.-M.; Camarasa, M. J.; Jochmans, D.; Leyssen, P.; Ng, L. F. P.; Querat, G.; Neyts, J.; Pérez-Pérez, M.-J. *ACS Infect. Dis.* **2018**, *4*, 605.
 - El-Nassan, H. B.; Naguib, B. H.; Beshay, E. A. *J. Enzym. Inhib. Med. Chem.* **2018**, *33*, 58.
 - Zhang, W. *Acc. Chem. Res.* **2017**, *50*, 2381.
 - Turco, S. D.; Sartini, S.; Sentieri, C.; Saponaro, C.; Navarra, T.; Dario, B.; Settimo, F. D.; Motta, C. L.; Basta, G. *Eur. J. Med. Chem.* **2014**, *72*, 102.
 - Wu, Y.-J. *Prog. Heterocycl. Chem.* **2012**, *24*, 1. Gordon W. Gribble and John A. Joule (Eds.)
 - Jain, K. S.; Chitre, T. S.; Miniyar, P. B.; Kathiravan, M. K.; Bendre, V. S.; Veer, V. S.; Shahane, S. R.; Shishoo, C. J. *Curr. Sci.* **2006**, *90*, 793.
- Kasralikar, H. M.; Jadhavar, S. C.; Bhansali, S. G.; Patwari, S. B.; Bhusare, S. R. *J. Heterocyclic Chem.* **2018**, *55*, 821.
 - Du, X.-X.; Huang, R.; Yang, C.-L.; Lin, J.; Yan, S.-J. *RSC Adv.* **2017**, *7*, 40067.
 - Oganesyan, É. T.; Kodonidi, I. P.; Bandura, A. F.; Sochnev, V. S.; Manvelyan, É. A.; Yu. Syra, V. *Pharm. Chem. J.* **2017**, *51*, 361.
 - Ali, F.; Khan, K. M.; Salar, U.; Iqbal, S.; Taha, M.; Ismail, N. H.; Perveen, S.; Wadood, A.; Ghufuran, M.; Ali, B. *Bioorg. Med. Chem.* **2016**, *24*, 3624.
 -

- Schenkel, L. B.; Olivieri, P. R.; Boezio, A. A.; Deak, H. L.; Emkey, R.; Graceffa, R. F.; Gunaydin, H.; Guzman-Perez, A.; Lee, J. H.; Teffera, Y.; Wang, W.; Youngblood, B. D.; Yu, V. L.; Zhang, M.; Gavva, N. R.; Lehto, S. G.; Geuns-Meyer, S. *J. Med. Chem.* **2016**, *59*, 2794.
3. (a) Zasada, A.; Mironiuk-Puchalska, E.; Koszytkowska-Stawinska, M. *Org. Process Res. Dev.* **2017**, *21*, 85. (b) Papanastasopoulos, P.; Stebbing, J. *Anticancer Res.* **2014**, *34*, 1531.
 4. Younkin, J.; Gaitonde, S. A.; Ellaithy, A.; Vekariya, R.; Baki, L.; Moreno, J. L.; Shah, S.; Drossopoulos, P.; Hideshima, K. S.; Eltit, J. M.; González-Maeso, J.; Logothetis, D. E.; Dukat, M.; Glennon, R. *ACS Chem. Neurosci.* **2016**, *7*, 1292.
 5. Marinello, J.; Marchand, C.; Mott, B. T.; Bain, A.; Thomas, C. J.; Pommier, Y. *Biochemistry* **2008**, *47*, 9345.
 6. (a) Tintori, C.; Brai, A.; Lang, D. M. C.; Deodato, D.; Greco, A. M.; Bizzarri, B. M.; Cascone, L.; Casian, A.; Zamperini, C.; Dreassi, E.; Crespan, E.; Maga, G.; Vanham, G.; Ceresola, E.; Canducci, F.; Ariën, K. K.; Botta, M. *J. Med. Chem.* **2016**, *59*, 2747. (b) Rotili, D.; Tarantino, D.; Nawrozki, M. B.; Babushkin, A. S.; Botta, G.; Marrocco, B.; Cirilli, R.; Menta, S.; Badia, R.; Crespan, E.; Ballante, F.; Ragno, R.; Esté, J. A.; Maga, G.; Mai, A. *J. Med. Chem.* **2014**, *57*, 5212 (c) Radi, M.; Pagano, M.; Franchi, L.; Castagnolo, D.; Schenone, S.; Casaluce, G.; Zamperini, C.; Dreassi, E.; Maga, G.; Samuele, A.; Gonzalo, E.; Clotet, B.; Esté, J. A.; Botta, M. *ChemMedChem* **2012**, *7*, 883. (d) Mugnaini, C.; Alongi, M.; Togninelli, A.; Gevariya, H.; Brizzi, A.; Manetti, F.; Bernardini, C.; Angeli, L.; Tafí, A.; Bellucci, L.; Corelli, F.; Massa, S.; Maga, G.; Samuele, A.; Facchini, M.; Clotet-Codina, I.; Armand-Ugón, M.; Esté, J. A.; Botta, M. *J. Med. Chem.* **2007**, *50*, 6580.
 7. (a) Helwa, A. A.; Gedawy, E. M.; Abou-Seri, S. M.; Taher, A. T.; El-Ansary, A. K. *Res. Chem. Intermed.* **2018**, *44*, 2685. (b) Al-Abdullah, E. S.; Al-Obaid, A. R. M.; Al-Deeb, O. A.; Habib, E. E.; El-Emam, A. A. *Eur. J. Med. Chem.* **2011**, *46*, 4642.
 8. (a) Gao, L.; Xu, Z.; Rao, Y.; Lu, Y.-T.; Hu, Y.-T.; Yu, H.; Xu, Y.-H.; Song, Q.-Q.; Ye J.-M.; Huang, Z.-S. *Eur. J. Med. Chem.* **2018**, *147*, 90. (b) Hameed, A.; Al-Rashida, M.; Uroos, M.; Ali, S. A.; Arshia; Ishtiaq, M.; Khan, K. M. *Expert Opin. Ther. Pat.* **2018**, *28*, 281. (c) Rao, Y.; Yu, H.; Gao, L.; Lu, Y.-T.; Xu, Z.; Liu, H.; Gu, L.-Q.; Ye J.-M.; Huang, Z.-S. *British J. Pharm.* **2017**, *174*, 2457. (d) Ajani, O. O.; Audu, O. Y.; Aderohunmu, D. V.; Owolabi, F. E.; Olomieja, A. O. *Am. J. Drug Discovery Dev.* **2017**, *7*, 1. (e) Khan, I.; Ibrar, A.; Ahmed, W.; Saeed, A. *Eur. J. Med. Chem.* **2015**, *90*, 124. (f) Abdou, I. M.; Al-Neyadi, S. S. *Heterocycl. Commun.* **2015**, *21*, 115. (g) He, L.; Li, H. J. C.; Wu, X. F. *RSC Adv.* **2014**, *4*, 12065. (h) Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. *Eur. J. Med. Chem.* **2014**, *76*, 193.
 9. Mohamed, M. A.; Ayyad, R. R.; Shawer, T. Z.; Abdel-Aziz, A. A. M.; El-Azab, A. S. *Eur. J. Med. Chem.* **2016**, *112*, 106.
 10. Peng, X. M.; Peng, L. P.; Li, S.; Avula, S. R.; Kannekanti, V. K.; Zhang, S.-L.; Tam, K. Y.; Zhou, C.-H. *Future Med. Chem.* **2016**, *8*, 1927.
 11. Bouley, R.; Ding, D.; Peng, Z.; Bastian, M.; Lastochkin, E.; Song, W.; Suckow, M. A.; Schroeder, V. A.; Wolter, W. R.; Mobashery, S.; Chang, M. *J. Med. Chem.* **2016**, *59*, 5011.
 12. Zhang, J.; Liu, J.; Ma, Y. M.; Ren, D.; Cheng, P.; Zhao, J.; Zhang, F.; Yao, Y. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2273.
 13. (a) Nkizinkiko, Y.; Koivunen, J.; Haikarainen, T.; Murthy, S.; Obaji, E.; Pihlajaniemi, T.; Lehtio, L.; Desantis, J.; Sancineto, L.; Massari, S.; Ianni, F.; Obaji, E.; Loza, M. I.; Pihlajaniemi, T.; Brea, J.; Tabarrini, O.; Lehtio, L. *Scientific Reports* **2018**, *8*, 1680. (b) Marzaro, G.; Castagliuolo, I.; Schirato, G.; Palu, G.; Dalla Via, M.; Chilina, A.; Brun, P. *Eur. J. Med. Chem.* **2016**, *115*, 416. (c) Johannes, J. W.; Almeida, L.; Barlaam, B.; Boriack-Sjodin, P. A.; Casela, R.; Croft, R. A.; Dishington, A. P.; Gingipalli, L.; Gu, C.; Hawkins, J. L.; Holmes, J. L.; Howard, T.; Huang, J.; Ioannidis, S.; Kazmirski, S.; Lamb, M. L.; McGuire, T. M.; Moore, J.; Ogg, D.; Patel, A.; Pike, K. G.; Pontz, T.; Robb, G.; Su, N.; Wang, H.; Wu, X.; Zhang, H.; Zhang, Y.; Zheng, X.; Wang, W. *ACS Med. Chem. Lett.* **2015**, *6*, 254. (d) Ravez, S.; Castillo-Aguilera, O.; Depreux, P.; Goossens L. *Expert Opin. Ther. Pat.* **2015**, *25*, 789. (e) Kahn, K. M.; Saad, S. M.; Shaikh, N. N.; Hussain, S.; Fakhri, M.; Perveen, S.; Taha, M.; Choudhary, M. I. *Bioorg. Med. Chem.* **2014**, *22*, 3449. (f) Padithem, M.; Annapurnapadmavathi, D.; Prasunamba, P. L.; Saraladevi, C. H. *Int. J. Pharm. Pharm. Sci.* **2013**, *5*, 179. (g) Nathubhai, A.; Wood, M. D.; Thompson, A. S.; Threadgill, M. D. *ACS Med. Chem. Lett.* **2013**, *4*, 1173.

14. (a) Kikuchi, H.; Horoiwa, S.; Kasahara, R.; Hariguchi, N.; Matsumoto, M.; Oshima, Y. *Eur. J. Med. Chem.* **2014**, *76*, 10. (b) McLaughlin, N. P.; Evans, P.; Pines, M. *Bioorg. Med. Chem.* **2014**, *22*, 1993.
15. Kelly, C.; Bhuvu, N.; Harrison, M.; Buckley, A.; Saunders, M. *Eur. J. Cancer* **2013**, *49*, 2303.
16. (a) Mathew, T.; Papp, A. A.; Paknia, F.; Fustero, S.; Prakash, G. K. S. *Chem. Soc. Rev.* **2017**, *46*, 3060. (b) Rohokale, R. S.; Kshirsagar, U. A. *Synthesis* **2016**, *48*, 1253. (c) Maiden, T. M. M.; Pines, M. *Org. Biomol. Chem.* **2016**, *14*, 8014. (d) Kshirsagar, U. A. *Org. Biomol. Chem.* **2015**, *13*, 9336. (e) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
17. Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787.
18. (a) Liang, J. L.; Cha, H. C.; Jahng, Y. *Molecules* **2011**, *16*, 4861. (b) Tseng, M.-C.; Chu, Y.-W.; Tsai, H.-P.; Lin, C.-M.; Hwang, J.; Chu, Y.-H. *Org. Lett.* **2011**, *13*, 920. (c) Servais, A.; Azzouz, M.; Lopes, D.; Courillon, C.; Malacria, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 576. (d) Ma, Z.; Hano, Y.; Nomura, T. *Heterocycles* **2005**, *65*, 2203. (e) Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 13628. (f) Ma, Z. Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, *46*, 541.
19. (a) Kamal, A.; Ramana, K. V.; Rao, M. V. *J. Org. Chem.* **2001**, *66*, 997. (b) Poi, R.; Adityachaudhury, N. *J. Indian Chem. Soc.* **1988**, *65*, 814.
20. (a) He, D.; Wang, M.; Zhao, S.; Shu, Y.; Zeng, H.; Xiao, C.; Lu, C.; Liu, Y. *Fitoterapia.* **2017**, 119. (b) Gahtory, D.; Chouhan, M.; Sharma, R.; Nair, V. A. *Org. Lett.* **2013**, *15*, 3942. (c) Sharma, P. C., Kaur, G., Pahwa, R., Sharma, A., Rajak, H. *Curr. Med. Chem.* **2011**, *18*, 4786.
21. (a) Kaur, R.; Manjal, S. K.; Rawal, R. K.; Kumar, K. *Bioorg. Med. Chem.* **2017**, *25*, 4533. (b) Bandekar, P. P.; Roopnarine, K. A.; Parekh, V. J.; Mitchell, T. R.; Novak, M. J.; Sinden, R. R. *J. Med. Chem.* **2010**, *53*, 3558. (b) Jao, C.-W.; Lin, W.-C.; Wu, Y.-T.; Wu, P.-L. *J. Nat. Prod.* **2008**, *71*, 1275.
22. (a) Huang, G.; Drakopoulos, A.; Saedtler, M.; Zou, H.; Meinel, L.; Heilmann, J.; Decker, M. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4937. (b) Son, J.-K.; Chang, H. W.; Jahng, Y. *Molecules* **2015**, *20*, 10800. (c) Granger, B. A.; Kaneda, K.; Martin, S. F. *Org. Lett.* **2011**, *13*, 4542. (d) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (e) Chiou, W.-F.; Liao, J.-F.; Chen, C.-F. *J. Nat. Prod.* **1996**, *59*, 374.
23. (a) Del Valle, P.; Martinez, A.-L.; Figueroa, M.; Raja, H. A.; Mata, R. *Planta Medica* **2016**, *82*, 1286. (b) Peng, J.; Zhang, X.-Y.; Tu, Z.-C.; Xu, X.-Y.; Qi, S.-H. *J. Nat. Prod.* **2013**, *76*, 983. (c) Tseng, M.-C.; Yang, H.-Y.; Chu, Y.-H. *Org. Biomol. Chem.* **2010**, *8*, 419. (d) Joshi, B. K.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod.* **1999**, *62*, 650. (e) Sun, H. H.; Barrow, C. J.; Cooper, R. *J. Nat. Prod.* **1995**, *58*, 1575.
24. (a) Dai, J.-R.; Carte, B. K.; Sidebottom, P. J.; Yew, A. L. S.; Ng, S.-B.; Huang, Y.; Butler, M. S. *J. Nat. Prod.* **2001**, *64*, 125. (b) Kshirsagar, U. A.; Argade, N. P. *Org. Lett.* **2010**, *12*, 3716.
25. Shakhidoyatov, K. M.; Elmuradov, B. Z. *Chem. Nat. Comp.* **2014**, *50*, 781.
26. Kumar, K. S.; Kumar, P. M.; Rao, V. S.; Jafar, A. A.; Meda, C. L. T.; Kapavarapu, R.; Parsac, K. V. L.; Pal, M. *Org. Biomol. Chem.* **2012**, *10*, 3098.
27. (a) Nguyen, T. L.; Fruit, C.; Héroult, Y.; Meijer, L.; Besson, T. *Expert Opin. Ther. Pat.* **2017**, *11*, 1183. (b) Hédou, D.; Godeau, J.; Loaëc, N.; Meijer, L.; Fruit, C.; Besson, T. *Molecules* **2016**, *21*, 578. (c) Guillon, R.; Pagniez, F.; Picot, C.; Hédou, D.; Tonnerre, A.; Chosson, E.; Duflos, M.; Besson, T.; Logé, C.; Le Pape, P. *ACS Med. Chem. Lett.* **2013**, *4*, 288. (d) Logé, C.; Testard, A.; Thiéry, V.; Lozach, O.; Blairvacq, M.; Robert, J.-M.; Meijer, L.; Besson, T. *Eur. J. Med. Chem.* **2008**, *43*, 1469.
28. (a) Choy, P. Y.; Wong, S. M.; Kapdi, A.; Kwong, F. Y. *Org. Chem. Front.* **2018**, *5*, 288. (b) Roudesly, F.; Oble, J.; Poli, G. *J. Mol. Catal. A: Chem.* **2017**, *426*, 275. (c) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (d) Rossi, R.; Lessi, M.; Manzini, C.; Marianetti, G.; Bellina, F. *Tetrahedron* **2016**, *72*, 1795. (e) Bheeter, C. B.; Chen, L.; Soulé, J.-F.; Doucet, H. *Catal. Sci. Technol.* **2016**, *6*, 2005. (f) Davies, H. M. L.; Morton, D. *J. Org. Chem.* **2016**, *81*, 343. (g) Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 66. (h) Rossi, R.; Bellina, F.; Lessi, M.; Manzini, C. *Adv. Synth. Catal.* **2014**, *356*, 17. (i) Bonin, H.; Sauthier, M.; Felpin, F.-X. *Adv. Synth. Catal.* **2014**, *356*, 645. (j) Shibahara, F.; Murai, T. *Asian J. Org. Chem.* **2013**, *2*, 624. (k) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (l) Hirano, K.; Miura, M. *Synlett* **2011**, *2011*, 294. (m) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57. (n) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (o) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (p) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036.

29. Aziz, J.; Piguel, S. *Synthesis* **2017**, *49*, 4562. For reviews focused on C-H bond functionalization of purine and pyrimidine nucleosides, see: (a) Gayakhe, V.; Sanghvi, Y. S.; Fairlamb, I. J. S.; Kapdi, A. R. *Chem. Commun.* **2015**, *51*, 11944. (b) Liang, Y.; Wnuk, S. F. *Molecules* **2015**, *20*, 4874.
30. (a) Fruit, C. *Science* **2016**, *352*, 1277. (b) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369.
31. For recent advances in direct C-C and C-X bond formation from C-H activation of pyrimidines, see: Verbitskiy, E. V.; Rusinov, G. L.; Chupakhin, O. N.; Charushin, V. N. *Synthesis* **2018**, *50*, 193.
32. (a) Majumdar, K. C.; Sinha, B.; Chattopadhyay, S. K. *Tetrahedron* **2009**, *65*, 2751. (b) Majumdar, K. C.; Debnath, P.; Taher, A.; Pal, A. K. *Can. J. Chem.* **2008**, *86*, 325.
33. Lee, H. S.; Kim, K. H.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2012**, *53*, 497.
34. Čerňová, M.; Čerňa, I.; Pohl, R.; Hocek, M. *Eur. J. Org. Chem.* **2009**, *2009*, 3698.
35. For a review focused on metal-catalyzed site-selective C-H activation, see: Théveau, L.; Schneider, C.; Fruit, C.; Hoarau, C. *ChemCatChem*, **2016**, *8*, 3183.
36. Čerňová, M.; Čerňa, I.; Pohl, R.; Hocek, M. *J. Org. Chem.* **2011**, *76*, 5309.
37. Kim, K. H.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2011**, *52*, 6228.
38. Liang, Y.; Gloudeman, J.; Wnuk, S. F. *J. Org. Chem.* **2014**, *79*, 4094.
39. Guchhait, S. K.; Priyadarshani, G. *J. Org. Chem.* **2015**, *80*, 8482.
40. Priyadarshani, G.; Amrutkar, S.; Nayak, A.; Banerjee, U. C.; Kundu, C. N.; Guchhait, S. K. *Eur. J. Med. Chem.* **2016**, *122*, 43.
41. Mondal, B.; Hazra, S.; Roy, B. *Tetrahedron Lett.* **2014**, *55*, 1077.
42. For the regioselective synthesis of 6-arylluracils via a Pd-catalyzed enolic C-OH activation-arylation of barbituric acids with arylboronic acids, see: Guchhait, S. K.; Priyadarshani, G. *J. Org. Chem.* **2015**, *80*, 6342. For a regioselective synthesis of 4-heteroarylpyrimidines via a Pd/Cu-catalyzed phosphonium coupling of pyrimidin-4-one and heteroaryls, see: Sharma, A.; Vachhani, D.; Van der Eycken, E. *Org. Lett.* **2012**, *14*, 1854.
43. Cheng, C.; Shih, Y.-C.; Chen, H.-T.; Chien, T.-C. *Tetrahedron* **2013**, *69*, 1387.
44. Cresswell, A. J.; Lloyd-Jones, G. C. *Chem. Eur. J.* **2016**, *22*, 12641.
45. Murakoshi, I.; Sekine, T.; Higuchi, Y.; Ohyama, N.; Yamada, T. *Chem. Pharm. Bull.* **1989**, *37*, 1984. For Pd-catalyzed oxidative coupling of uridine and 2'-deoxyuridine with maleimides, see: Itahara, T. *Chem. Lett.* **1986**, *15*, 239.
46. For recent reviews on CDC, see: (a) Bruneau, C. Dixneuf, P. H. *Top Organomet. Chem.* **2016**, *55*, 137. (b) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138.
47. Do, H.Q.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 13577.
48. Kim, K. H.; Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2012**, *53*, 1323.
49. Kianmehr, E.; Rezaeefard, M.; Khalkhalia, M. R.; Khan, K. M. *RSC Adv.* **2014**, *4*, 13764.
50. Kianmehr, E.; Torabi, M.; Khalkhalia, M. R.; Faghieh, N.; Khan, K. M. *Eur. J. Org. Chem.* **2015**, *2015*, 2796.
51. Roy, B.; Hazra, S.; Mondal, B.; Majumdar, K.C. *Eur. J. Org. Chem.* **2013**, *2013*, 4570.
52. Mondal, B.; Hazra, S.; Panda, T. K.; Roy, B. *Beilstein J. Org. Chem.* **2015**, *11*, 1360.
53. Hirota, K.; Isobe, Y.; Kitade, Y.; Maki, Y. *Synthesis* **1987**, *1987*, 495.
54. Yu, Y.-Y.; Georg, G. I. *Chem. Commun.* **2013**, *49*, 3694.
55. Zhang, X.; Su, L.; Qiu, L.; Fan, Z.; Zhang, X.; Lin, S.; Huang, Q. *Org. Biomol. Chem.* **2017**, *15*, 3499.
56. Kianmehr, E.; Khalkhali, M. R.; Rezaeefard, M.; Khan, K. M.; Ng, S. W. *Aust. J. Chem.* **2015**, *68*, 165.
57. Liu, W.; Wang, S.; Zhang, Q.; Yu, J.; Li, J.; Xie, Z.; Cao, H. *Chem. -Asian J.* **2014**, *9*, 2436.
58. Lv, J.; Liang, Y.; He, P.; Cai, Z.; Liu, J.; Huang, F. *RSC Adv.* **2015**, *5*, 36171.
59. Uruguchi, D.; Yamamoto, K.; Ohtsuka, Y.; Tokuhisa, K.; Yamakawa, T. *Appl. Catal. A: General* **2008**, *342*, 137. For perfluoroalkylation of 2'-deoxyuridine using xenon difluoride and a perfluoro carboxylic acid, see: Tanabe, Y.; Matsuo, N.; Ohno, N. *J. Org. Chem.* **1988**, *53*, 4582.
60. Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224.
61. Cernova, M.; Pohl, R.; Klepetarova, B.; Hocek, M. *Heterocycles* **2014**, *89*, 1159.
62. Lee, H. S.; Kim, S. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2010**, *31*, 238. For a recent review of acetoxylation, see: Moghimi, S.; Mahdavi, M.; Shafiee, A.; Foroumadi, A. *Eur. J. Org. Chem.* **2016**, *2016*, 3282.

63. Kim, S. H.; Kim, S. H.; Lim, C. H.; Kim, J. N. *Tetrahedron Lett.* **2013**, *54*, 1697.
64. (a) Nacro, K.; Zha, C.; Guzzo, P. R.; Herr, R. J.; Peace, D.; Friedrich, T. D. *Bioorg. Med. Chem.* **2007**, *15*, 4237. (b) Harayama, T.; Hori, A.; Serban, G.; Morikami, Y.; Matsumoto, T.; Abe, H.; Takeuchi, Y. *Tetrahedron* **2004**, *60*, 10645. (c) Harayama, T.; Morikami, Y.; Shigeta, Y.; Abe, H.; Takeuchi, Y. *Synlett* **2003**, *2003*, 847. For a recent example of silver-mediated oxidative decarboxylative intramolecular radical C-H alkylation, see: Mahajan, P. S.; Mhaske, S. B. *Org. Lett.* **2018**, *20*, 2092.
65. Banerjee, A.; Subramanian, P.; Kaliappan, K. P. *J. Org. Chem.* **2016**, *81*, 10424.
66. Naik, N. H.; Urmode, T. D.; Sikder, A. K.; Kusurkar, R. S. *Aust. J. Chem.* **2013**, *66*, 1112.
67. For recent reviews on C-H arylation under microwave irradiation, see: (a) Besson, T.; Fruit, C. *Synthesis* **2016**, *48*, 3879. (b) Rathia, A. K.; Gawandea, M. B.; Zborila, R.; Varmab, R. S. *Coord. Chem. Rev.* **2015**, *291*, 68. (c) Gupta, A. K.; Singh, N.; Singh, K. N. *Curr. Org. Chem.* **2013**, *17*, 474. (d) Sharma, A.; Vacchani, D.; Van der Eycken, E. *Chem. Eur. J.* **2013**, *19*, 1158. (e) Mehta, V. P.; Van der Eycken, E. *Chem. Soc. Rev.* **2011**, *40*, 4925. (f) Baghbanzadeh, M.; Pilger, C.; Kappe, C. O. *J. Org. Chem.* **2011**, *76*, 8138.
68. Laclef, S.; Harari, M.; Godeau, J.; Schmitz-Afonso, I.; Bischoff, L.; Hoarau, C.; Levacher, V.; Fruit, C.; Besson, T. *Org. Lett.* **2015**, *17*, 1700.
69. Godeau, J.; Harari, M.; Laclef, S.; Deau, E.; Fruit, C.; Besson, T. *Eur. J. Org. Chem.* **2015**, *2015*, 7705.
70. (a) Das, D.; Poddar, P.; Maity, S.; Samanta, R. *J. Org. Chem.* **2017**, *82*, 3612. (b) Das, D.; Biswas, A.; Karmakar, U.; Chand, S.; Samanta, R. *J. Org. Chem.* **2016**, *81*, 842.
71. Molander, G. A.; Colombel, V.; Braz, V. *Org. Lett.* **2011**, *13*, 1852. For a metal-free C-H alkylation using alkyltrifluoroborate, see: Matsui, J. K.; Primer, D. N.; Molander, G. A. *Chem. Sci.* **2017**, *8*, 3512. For recent examples of Minisci-type radical alkylation of quinazolinone with an alkyl boronic acid or carboxylic acid, see: Zhang, L.; (a) Sherwood, T. C.; Li, N.; Yazdani, A. N.; Murali Dhar, T. G. *J. Org. Chem.* **2018**, *83*, 3000. (b) Liu, Z.-Q. *Org. Lett.* **2017**, *19*, 6594. (c) Li, G.-X.; Morales-Rivera, C. A.; Wang, Y.; Gao, F.; He, G.; Liu, P.; Chen, G. *Chem. Sci.*, **2016**, *7*, 6407. For a metal-free oxidative cross-coupling of quinazolinone with unfunctionalized cyclohexane, see: Antonchick, A. P.; Burgmann, L. *Angew. Chem. Int. Ed.* **2013**, *52*, 3267.
72. Subba Reddy, B. V.; Narasimhulu, G.; Umadevi, N.; Yadav, J. S. *Synlett* **2012**, *23*, 1364.
73. Yang, W.; Chen, J.; Huang, X.; Ding, J.; Liu, M.; Wu, H. *Org. Lett.* **2014**, *16*, 5418.
74. Zhang, Y.; Huang, J.; Deng, Z.; Mao, X.; Peng, Y. *Tetrahedron* **2018**, *74*, 2330.
75. Lee, J. B.; Kang, M. E.; Kim, J.; Lee, C. Y.; Kee, J.-M.; Myung, K.; Park, J.-U.; Hong, S. Y. *Chem. Commun.* **2017**, *53*, 10394.
76. Garad, D. N.; Viveki, A. B.; Mhaske, S. B. *J. Org. Chem.* **2017**, *82*, 6366.
77. Gupta, P. K.; Yadav, N.; Jaiswal, S.; Asad, M.; Kant, R.; Hajela, K. *Chem. Eur. J.* **2015**, *21*, 13210.
78. Yu, Y.; Yue, Y.; Wang, D.; Li, X.; Chen, C.; Peng, J. *Synthesis* **2016**, *48*, 3941.
79. Zheng, Y.; Song, W.-B.; Zhang, S.-W.; Xuan, L.-J. *Org. Biomol. Chem.* **2015**, *13*, 6474.
80. Jiang, X.; Yang, Q.; Yuan, J.; Deng, Z.; Mao, X.; Peng, Y.; Yu, C. *Tetrahedron* **2016**, *72*, 1238.
81. Viveki, A. B.; Mhaske, S. B. *J. Org. Chem.* **2018**, *83*, 8906. For recent examples of gold and ruthenium-catalyzed cross-coupling of quinazolinones with alkynes for access to fused quinazolinone scaffolds, see: (a) Wei, L.-S.; He, G.-X.; Kong, X.-F.; Pan, C.-X.; Mo, D.-L.; Su, G.-F. *J. Org. Chem.* **2018**, *83*, 6719. (b) Lu, H.; Yang, Q.; Zhou, Y.; Guo, Y.; Deng, Z.; Ding, Q.; Peng, Y. *Org. Biomol. Chem.* **2014**, *12*, 758.
82. (a) Harari, M.; Couly, F.; Fruit, C.; Besson, T. *Org. Lett.* **2016**, *18*, 3282. (b) Couly, F.; Dubouilh-Benard, C.; Besson, T.; Fruit, C. *Synthesis* **2017**, *49*, 4615.