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Recent Developments in Transition Metal Catalysis for Quinazolinone Synthesis

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Quinazolinones are an important class of heteroaromatic compound, and they are prevalent in a variety of important bio-active scaffolds. Traditionally, their synthesis has been achieved *via* classical condensation procedures, however over recent years catalytic methodologies have emerged as effective alternatives. This review examines recent developments in the employment of catalytic approaches towards this highly important heterocyclic motif.

1. Introduction

Quinazolinones are prevalent in a wide range of both natural and non-natural products. For example, febrifugine, fumiquinaoline A, luotonin A and (-)-asperlicin (Figure 1) have all been found to display noteworthy biological activities including anti-malarial and anti-cancer properties.1-4 With a high occurrence of quinazolinone derivatives displaying broad and diverse biological profiles, efficient routes for the synthesis of these heteroaromatic structures has attracted significant attention over many years.5 Classical methodologies used in the synthesis of quinazolinones rely primarily upon condensation pathways from 1,2-disubstituted aromatics such as anthranilic acid derivatives, and formamide equivalents.5-7 Whilst methods of this nature are well established and able to provide the desired scaffolds, they suffer from a multitude of drawbacks. For example, high temperatures, long reaction times are typically employed and these methods suffer particularly from displaying a very limited scope (Scheme 1). Over recent years, attempts to improve upon classical syntheses have moved in the direction of catalytic methodologies in order to overcome these limitations. Indeed, catalysis offers numerous synthetic benefits including; shorter reaction times, extended scope and reduced reaction temperatures, as well as offering the opportunity to explore exciting new methodologies. This review will discuss recent developments in the exploitation of transition metal catalysed organic synthesis as it has been applied towards quinazolinones. There will be a particular focus on those methods that generate 2-substituted and 2,3-disubstituted quinazolinones, and will highlight how strategies have evolved from those that require 1,2-disubstituted aromatic substrates to more recent methods that exploit the more available and attractive mono-substituted aromatics as starting materials.



Figure 1. Important structural motifs containing the quinazolinone heterocycle



Scheme 1. Traditional and catalytic approaches towards quinazolinones

2. Catalytic Methods that use 1,2-Disubstituted Aromatic Substrates

Since the first documented synthesis of a quinazolinone by Griess in the late 1860’s, 1,2-disubstituted aromatics have represented popular starting materials for the preparation of this heteroaromatic scaffold.8 More specifically, and as exemplified in Griess’ initial discovery, anthranillic acids and their analogues offer robust and reliable routes to these compounds. It is then no surprise that the first catalytic approaches towards quinazolinones began by accessing these precursors.

**2.1 Catalytic-Carbonylation Towards Quinazolinones**

The palladium-catalysed carbonylation reaction offers a mild and general method to produce aromatic carboxylic acid derivatives.9 This transformation typically comprises the reaction of an arylhalide with carbon monoxide to form a acylpalladium intermediate, which is in turn trapped by a variety of nucleophiles.10 Over the past decade there have been many reports that demonstrate the application of this transformation to heterocycle synthesis, and quinazolinones in particular.

During ongoing research into the application of carbonylation reactions for heterocyclic synthesis, Beller described a cascade reaction that took place under Pd-catalysis to build the quinazolinone framework, employing 2-aminobenzamides and aryl bromides.11 Despite demonstrating a broad range of aryl bromides were compatible with the procedure, a narrow scope of the 2-aminobenzamides greatly limited the methodology. In

an effort to improve upon their preliminary work and extend their methodology to more available reagents, it was decided to replace the limited 2-aminobenzamides with 2-aminobenzonitriles (scheme 2).12 An *in situ* hydration of the nitrile group would in theory allow these more available starting materials to be used. After optimisation of the procedure, various quinazolinones were produced in moderate to excellent yields, and purified by the simple recrystallisation. With respect to reaction scope, a selection of aryl bromides and 2-aminobenzonitriles were shown to participate in the reaction, allowing for the production of some novel 2-aryl-4(3H)quinazolinones (**1**-**3**). Additionally, low palladium loadings were sufficient to promote the annulation reaction.



Scheme 2. Beller’s palladium-catalysed carbonylative cyclisation of 2-aminobenzonitriles

In 2008 Alper reported the use of imidoyl chlorides as a useful reagent for the synthesis of quinazolinones in conjunction with palladium catalysis and *ortho*-iodoanilines (scheme 3).13 The reaction utilised a catalyst system of palladium acetate and triphenylphosphine. Despite an impressive reaction scope with respect to both synthetic partners, the method required reaction times of 48 - 72 h, with reaction temperatures of 150 °C. In 2010, Alper extended this methodology to encompass a tandem palladium-catalysed addition/cyclocarbonylation reaction of *N*-(2-iodophenyl)-*N*’-arylcarbodiimide to access a 2-substituted quinazolinone scaffold.14 In comparison to his initial report, a shorter reaction time, lower reaction temperature and lower pressure of carbon monoxide was required. However, whilst a variety of nucleophile sources were utilised, inclusive of secondary amines (both cyclic and linear) and phenols with good to excellent yields, the process was found to be incompatible with thiols. In addition, a limited scope of *N*-(2-iodophenyl)-*N*’-arylcarbodiimides was demonstrated, likely because of their scarce availability. Only the *N*-aryl substituent was varied to include phenyl, 4-Cl- and 4-MeO-phenyl as well as 1-naphthyl substituents. Further reaction scope was demonstrated later that year when the same reaction conditions were applied towards the synthesis of quinazolino[3,2-a]quinazolinones.15 As before, a variety of amino sources were shown to be successfully incorporated into this novel framework.



Scheme 3. Alper’s carbonylative cyclisation towards quinazolinone scaffolds

Willis and co-workers have developed an interesting palladium-catalysed route to biologically important benzimidazoles and quinazolinones from *N*-(*o*-halophenyl)imidoyl chlorides and their corresponding imidates, using a strategically related route to that described by Alper (scheme 4).16 *N*-(*o*-halophenyl)imidoyl chlorides were found to be successful substrates for the synthesis of benzimidazoles. However, for the synthesis of the corresponding quinazolinones, the imidate precursors was found to be more effective. Formation of the quinazolinone in this case is believed to occur after an initial palladium-catalysed aminocarbonylation of the aryl halide to form an amide intermediate which undergoes a base-induced cyclisation. Synthesis of the required imidate precursors could be achieved from 2-bromoanilines and orthoesters. Sodium *tert*-butoxide and potassium carbonate were successful bases for the cyclisation reaction, however caesium carbonate was found to be optimal, giving the quinazolinone in a 75% yield. Optimisation of the catalyst and the ligand highlighted palladium acetate and Beller’s ligand to be the most suitable for this transformation. Overall, a diverse selection of quinazolinones were successfully synthesised in moderate to good yields under these optimised conditions (**4**-**7**). For example, electron rich and deficient arylbromides were tolerated, and both aromatic and alkyl amines were successfully incorporated. Notably however, imidates derived from 2-chloroanilines were found to be unreactive.



Scheme 4. Willis’ palladium-catalysed aminocarbonylation route

More recently, Beller developed a one-pot variant of the aminocarbonylation route to quinazolinones *via* an *in situ* generation of imidates.17 In this instance, 2-bromoanilines, trimethyl orthoformate, a variety amines and CO were subjected to a multicomponent palladium-catalysed cyclisation reaction. In comparison to the stepwise process devised by Willis, this one-pot approach offers lower catalyst loading and shorter reaction times. Good yields of the quinazolinones were achieved, and a tolerance for various reactive functional groups was also demonstrated (scheme 5).

In 2012, Lu and Wang reported a synthesis of 4(*3H*)quinazolinones by a combination of azides, alkynes, anilines and CO.18 The procedure involves a three component copper-catalysed cascade reaction to yield an amidine intermediate **8**, which is subjected to a palladium-catalysed carbonylation that leads to the desired quinazolinone **9** after hydrolysis of the sulfonamide. The formation of the amidine is proposed to proceed *via* a ketenimine intermediate. Ketenimines are a class of easily accessible intermediates which demonstrate high reactivity and tolerance to a wide range of substrates.19 Moreover, palladium acetate is believed to have dual roles within the reaction; as well as catalysing the carbonylation, it is believed to function as a Lewis acid to promote the hydrolysis of the sulfonamide by trace water present in the solvent. While initial studies were devoted to developing a stepwise procedure that involved isolation of the amidine **8**, a more efficient one-pot transition metal catalysed cascade process was realised that yielded the quinazolinone in an impressive yield of 74%. Having optimised this one-pot procedure, the substrate diversity was next investigated. A range of aromatic and aliphatic terminal alkynes were shown to be effective, in contrast, only a few 2-haloanilines were shown to be applicable in the reaction.

Wu and co-workers recently reported that a four component coupling reaction between 2-iodoanilines, CO, trimethyl orthoformate and an amine could be catalysed by Pd/C in loadings as low as 0.5 mol% (scheme 7).20 The reaction scope encompassed an array of functionalised anilines and amines, although only a small number of 2-iodoanilines were successfully explored and



Scheme 5. Beller’s one-pot multicomponent palladium-catalysed reaction



Scheme 6. Lu and Wang’s synthesis of quinazolinones

these appeared to be restricted to electron deficient/neutral substrates. However, the procedure did offer the significant benefit of recyclability of the Pd/C catalyst (up to 4 cycles), and its relevance to organic chemistry was confirmed by the generation of a key intermediate towards the synthesis of rutaecarpine precursor **12**.

Whilst the aforementioned examples successfully afford the quinazolinone heterocycle, they all rely on the use of carbon monoxide gas, which due to its toxicity, raises practical challenges and safety concerns. In order to address the limitations associated with the use of carbon monoxide gas, Beller reported the use of Mo(CO)6 as a safer source of CO (scheme 8).21



Scheme 7. Pd/C catalysed carbonylation of quinazolinones



Scheme 8. Beller’s alternative palladium-catalysed carbonylative cyclisation using Mo(CO)6

Indeed, a reaction between 2-bromoformanilides and aryl- and alkyl-nitro compounds was found to be catalysed by palladium(II) in the presence of Mo(CO)6 to generate a series *N*-substituted quinazolinones in good yields. In this case, Mo(CO)6 is believed to play a number of key roles; it acts as a CO source, nitro reducing agent and cyclisation promoter. Optimisation of the reaction system highlighted that a catalyst comprising of Pd(OAc)2 and Beller’s ligand was the most successful. Additionally, screening of the CO sources showed carbon monoxide gas to be less effective than Mo(CO)6, along with other metal carbonyl complexes such as Co2(CO)8 and Fe3(CO)12. A variety of nitro alkanes/arenes could be incorporated into the quinazolinone scaffold in good to excellent yields, moreover, a small selection of 2-bromoformanilides could be successfully coupled. Mechanistic studies demonstrated the nitro compounds were initially reduced to the corresponding amines which, following addition to the *in situ* generated acylpalladium complex and subsequent cyclisation, formed the desired heterocycle.

**2.2 Catalytic-Domino and Multi-Component Processes Towards Quinazolinones**

Domino and multi-component reaction processes are highly sought after within organic synthesis. Domino reactions are defined as chemical processes involving two or more bond-forming transformations which take place under the same reaction conditions, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step.22 In terms of multi-component reactions, the ability to develop methodologies in which more than two molecules come together in a controlled and predictable manner to yield a single product encompassing part of each substrate represents an attractive strategy to build molecular diversity by a fast and efficient means.23 Both reaction classes have been successfully applied to quinazolinone synthesis. Notably, in addition to reports described below, some of the carbonylative methods previously described embody the requirement of multi-component or domino reaction profiles.

In 2008, Fu reported a copper-catalyzed cascade synthesis of quinazoline and quinazolinone derivatives *via* the reaction of amidine hydrochlorides with 2-halobenzene-aldehydes, -ketones and -esters (scheme 9).24 Optimisation highlighted that a CuI catalyst in combination with L-proline as the ligand and Cs2CO3 as a base, afforded very good yields of the desired quinazoline and quinazolinone derivatives, the latter being generated at relatively low temperatures (80 versus 110 °C). Both alkyl and aryl amidines were successfully employed, and heteroaromatic scaffolds could be utilised to afford the corresponding azaquinazolinone scaffolds. Furthermore, the work was extended to include 2-halobenzoic acid substrates.25 Compared to the previous reaction conditions, when 2-halobenzoic acids were used, no ligand was required to promote the cascade and the reaction proceeded successfully at room temperature. Additionally, 2-iodo, 2-bromo and 2-chlorobenzoic acids were found to be effective substrates, although 2-chlorobenzoic acids typically required a higher temperature of 80 °C. With regard to the scope, functionalised chloro and dioxolane 2-bromobenzoic acid derivatives were found to be viable substrates. Switching from amidines to guanidines allowed 2-amino quinazolines to be generated, albeit these reactions again required the use of elevated temperatures. Furthermore, the replacement of CuI catalyst with FeCl3 for the conversion of 2-bromobenzoic acids to quinazolinones was described by Fu in 2009.26 These reactions offered similar scope to the Cu-catalysed process although they required an elevated temperature of 120 °C.



Scheme 9. Fu’s Copper-catalysed synthesis of quinazolines and quinazolinones

Fu *et al.* further extended their investigations into the copper-catalysed domino synthesis of 2-substituted-4(3H)-quinazolinones by exploiting 2-halobenzamides (scheme 10).27 The ring forming reaction involved a sequential Ullmann-type coupling under air, together with aerobic oxidative C-H amidation. The methodology is simple, practical and efficient, and uses commercially available starting materials. Moreover, the procedure affords the product quinazolinones in good to excellent yields, without the need for ligands or additives. With regard to the reaction scope, 2-iodo, 2-bromo and 2-chlorobenzamides bearing both electron withdrawing and electron donating substituents were tolerated. An array of (aryl)methanamines were also successfully employed, including (heteroaryl)methanamines based on pyridine, furan and thiophene (**18** and **20**). This work was later extended at the quinazolinone C2 position *via* use of α-amino acids.28 The ready availability of α-amino acids, along with their prevalence in nature, makes this class of compounds one of the most attractive sources of amines for organic synthesis. The optimal reaction conditions were found to be somewhat harsher than that required of (aryl)methanamine substrates with an increase in both reaction time (10 h) and temperature (120 °C). Nonetheless, a small selection of α-amino acids were found to be compatible with this transformation.



Scheme 10. Fu’s copper-catalysed domino process with (aryl)methanamines and α-amino acids

Yokoyama *et al.* reported a novel synthesis of 2,3-disubstituted-4(*3H*)quinazolinones *via* a palladium-catalysed reaction of 2-aminobenzamides with benzyl alcohols (scheme 11).29 The reaction is believed to involve *N*-benzylation, benzylic *C-H* amidation and dehydrogenation in a one-pot domino process. As well as being the first reported palladium-catalysed benzylic *C-H* amidation reaction, the preceding aniline benzylation step is also noteworthy. Examples of palladium-catalysed benzylation of amines with benzylic alcohols are scarce in literature.30 Optimisation showed Pd(OAc)2and TPPMS to give the best catalyst combination for the formation of the quinazolinone heterocycle. A small range of benzylic alcohols with electron donating substituents were shown to be applicable to the reaction conditions, producing the corresponding quinazolinones in yields of 65 to 96%. Substituents in all three of the *ortho*, *meta* and *para* positions were tolerated on the benzylic alcohol, although it is not clear whether or not the method is compatible with benzylic alcohols bearing electron withdrawing substituents. In addition, only a small range of 2-aminobenzamides were shown to take part in the reaction. Nonetheless, the methodology is effective and can produce quinazolinones in good yields of 72 to 90%.

More recently in 2014, Ji disclosed a palladium-catalysed three-component reaction sequence to generate quinazolinones *via* the reaction of 2-aminobenzamides and aryl halides in the presence of an isocyanide (scheme 12).31 A catalyst system consisting of PdCl2 and DPPP was found to be optimal, promoting the reaction of *tert*-butyl isocyanide with a range of aryl iodides bearing electron donating and electron withdrawing substituents. In addition, aryl bromides could also be used with no significant change in product yield. A single



Scheme 11. Yokoyama’s palladium-catalysed coupling of benzylic alcohols with 2-aminobenzamides



Scheme 12. Ji’s palladium catalysed *tert*-butyl isocyanide insertion reaction to quinazolinones

heteroaromatic iodide was also demonstrated producing 2-(thiophene-2-yl)quinazoline-4(3H)-one in a good yield of 65%. In comparison to the relatively large reaction scope of the aryl halide counterpart, only 4 examples of substituted anthranilamide substrates were disclosed.

**2.3 Catalytic Hydrogen Transfer Processes Towards Quinazolinones**

Hydrogen transfer methodologies have emerged in the literature as catalytic and green protocols that significantly enable organic synthesis. This process allows functional groups such as ketones and imines to be reduced, and alcohols and amines to be oxidised under relatively mild conditions.32, 33 The embodiment of this useful methodology in heterocycle synthesis has now been realised and reported upon in the context of quinazolinone synthesis.

An iridium-catalysed route to quinazolinones was reported by Zhou in 2011.34 A one pot oxidative cyclisation of primary alcohols with 2-aminobenzamides to quinazolinones was demonstrated via use of [Cp\*IrCl2]2 as a catalyst under hydrogen transfer conditions (scheme 13). The reaction is believed to occur in a domino sequence in which initially the primary alcohol is oxidised to an aldehyde *via* catalytic hydrogen transfer. Condensation of the aldehyde with 2-aminobenzamide after loss of water leads to an aminal intermediate. The aminal intermediate is then further oxidised to the desired quinazolinone under the same hydrogen transfer catalysis. The procedure is tolerant of a range of aromatic alcohols, bearing electron withdrawing and electron donating substituents in *ortho*, *meta* and *para* positions. Heteroaromatic and alkyl substituted primary alcohols were also shown to be suitable substrates for the reaction, demonstrated by the reactions of 2-thiophenemethanol and 1-pentanol. A variety of substituted 2-aminobenzamides were also tolerated in the reaction. On the whole, this method offers generally good to excellent yields of the quinazolinone product, although the reaction times are rather long, taking generally 3 to 5 days to reach completion.

A similar process was reported by Watson and co-workers in



Scheme 13. Zhou’s iridium-catalysed hydrogen transfer conditions

2012, who also used catalytic hydrogen transfer methodology as a means to access quinazolinone derivatives.35 They reported a ruthenium-catalysed oxidation of a benzylic alcohol in a tandem process with 2-aminobenzamide to generate the quinazolinone heterocycle (scheme 14). Interestingly, they found that that the oxidation level of the product could be modulated by judicious choice of reaction conditions. Specifically, the inclusion of ammonium chloride as an additive led to the preferential production of the 2,3-dihydroquinazoline, whereas in the absence of this reagent the reaction generated the corresponding quinazolinone. A small selection of primary alcohols were shown to participate, including benzylic alcohols bearing methyl, methoxy and halide substituents. The scope of substituents upon the 2-aminobenzamide reagent was not demonstrated for this particular procedure.

A very recent hydrogen transfer methodology was reported by Li in 2016, where methanol was demonstrated as a *C*1 source for the construction of quinazolinones.36 After optimisation, it was found that *ortho*-aminobenzamide could be transformed into the corresponding quinazolinone under microwave conditions by utilisation of an iridium based catalyst, [Cp\*Ir(2,2’-bpyO)(H2O)]. The ligands in this instance were found to be crucial to catalyst activity. Iridium catalysts based solely upon Cp\* and COD were found to give low yields, whereas functionalised bipyridine motifs were more optimal. The scope of the *ortho*-aminobenzamide derivatives was broad; aromatic groups bearing both electron rich and electron poor substituents were found to participate, furthermore a *N*-substituted amide was shown to be viable, furnishing the corresponding heterocyclic product in a very good yield of 66%. Moreover, alternative alcohol sources were found to be compatible, allowing for incorporation of substituents in the 2-position of the quinazolinone scaffold (scheme 15).

3. Catalytic Methods via C-H Activation

Over recent years, there has been significant research activity towards the development of C-H activation/functionalisation, and this has led to many useful advances for organic synthesis.37 The ability to turn a relatively inert C-H bond into a functional group is a highly attractive methodology, avoiding the need for pre-functionalised scaffolds and greatly simplifying synthetic strategies. With regard to heterocycle synthesis, C-H



Scheme 14. Watson’s catalytic hydrogen transfer methodology to quinazolinones



Scheme 15. Li’s dehydrogenative coupling of *ortho*-aminobenzamide with alcohols

functionalisation has allowed for novel synthetic approaches to be accessed, thereby allowing the introduction of new substrates that are often more readily available than the required starting materials used in classical chemistries.38-43 With respect to quinazolinones, established synthetic routes very often used anthranillic acid derivatives which can be expensive or require long and linear syntheses, especially highly functionalised examples. C-H Activation removes the need for such 1,2-difunctionalisation as the required *ortho*-substituents can be readily installed allowing direct access to 1,2-disubstituted reaction precursors, which upon subsequent transformation can yield diverse heterocyclic scaffolds. In this respect, systems such as benzoic acids, or benzaldehydes can be considered as attractive starting materials to afford highly-functionalised quinazolinones.

**3.1 C-H Carboxylation/Carboxamidation Towards Quinazolinones**

An important example that demonstrated the applicability of the C-H amidation concept for quinazolinone synthesis was reported by Yu in 2009.44 Palladium (II) catalysed *ortho*-carboxylation of benzanilides with CO was successfully demonstrated on a range of highly functionalised aromatic systems in good to excellent yields (scheme 16). Electron rich aromatic systems were shown to be successful in addition to arenes bearing chloro- and bromo-substituents. Transformation of the functionalised products to afford the corresponding quinazolinones was achieved using PCl3 in the presence of anilines. The cyclisation was shown to be tolerant of both electron donating and electron withdrawing aniline functionalities, achieving the target heterocyclic motif in excellent yields (85 – 96%, **33**-**34**). In addition, benzoxazinone synthesis was demonstrated using the *ortho*-carboxylation products – highlighting the overall utility of this methodology.

In a related study, Zhu described a palladium(II)-catalysed intramolecular C(sp2)-H carboxamidation of *N*-arylamidines to access quinazolinones.45 The reaction exploits *N*-phenylbenzamidines in conjunction with CO, a palladium acetate catalyst and a copper oxide oxidant in acetic acid to afford the heterocyclic scaffold. Whilst a number of examples were demonstrated, only few functional groups were shown to be tolerant to these conditions. The aromatic ring of the quinazolinone could only be substituted with methyl and methoxy groups in the 6-, 7- and 8-positions, whilst the 2-position of the quinazolinone could be substituted by both alkyl and aryl substituents in good to excellent yields. No incorporation of heteroaryl functionalities were demonstrated in this case. Deuterium labelling experiments found C-H palladation *via* formation of intermediate **36** to be a key step in the reaction pathway (scheme 17).

**3.2 C-H Amination/Amidation Towards Quinazolinones**

In 2014, Chiba described a copper-catalysed redox-neutral C-H amination reaction of amidoximes to afford quinazolinones.46 Interestingly, the CuI-catalysed reaction afforded dihydroimidazoles when *N*-alkylamidoximes were used, a process that likely occurs *via* an sp3 C-H amination. Nonetheless, when changing to the alternative *N*-benzoylamidoximes the reaction proceeded via sp2 C-H amination to yield quinazolinones. The reaction was found to be compatible with a range of substituents at the amidoxime aryl group, and at the motif, with electron donating and withdrawing groups all demonstrated to be effective. In addition, this process could also be used to generate *N*-benzyl and *N*-alkyl quinazolinones. The reaction is believed to proceed *via* the formation of an amidinyl radical that undergoes cyclisation onto the benzoyl benzene ring. Not surprisingly therefore, unsymmetrically substituted benzamide groups led to regiosomeric mixtures, although in promising regioselectivities (**44**-**47**). Nonetheless, despite an attractive scope and good to excellent yields, the



Scheme 16. Yu’s Pd-catalysed C-H activation methodology towards quinazolinones

procedure does require high reaction temperatures and extended reaction times.

Recent studies conducted in our laboratory has uncovered an oxazoline-directed, rhodium-catalysed *ortho*-amidation cyclocondensation sequence using trifluoroacetamide that affords functionalised 4-aminoquinazolines, which upon acidic cleavage delivers the corresponding quinazolinones (scheme 19).47 This method boasts a number of benefits including low catalyst loadings and mild reaction temperatures. Furthermore, it is compatible with a range of functionalised aromatic motifs and offers high regioselectivity for mono-amidation products. Subsequent transformation of these motifs with formamidine



Scheme 17. Zhu’s Pd-catalysed intramolecular carboxamidation to quinazolinones

acetate allowed rapid access to the quinazoline scaffold. An excess of oxazoline substrate was found necessary (typically 1.2 to 2.0 equivalents) to avoid unwanted di-amidation occurring. We demonstrated the value of our methodology in target orientated synthesis by preparing the tyrosine kinase inhibitor Erlotinib.1, 48 A close variant of this methodology that exploited cobalt-catalysis was recently disclosed by Ackermann.49 Furthermore, we have recently shown the applicability of our sequence towards the synthesis of an aza-quinazolinone scaffold, by the utilisation of 2-substituted pyridine scaffolds under rhodium-catalysis.50

More recently, benzimines and benzimidates have been employed in conjunction with azides or dioxazolones for the metal-catalysed synthesis of quinazolinones *via* C-H activation. Indeed, near-simultaneous reports by Zhu, Jiao, Glorius and Li all demonstrated the ability of the imine-type directing group to promote a mild intermolecular annulation to generate a range of highly-functionalised quinazolines, which upon hydrolysis can afford the parent quinazolinones (scheme 20).51-54 Zhu’s report utilised rhodium-catalysis in conjunction with dioxazolones as the amine source, and highlighted the successful implementation of a range of functionalised methyl phenylimidates under these reaction conditions. Moreover, a variety of substitution patterns and functional groups were well tolerated, and a range of dioxazolones bearing both aryl and alkyl substituents were accommodated in good to excellent



Scheme 18. Chiba’s Cu-catalyzed *N*-benzoylamidoxime C-H amination

yield.53 Jiao described a similar rhodium-catalysed reaction pathway, however this group utilised alkyl azide sources in place of dioxazolones and they required the use of an a copper co-catalyst.52 Again, a large substrate scope was demonstrated, however in comparison to Zhu’s methodology, the use of this method for the incorporation of alkyl substituents in the 2-position of the products was less successful. Glorius’ report disclosed a reaction between dioxazolones and benzimines/benzimidates to afford quinazoline heterocycles.51 Interestingly, and in contrast to the work demonstrated by Zhu, rhodium-catalysis was found to afford over amidated products, whilst iridium-catalysts was found to be sluggish promoters of this transformation. However, cobalt-based catalyst systems proved to be optimal and delivered a range of heterocycle products. Finally, Li also described a cobalt(III)-catalysed quinazoline synthesis that promoted the reaction between *N*-sulfinylimines and benzimidates, with dioxazolones.54 When *N*-sulfinylimines were employed a AgNTf2 additive was required.



Scheme 19. Harrity’s Rh-catalysed C-H amidation cyclocondensation sequence to quinazolinones

However, AgSbF6 proved to be the promoter of choice when the corresponding benzimidates were used and the reactions proceeded at slightly lower temperatures (100 versus 120 °C). In all of the aforementioned cases, hydrolysis of the primary product (a 4-alkoxyquinazoline) was achieved by treatment with aqueous acid to afford the quinazolinone motif in excellent yields. Overall, the approaches demonstrated in scheme 20 benefit from generally low catalyst loadings and wide substrate scope. At present, the cobalt-catalysed systems suffer from limited commercial availability of the required catalysts. However, the procedures do offer more direct access to the desired heterocycles - and obviate subsequent transformations from the C-H functionalised products as required in the methods reported by Yu and Harrity.

4. Conclusions and Future Directions

Quinazolinones are an important class of heterocycles and can be found as core motifs in a range of medicines and agrichemicals. The synthesis of these important heterocycles has been known since the late 1800’s, but since that time more efficient strategies have been realised with very recent attention paid to the use of catalytic approaches. Milder reaction conditions, larger and more diverse scope are amongst the many benefits that catalysis has provided by encompassing carbonylative, domino, hydrogen transfer and C-H activation/functionalisation processes. In addition, an array of metal catalysts have been found to be effective including those based on precious metals such as palladium, iridium and rhodium, as well as more abundant salts derived from copper



Scheme 20. Zhu, Jiao, Glorius and Li’s benzamine, benzimidate and *N*-sulfinylimine directed C-H aminations towards quinazolinones

and cobalt. Another major improvement derived from these catalytic reactions has been the ability to access simpler starting materials. The application of catalysis in this context, allows the quinazoline scaffold to be constructed from a wide variety of 1,2-disubstituted substrates as well as simpler arenes. Further studies in this area will undoubtedly result in an even wider variety of quinazolinone derivatives to be accessed, using sustainable and atom economic reaction processes.

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