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RECENT ADVANCES IN TRANSITION-METAL-CATALYZED SYNTHESIS OF 3- AND/OR 4-ARYL-2(1H)-QUINOLONES

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Abstract – 2(1H)-Quinolone is a privileged nitrogen heterocycle that is found in various bioactive compounds and functional molecules. In particular, derivatives possessing aryl substituents at the 3- and/or 4-positions are significant synthetic targets as they are promising drug leads. This review surveys the synthetic methods for 3- and/or 4-aryl-2(1H)-quinolones that involve transition-metal-catalyzed construction of the 2(1H)-quinolone framework. Transition-metal-catalyzed arylations of 2(1H)-quinolone scaffolds are also surveyed.

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1. INTRODUCTION

2(1H)-Quinolone (2-quinolone) is a privileged nitrogen heterocyclic motif that is found in various bioactive compounds and functional molecules. In particular, 2-quinolone derivatives possessing aryl substituents at the 3- and/or 4-positions are significant synthetic targets, as they are promising leads for

drugs such as farnesyl transferase inhibitors (e.g., anticancer drug Tipifarnib), maxi-K channel opening relaxants, p38aMAP kinase inhibitors, anticonvulsant agents, and adenosine A_{2B} antagonists (Figure 1).¹⁻⁵ For this reason, efficient synthetic methods for arylated 2-quinolones have been sought. Conventional methods such as the Friedländer-type synthesis are inefficient because they involve multiple synthetic steps, require harsh reaction conditions, and have poor functional group compatibility.⁶ Toward meeting the high demands for mild and efficient access to the 2-quinolone motif, transition-metal-catalyzed synthetic methods are explored continuously.⁷ This review surveys the synthetic methods for 3- and/or 4-aryl-2(1*H*)-quinolones that involve the transition-metal-catalyzed construction of the 2(1*H*)-quinolone framework. Transition-metal-catalyzed arylations of 2(1*H*)-quinolone scaffolds are also surveyed. Examples, in which transition metals are used as nitro reduction catalysts or radical initiators, were excluded.

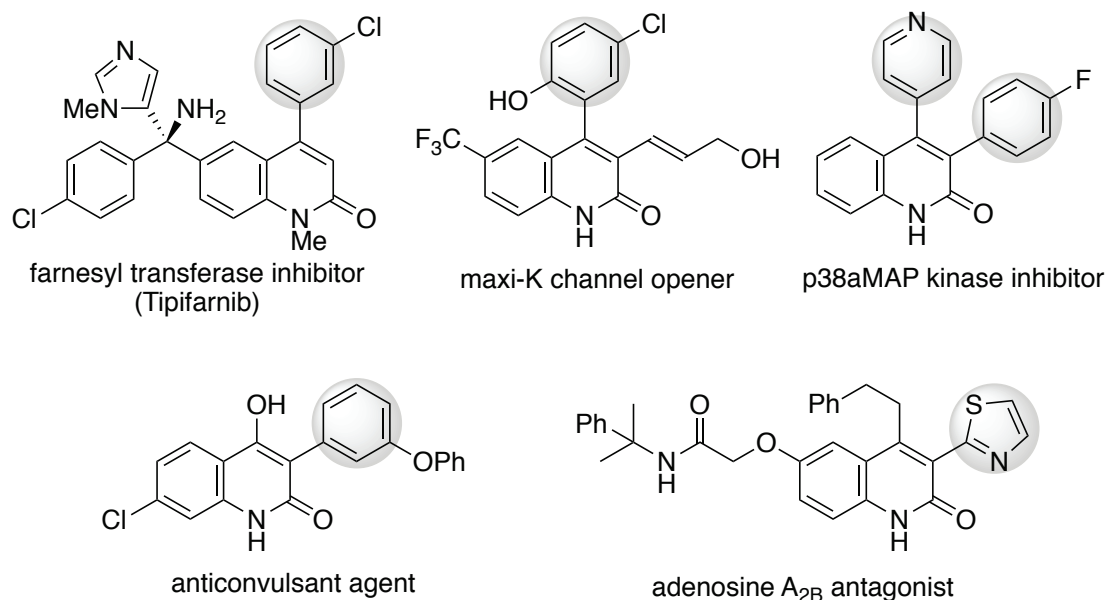


Figure 1. Examples of bioactive arylated 2-quinolones

2. CONSTRUCTION OF 2(1*H*)-QUINOLONE FRAMEWORK

In this section, the synthesis of 3- and/or 4-aryl-2-quinolones *via* the construction of the 2-quinolone framework is surveyed; this section is divided into three major subsections (Figure 2). The first subsection (2-1) surveys synthetic methods that use acrylic acid derivatives as synthons. Synthetic methods that use alkynes and arynes as synthons are discussed in the second subsection (2-2). The third subsection (2-3) surveys synthetic methods that involve cyclocarbonylation using CO or CO₂ as C1 synthons. Other synthetic methods that do not fit into the abovementioned subsections are discussed in subsection 2-4.

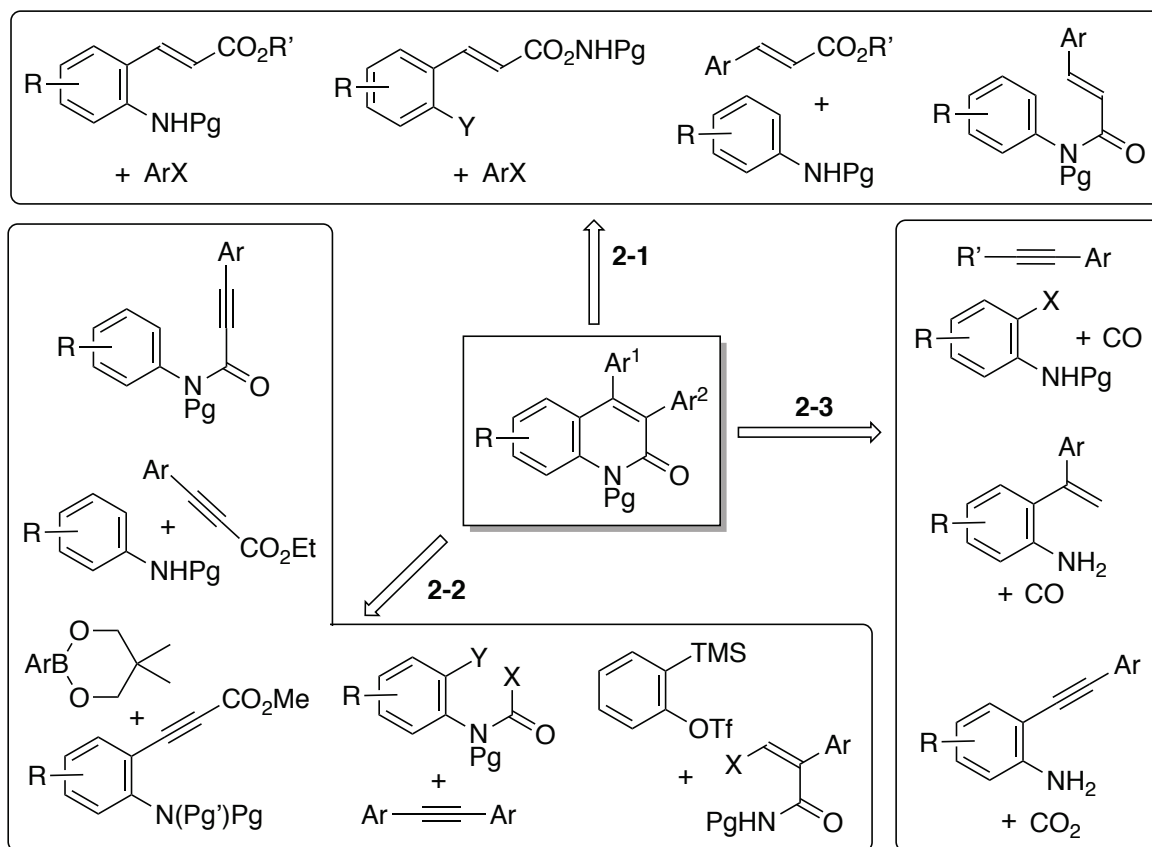
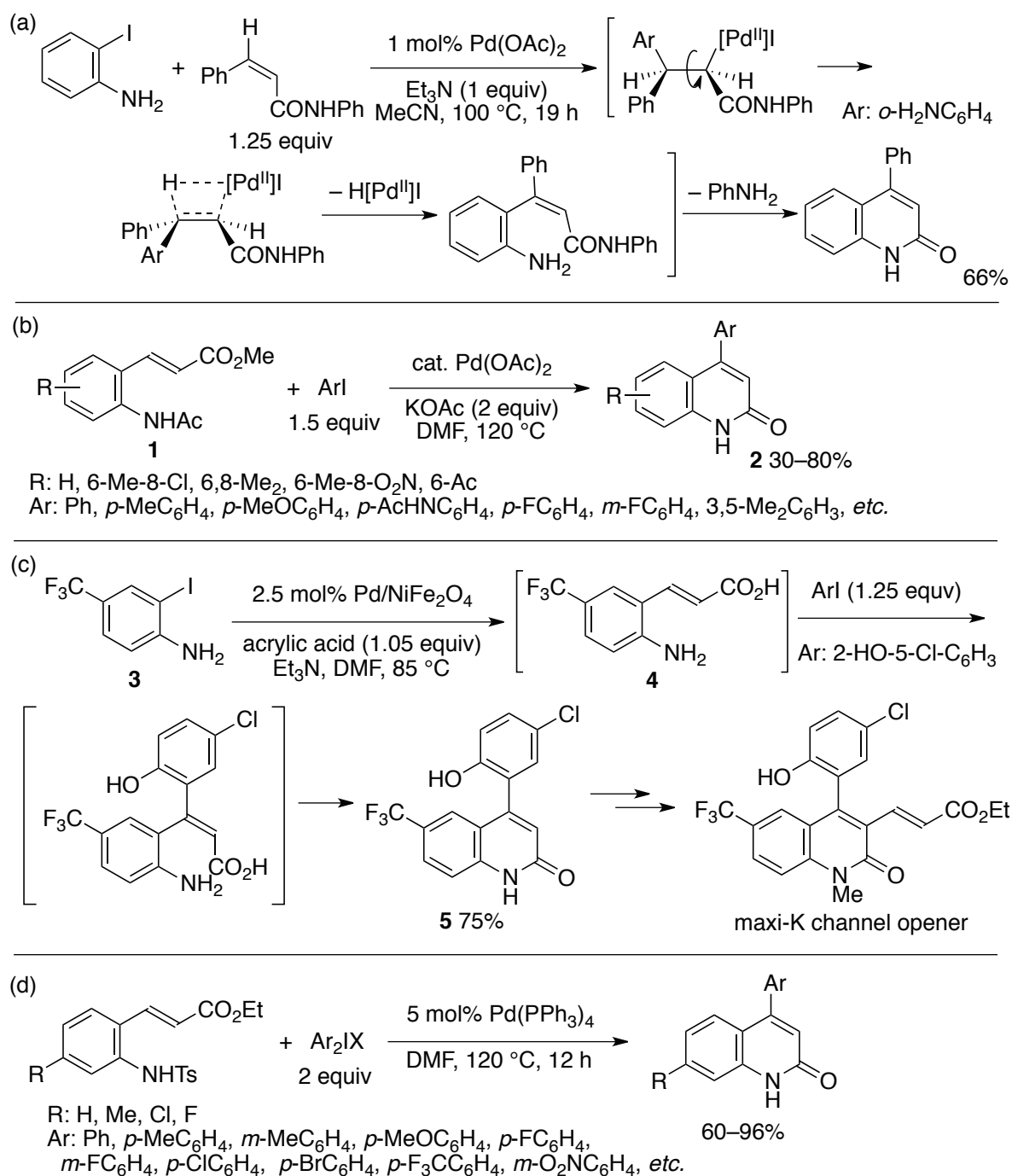


Figure 2. Synthetic methods for 3- and/or 4-aryl-2-quinolones that involve the construction of the 2-quinolone framework

2-1. SYNTHESIS USING ACRYLIC ACID DERIVATIVES

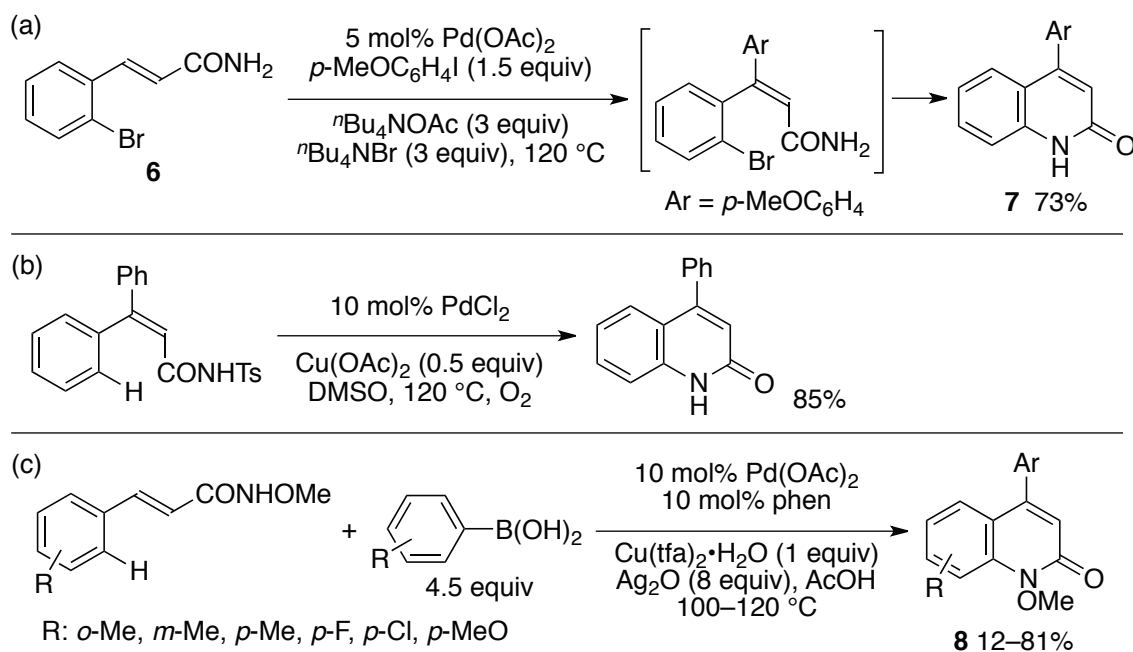
The Mizoroki–Heck (M–H) reaction is a powerful palladium-catalyzed reaction that produces cinnamates *via* dehydrohalogenative cross coupling between aryl halides and acrylates.⁸ One of the oldest examples of 4-aryl-2-quinolone synthesis using transition-metal catalysis was reported by Heck and coworkers in 1978.^{9,10} They observed that domino arylation/lactamization of (*Z*)-*N*-phenylcinnamamide with *o*-iodoaniline in the presence of Pd(OAc)₂ (10 mol%) and Et₃N (1 equiv) in MeCN at 100 °C afforded 4-phenyl-2-quinolone in 66% yield (Scheme 1a). The same product was obtained in a much lower yield (15%) from the (*E*)-cinnamamide substrate, showing the importance of the olefin configuration. In a similar manner, the same quinolone was also obtained in an improved yield (71%) from (*E*)-*o*-aminocinnamic acid and iodobenzene. Later, the domino M–H reaction/lactamization was revisited by Cacchi, Fabrizi, and coworkers in 2006 (Scheme 1b).¹¹ They investigated the synthetic scope by using combinations of *N*-acetyl-protected methyl 3-(*o*-aminophenyl)acrylates **1** and aryl iodides under modified conditions (cat. Pd(OAc)₂, KOAc, *N,N*-dimethylformamide (DMF), 120 °C). 4-Aryl-2-quinolones **2** were obtained in 30–80% yields. After these seminal studies, several improvements were made for the domino process. Das and coworkers reduced the Pd catalyst loadings by utilizing a benzimidazole-based *N*-heterocyclic carbene ligand for the reaction of methyl 3-(*o*-aminophenyl)acrylate with seven aryl

iodides.¹² Borthade and Waghmode achieved a domino double arylation/lactamization process using a Pd/nickel ferrite catalyst (Scheme 1c).¹³ In the presence of 2.5 mol% catalyst, *o*-iodoaniline **3** reacted with acrylic acid to produce the first M–H product **4**, which was then converted into the second M–H reaction/lactamization product **5** without isolation. This process streamlined the synthesis of a maxi-K channel opener. Han, Wan, and coworkers demonstrated that the use of diaryliodonium salts instead of aryl iodides in a similar M–H method enabled the synthesis of various 4-aryl-2-quinolones in good yields under base-free conditions (Scheme 1d).¹⁴



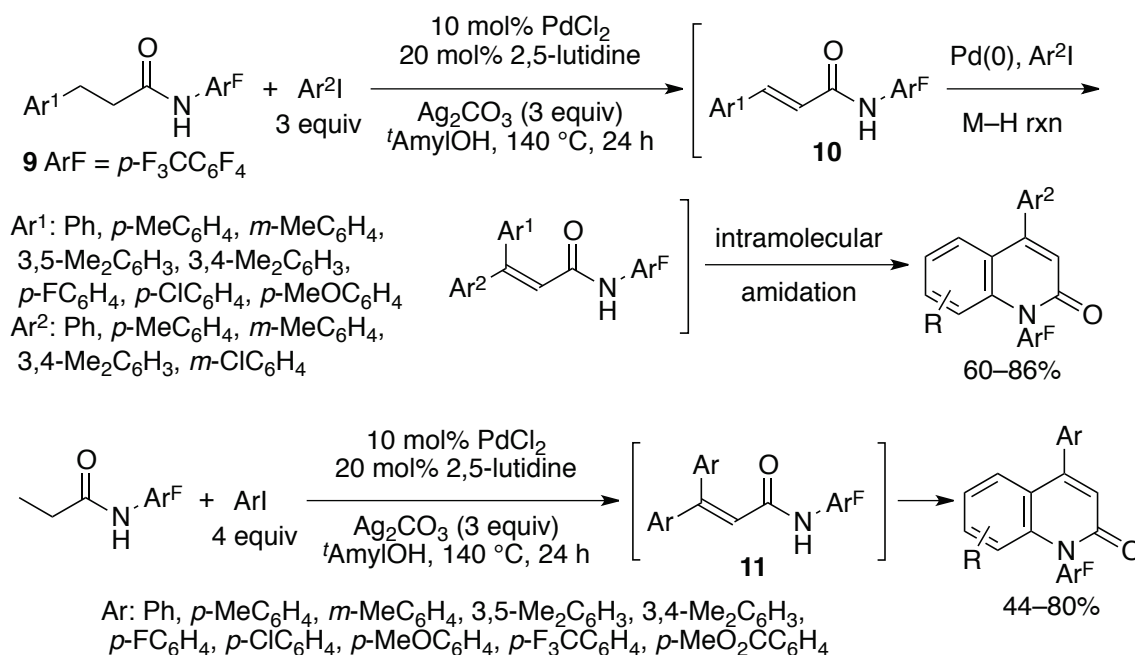
Scheme 1. Synthesis of 4-aryl-2-quinolones *via* Mizoroki–Heck arylation

Cacchi, Fabrizi, and coworkers investigated a sequential process involving the M–H reaction of 3-(*o*-bromophenyl)acrylamide with aryl iodides and subsequent Cu-catalyzed intramolecular C–N bond formation (Ullmann–Goldberg reaction)¹⁵ for 4-aryl-2-quinolone synthesis.¹⁶ Then, the Cacchi group developed a domino M–H/Buchwald–Hartwig¹⁷ process that directly transformed cinnamamide **6** into 4-(*p*-anisyl)-2-quinolone **7** in 73% yield (Scheme 2a).¹⁸ Although this example is interesting because a single palladium catalyst induces both C–C and C–N bond formations, an *o*-bromophenyl moiety must be installed on the substrates in advance. Thus, cyclization of β,β -diarylacrylamides *via* direct C–H amidation was developed by several research groups. Wasa and Yu achieved the Pd-catalyzed aromatic C–H amidation of β,β -diarylacrylamides.¹⁹ Their method requires *N*-alkoxyamides as directing groups and only two examples of 4-phenyl-2-quinolones were synthesized. Later, Inamoto, Doi, and coworkers reported a similar Pd-catalyzed cyclization of β,β -diarylacrylamides (Scheme 2b).²⁰ They found that the reaction of *N*-Ts substrates directly afforded *N*-unprotected 4-aryl-2-quinolones, but harsh conditions were required. This method is compatible with substrates containing both electron-donating and -withdrawing groups on the aryl substituents. The same group also developed a domino oxidative Heck/intramolecular C–H amidation process to obtain 1-methoxy-4-aryl-2-quinolones **8** in a single operation (Scheme 2c).²¹ Cacchi and coworkers also reported a sequential process involving the two-fold M–H reaction and copper-catalyzed intramolecular amidation.²²



Scheme 2. Synthesis of 4-aryl-2-quinolones *via* intramolecular amidation of β,β -diarylacrylamides (phen = 1,10-phenanthroline, tfa = trifluoroacetate)

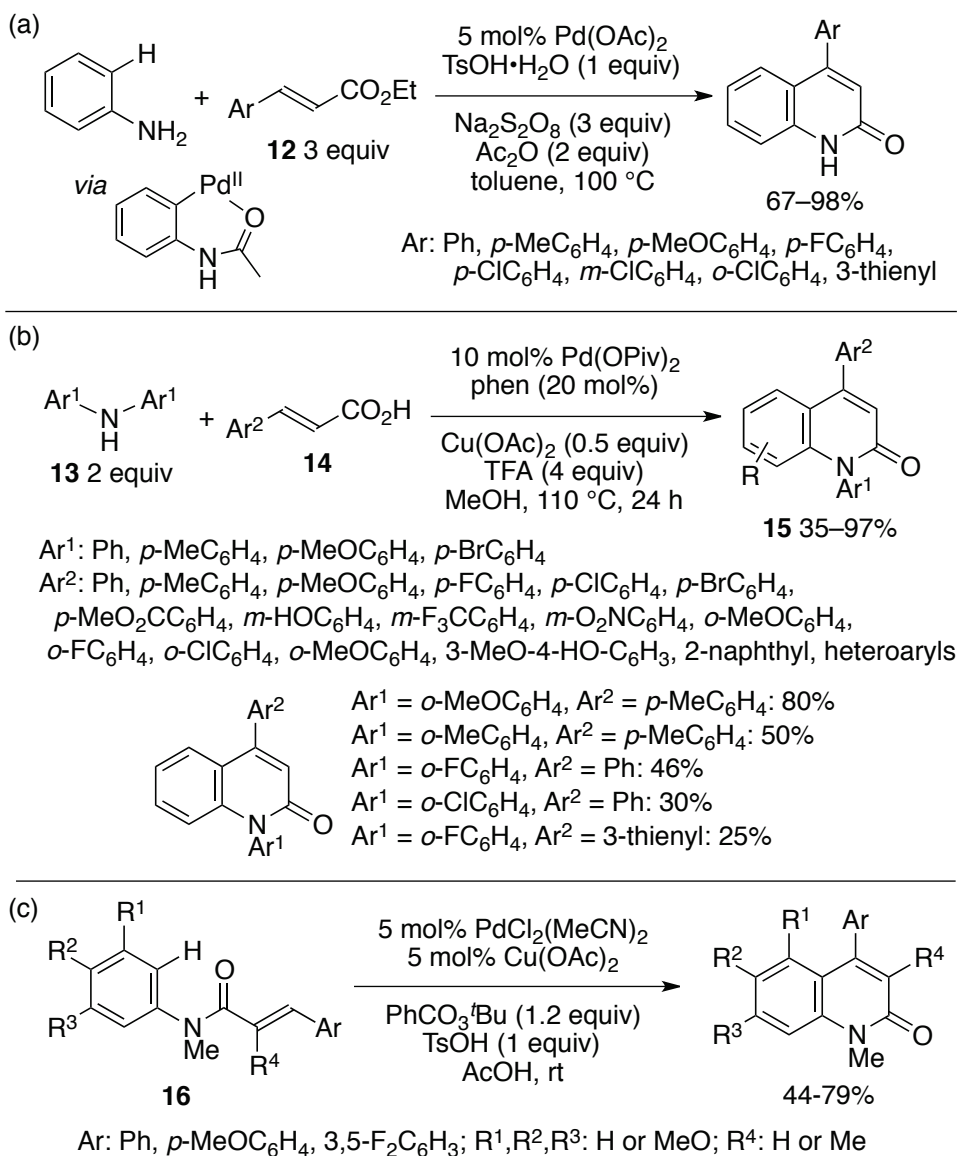
Yu and coworkers achieved an even more complex transformation involving dehydrogenation of 3-arylpropionamides **9** bearing an electron-withdrawing *N*-aryl group (Ar^{F}) and the M–H reaction of resultant acrylamides **10**, and finally intramolecular C–H amidation of β,β -diarylacrylamides (Scheme 3).²³ 2,5-Lutidine was slightly superior to 2,6- and 2,4-lutidines as the ligand. The use of electron-rich *N*-aryl groups instead of Ar^{F} reduced the product yields significantly. When a β -unsubstituted propionamide was used, C(*sp*³)–H arylation, dehydrogenation of the resultant 3-arylpropionamides, and M–H reaction occurred to produce similar 4-aryl-2-quinolones *via* β,β -diarylacrylamide intermediates **11**.



Scheme 3. Synthesis of 4-aryl-2-quinolones *via* dehydrogenation of 3-arylpropionamides, M–H reaction, and intramolecular amidation

The M–H reaction requires aryl halides as arylating agents. In modern organic synthesis, direct transformations of aromatic C–H bonds are sought as greener processes.²⁴ Toward this, dehydrogenative coupling of aniline with β -arylacrylates **12** was achieved using a palladium catalyst under acidic conditions by Liu and coworkers (Scheme 4a).²⁵ In this reaction, acetanilide, which was produced *in situ* from aniline and Ac_2O , underwent amide-directed ortho palladation. Subsequent M–H-type reaction of the resultant arylpalladium species with **12** and lactamization afforded *N*-unsubstituted 4-aryl-2-quinolones with concomitant deacetylation. Maiti and coworkers also developed a 4-aryl-2-quinolone synthesis but from diarylamines **13** and β -arylacrylic acids **14** (Scheme 4b).²⁶ The use of unsymmetrical diarylamines produced regioisomers. However, regioselective formation of *N*-(2-substituted phenyl) products was observed when diphenylamines bearing a 2-substituted phenyl ring were employed. Intramolecular reaction of *N*-phenylacrylamides **16** was also achieved using a

palladium/copper dual catalyst system (Scheme 4c).²⁷ In this case, at least one methoxy substituent is required on the *N*-aryl ring to obtain cyclization products.

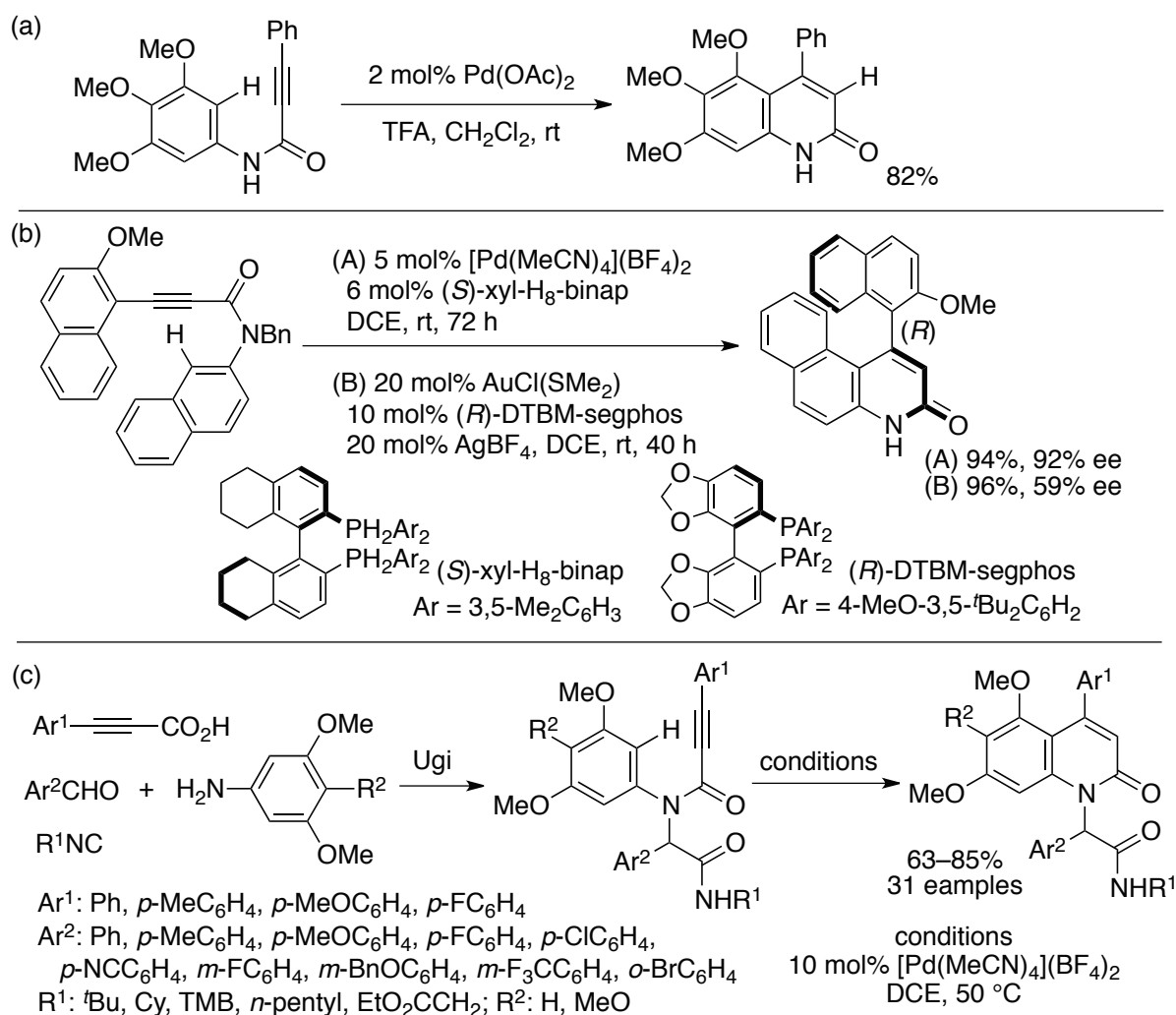


Scheme 4. Synthesis of 4-aryl-2-quinolones *via* ortho C–H olefination of aniline derivatives

2-2. SYNTHESIS USING ALKYNES AND ARYNES

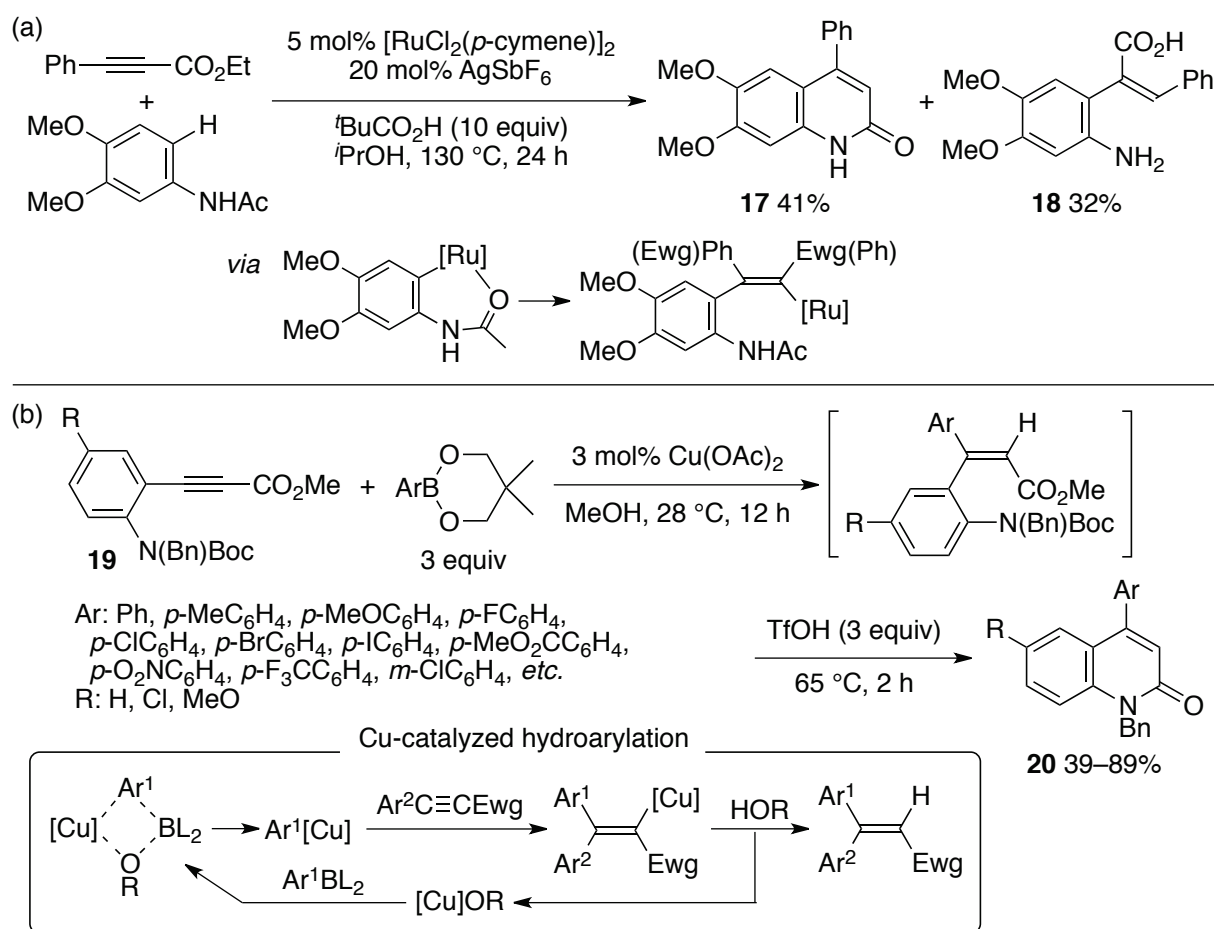
In 2000, Fujiwara and coworkers reported Pd-catalyzed *trans*-hydroarylation of propiolates, which provides direct access to (*E*)-cinnamates.²⁸ Thus, this method can be utilized for the synthesis of 4-aryl-2-quinolones similarly to M–H-type reactions. In fact, the Fujiwara group reported one example of 4-aryl-2-quinolone synthesis *via* intramolecular hydroarylation of an *N*-aryl-3-phenylpropionamide (Scheme 5a).²⁹ This method requires acidic conditions (CF₃CO₂H/CH₂Cl₂) and electron-rich *N*-aryl groups. Since these seminal studies, several different catalytic systems, such as Hf(OTf)₄/ionic liquid solvent, Pd(OAc)₂/PPh₃/AgOAc/PivOH, and [Au(Xphos)(MeCN)]SbF₆/1,2-dichloroethane (DCE), have

been applied for intramolecular hydroarylation; however, the scope of 4-aryl-2-quinolones remains less studied.³⁰⁻³² A significant extension of the intramolecular hydroarylation method was reported by Tanaka and coworkers in 2011. Asymmetric intramolecular hydroarylation of *N*-aryl-3-(2-methoxy-1-naphthyl)propiolamides was achieved using a cationic chiral palladium catalyst.³³ Various axially chiral 4-aryl-2-quinolones were obtained with good enantioselectivities. A cationic gold catalyst was also used but lower enantioselectivities were observed.³⁴ Representative examples are shown in Scheme 5b. Sharma and coworkers introduced the Ugi four-component reaction³⁵ of 3-arylpropionic acids, benzaldehydes, isocyanates, and polymethoxyanilines for the preparation of *N*-aryl-3-phenylpropiolamide substrates (Scheme 5c).³⁶ They used a cationic palladium catalyst for post-Ugi cyclization to obtain various 4-aryl-2-quinolones in 63–85% yields. A similar Ugi/intramolecular hydroarylation sequence was developed using a gold catalyst, but only one example of 4-aryl-2-quinolone synthesis was described.³⁷

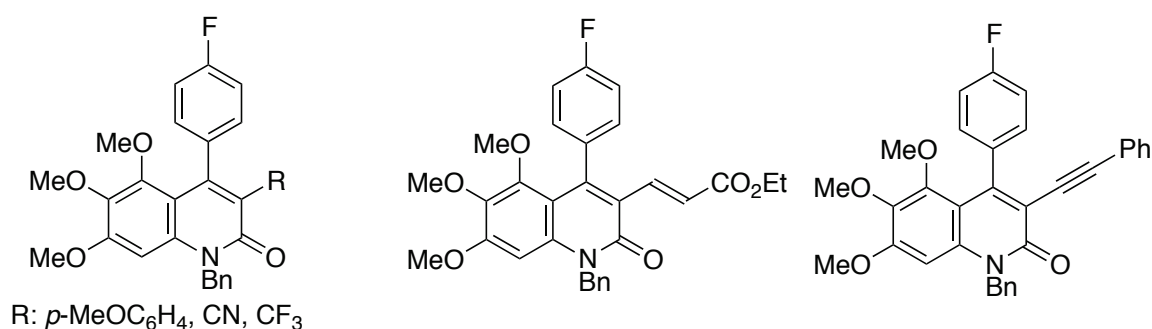
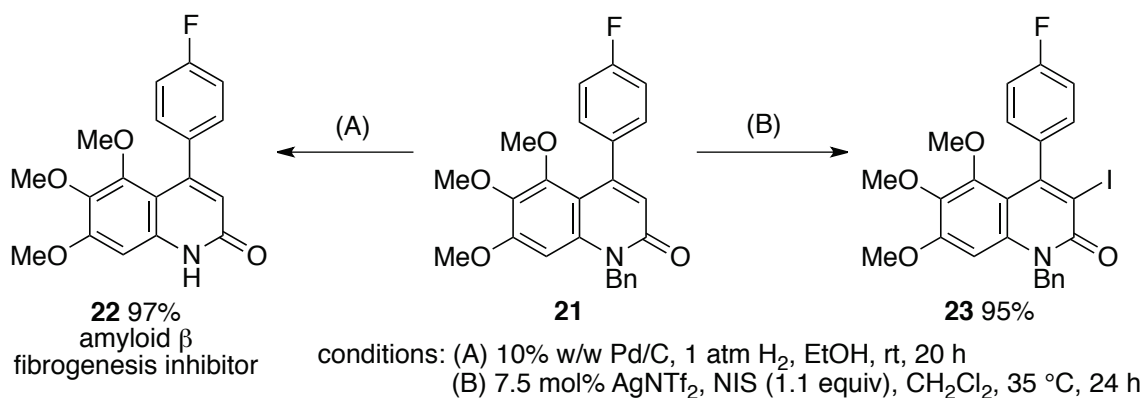


Scheme 5. Synthesis of 4-aryl-2-quinolones *via* intramolecular hydroarylation (TMB = 1,1,3,3-tetramethylbutyl)

Intermolecular hydroarylation *via* directed ortho metalation has been found to be problematic in terms of regioselectivity; it has been reported that the Ru-catalyzed reaction of ethyl 3-phenylpropiolate with 3,4-dimethoxyacetanilide produced the desired 2-quinolone product **17** along with byproduct **18** as a result of unselective hydroarylation (Scheme 6a).³⁸ Formal intermolecular hydroarylations of alkynes with bench-stable arylboron reagents have been developed as efficient and stereoselective approaches to highly substituted alkenes.³⁹ Yamamoto and coworkers developed a one-pot Cu-catalyzed hydroarylation/lactamization using orthogonally *N*-protected 3-(2-aminophenyl)propiolates **19** and various arylboronates (Scheme 6b).⁴⁰ The hydroarylation proceeded at 28 °C under ligand- and additive-free conditions in MeOH, and subsequent acidic removal of the Boc group afforded 1-benzyl-4-aryl-2-quinolones **20** in 39–89% yields. This one-pot method was further applied to the synthesis of polymethoxylated analog **21** featuring a *p*-fluorophenyl substituent at the 4-position (Scheme 7).⁴¹ Hydrogenolysis of the *N*-benzyl group furnished amyloid β fibrogenesis inhibitor **22** in 97% yield. 3-Iodo-2-quinolone **23** was also obtained from **21** in a high yield, and successfully underwent divergent derivatizations *via* various cross couplings at the 3-position.



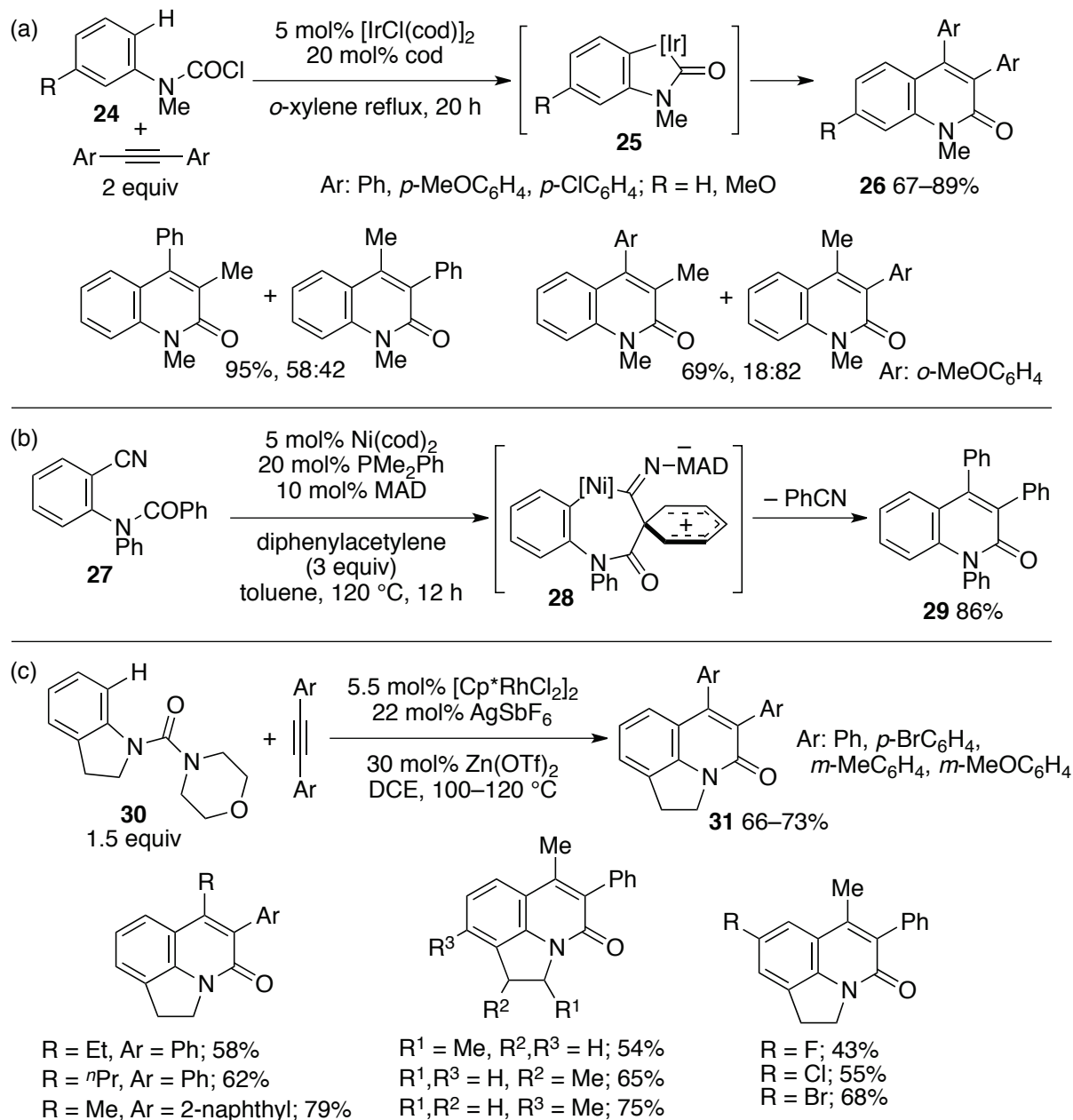
Scheme 6. Synthesis of 4-aryl-2-quinolones *via* intermolecular hydroarylation of 3-arylpropiolates



Scheme 7. Synthesis of polymethoxylated 4-aryl-2-quinolones and derivatizations

Transition-metal-catalyzed annulations of *N*-acylaniline derivatives *via* bond fissions have been reported as straightforward approaches to arylated 2-quinolones. In 2010, Tsuji and coworkers reported that, in the presence of an iridium catalyst, carbamoyl chlorides **24** reacted with diarylalkynes under *o*-xylene reflux, affording 3,4-diaryl-2-quinolones **26** in 67–89% yields (Scheme 8a).⁴² It was proposed that the reaction proceeds *via* five-membered iridacycle intermediates **25**, which are produced through C–H and C–Cl bond fissions. In fact, a related iridacycle was prepared from **24** (R = H) and unambiguously characterized using X-ray crystallography. When unsymmetrical monoaryl alkynes were used, the corresponding products were obtained as regioisomeric mixtures. The Matsubara group reported the Ni-catalyzed reaction of *o*-cyanophenylbenzamide **27** with diphenylacetylene *via* fissions of two C–C bonds, affording 1,3,4-triphenyl-2-quinolone **29** in 86% yield (Scheme 8b).⁴³ An aluminum Lewis acid catalyst (MAD) is required to activate the cyano moiety. The *N*-benzoyl group also plays an important role; the *N*-acetyl derivative failed to give the corresponding product. Therefore, it was proposed that *ipso*-electrophilic attack of the leaving aryl group generates seven-membered nickellacycle intermediate **28**. When 1-pentynylbenzene was used instead of diphenylacetylene, the corresponding product was obtained as a 1:1 regioisomeric mixture. The Loh group used *N*-carbamoyl indoline **30** as the precursor for the synthesis of tricyclic pyrroloquinolones **31** (Scheme 8c).⁴⁴ The combination of a cationic rhodium catalyst and zinc Lewis acid proved to be effective. Notably, the use of unsymmetrical aryl alkyl alkynes resulted in the regioselective formation of the corresponding products, which bear aryl substituents on the

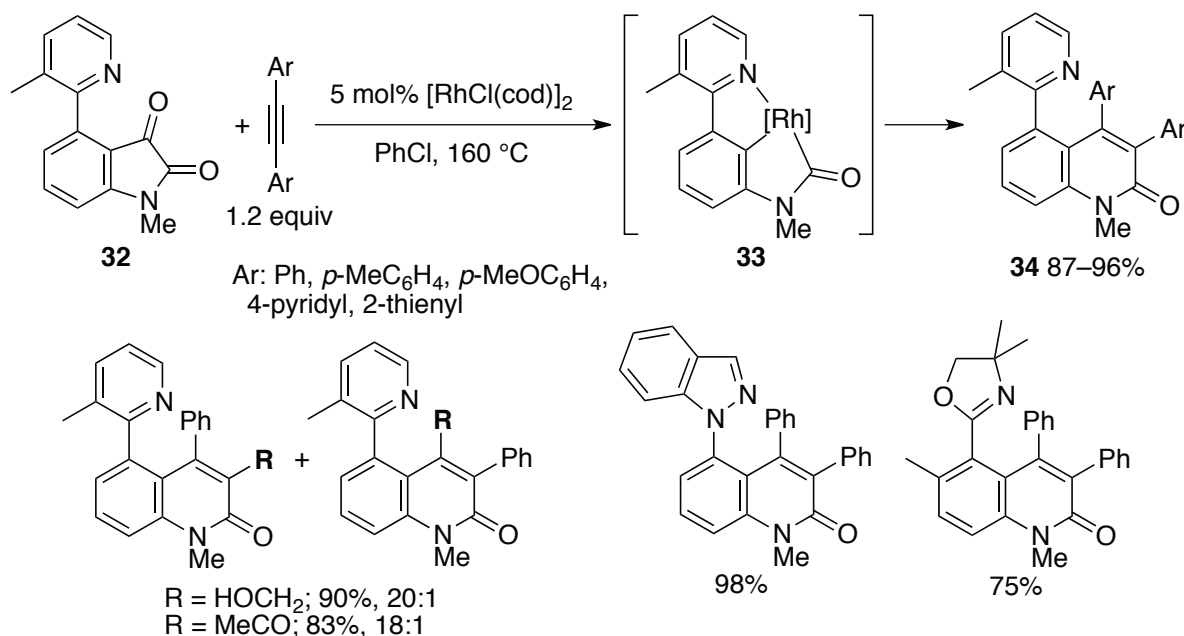
carbon α to the carbonyl group. Moreover, substituents can be introduced at various positions on the pyrroloquinolone framework.



Scheme 8. Synthesis of 3,4-diaryl-2-quinolones *via* annulation of *N*-acylaniline derivatives with diarylalkynes (cod = 1,5-cyclooctadiene, MAD = methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxy))

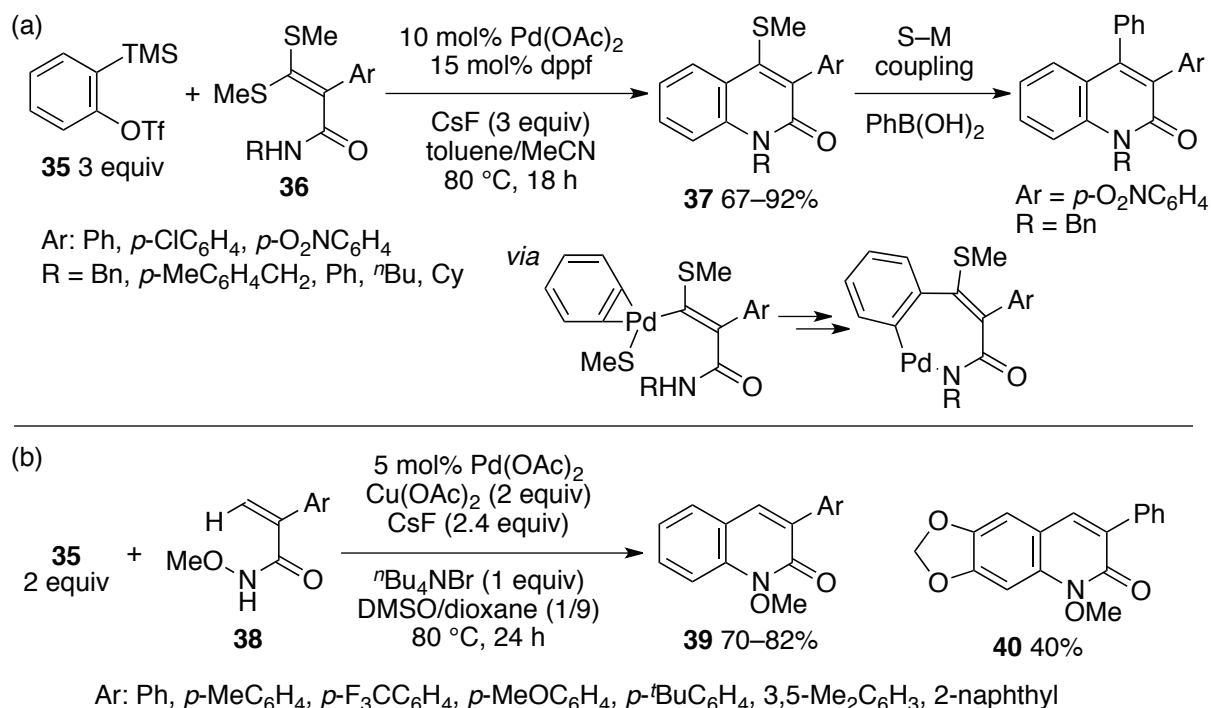
Zeng and Dong obtained 3,4-diaryl-2-quinolones **34** in high yields *via* Rh-catalyzed decarbonylative insertion of diaryl alkynes into isatin derivative **32**, but a pyridyl directing group was required (Scheme 9).⁴⁵ When unsymmetrical aryl alkynes bearing a hydroxyalkyl or ketone moiety on the other terminal carbon were used, the corresponding 4-aryl-2-quinolones were produced with good regioselectivity. As

the directing group, 1*H*-indazol-1-yl and oxazolinyll groups were also effective. Rhodacycle **33** was proposed as the key intermediate based on the preparation of a related rhodacycle from **32**, which was characterized using X-ray crystallography.



Scheme 9. Synthesis of 3,4-diaryl-2-quinolones *via* decarbonylative insertion of diaryl alkynes into isatin derivatives

Transition-metal-catalyzed reactions involving arynes have attracted great attention.⁴⁶ An alternative annulation approach to 2-quinolones has also been investigated using arynes instead of alkynes. Liu, Wang, and coworkers reported that the palladium-catalyzed reaction of α -carbamoyl ketene dithioacetal **36** with benzyne precursor **35** produced 3-aryl-2-methylthio-2-quinolones **37** (Scheme 10a).⁴⁷ They suggested a plausible mechanism involving oxidative addition of **36** with a palladium species bearing an η^2 -benzyne ligand *via* C–S bond fission, extrusion of MeSH, and finally C–N bond-forming reductive elimination. Methyl-, fluoro-, and methoxy-substituted benzynes also participated in this annulation. The methylthio group remaining in **37** can be utilized for Suzuki–Miyaura coupling⁴⁸ with phenylboronic acid. Thus, this method can be combined with various cross couplings to provide efficient access to various 3,4-diaryl-2-quinolones. Ma, Xu, and coworkers reported the annulation of *N*-methoxyacrylamide **38** with benzyne, leading to 3-aryl-2-quinolones **39** in good yields (Scheme 10b).⁴⁹ The use of substituted benzyne precursors reduced the product yields. For example, **40** was obtained in 40% yield. The *N*-methoxy group is necessary for efficient annulation; the reaction of *N*-methyl-2-phenylacrylamide afforded the corresponding product in only 25% yield.

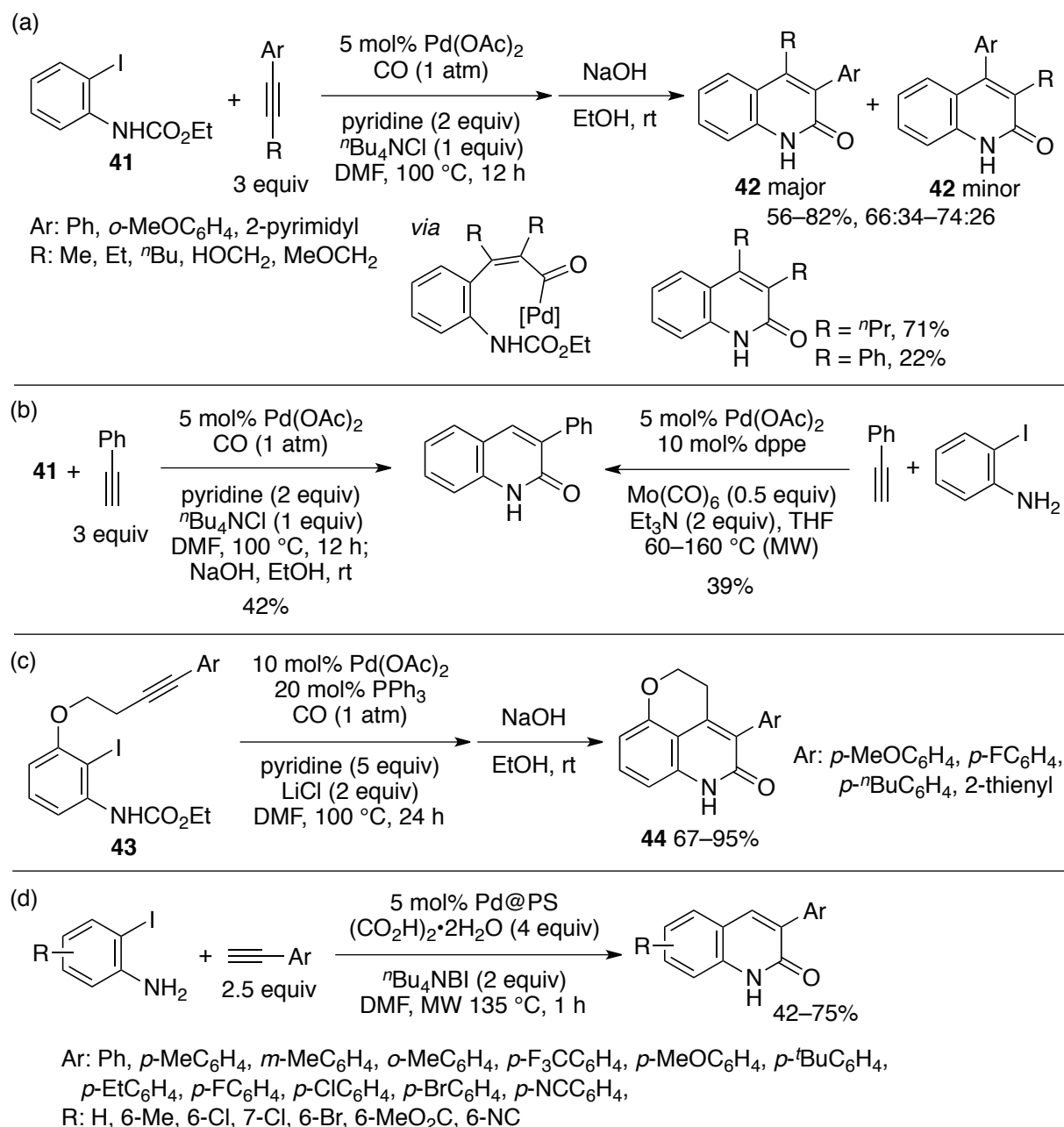


Scheme 10. Synthesis of 3-aryl-2-quinolones *via* annulation of acrylamides with benzynes (dppf = 1,1'-bis(diphenylphosphino)ferrocene)

2-3. SYNTHESIS USING CO AND CO₂

Carbonylative cyclization (cyclocarbonylation) is a powerful approach for the construction of bioactive compounds and natural products containing a carbonyl group.⁵⁰ Naturally, cyclocarbonylation has been employed to construct the 2-quinolone framework. In the pioneering study on Pd-catalyzed carbonylative cyclocoupling, Kadnikov and Larock found that the reaction of ethyl *N*-(2-iodophenyl)carbamate **41** and diphenylacetylene under a CO atmosphere afforded 3,4-diphenyl-2-quinolone in only 22% yield, but 2-quinolones could be obtained efficiently from dialkyl alkynes (Scheme 11a).⁵¹ Moreover, unsymmetrical phenyl alkyl alkynes led to regioisomeric mixtures (**42**), albeit in improved yields. When phenylacetylene was used instead of diphenylacetylene, 3-phenyl-2-quinolone was obtained regioselectively, albeit in a moderate yield (Scheme 11b).⁵² The Pd-catalyzed cyclocarbonylation between *o*-iodoaniline and phenylacetylene was revisited by Xiao and coworkers using Mo(CO)₆ as the CO source with microwave (MW) irradiation (Scheme 11b).⁵³ Although the reaction of 4-methyl-2-iodoaniline selectively afforded the corresponding 3-phenyl-2-quinolone in 73% yield, those of other *o*-iodoanilines gave yields lower than 40%. These seminal reports showed that aryl alkyl alkynes generally afford higher yields than phenylacetylene, but lower regioselectivity. To address the regioselectivity problem in the reactions of unsymmetrical internal alkynes, Jia and coworkers investigated intramolecular cyclocarbonylation using *o*-iodoanilines with a tethered alkyne (Scheme 11c).⁵⁴ Thus, 2-iodoaniline **43** was subjected to Pd-catalyzed carbonylation conditions, affording 4,5-fused 3-aryl-2-quinolones **44** in

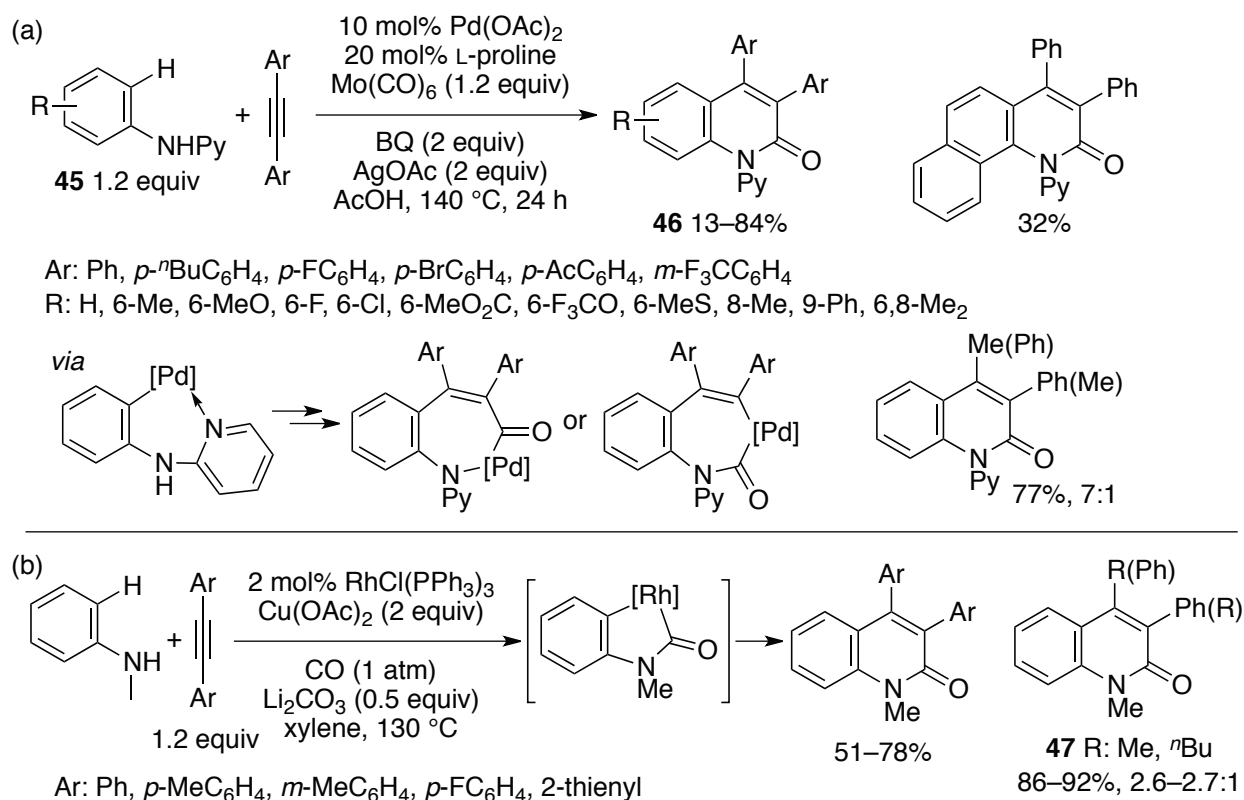
67–95% yields after the removal of the *N*-ethoxycarbonyl group. Cyclocarbonylation of *o*-iodoanilines with terminal aryl alkynes was improved using a supported Pd-nanoparticle catalyst and $(\text{CO}_2\text{H})_2 \cdot 2\text{H}_2\text{O}$ as the CO source (Scheme 11d).⁵⁵ Nineteen examples of 3-aryl-2-quinolones were obtained in 42–75% yield. This protocol is compatible with reactive moieties such as esters, nitriles, and aryl halides. Moreover, the catalyst can be recycled up to four times.



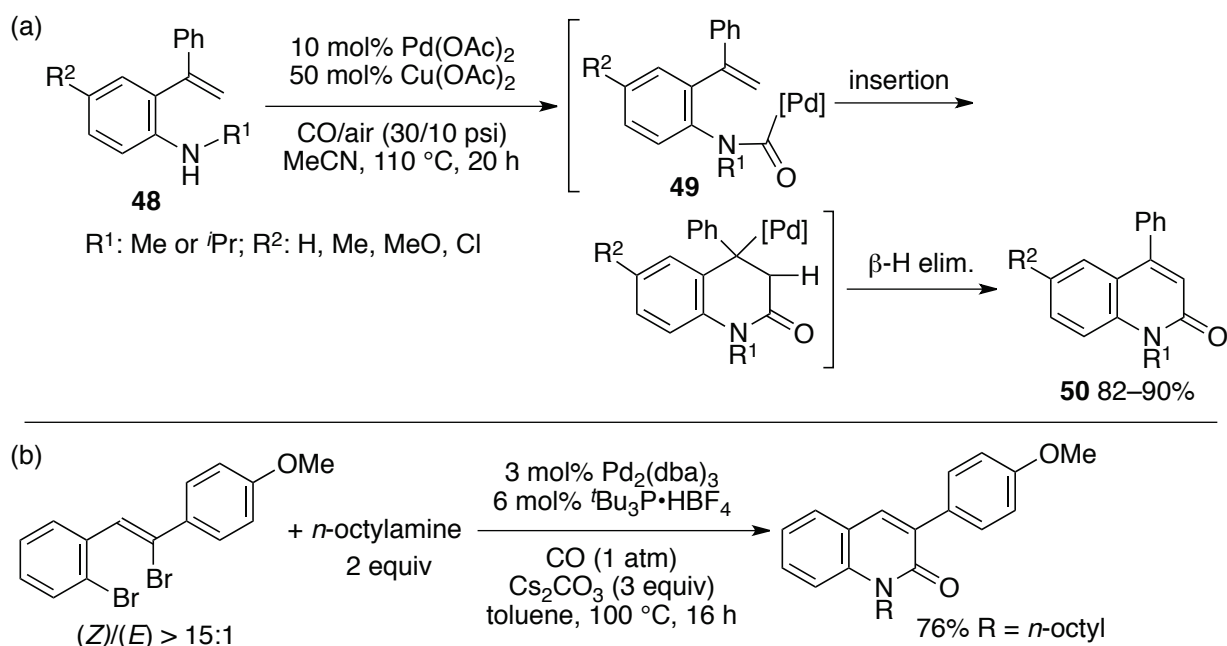
Scheme 11. Cyclocarbonylation of *o*-iodoanilines with alkynes leading to 3-aryl-2-quinolones

Larock-type cyclocarbonylation requires *o*-iodoanilines as the aromatic precursors. Wu and coworkers developed a more atom-efficient method by utilizing pyridine-directed ortho C–H activation, eliminating the need for *o*-iodoanilines.⁵⁶ They used *N*-phenyl-2-aminopyridines **45** for the cyclocarbonylation with

diaryl alkynes using a Pd/L-proline catalyst and Mo(CO)₆ as the CO source (Scheme 12a). A variety of 3,4-diaryl-2-quinolones was obtained in various yields. The use of 1-propynylbenzene afforded 1-(2-pyridyl)-3-phenyl-4-methyl-2-quinolone in 77% yield with 7:1 regioselectivity. Jiao and coworkers achieved a similar cyclocarbonylation of *N*-methylaniline with aryl alkynes using Wilkinson's catalyst (Scheme 12b).⁵⁷ In contrast to Wu's protocol, no directing group is necessary. When 1-alkynylbenzenes were used, 3-phenyl-4-alkyl-2-quinolones **47** were obtained in high yields with selectivities of 2.6:1 to 2.7:1. Alper and coworkers developed a different cyclocarbonylation of 2-vinylanilines **48** (Scheme 13).⁵⁸ In the presence of catalytic amounts of Pd(OAc)₂ and Cu(OAc)₂, **48** underwent cyclocarbonylation under a CO/air (30/10 psi) atmosphere to afford 4-phenyl-2-quinolones **50** in high yields. When R² = H, both *N*-methyl and *N*-isopropyl groups were compatible. However, no product was obtained when R² was a methoxy group. It was proposed that cyclocarbonylation proceeds *via* carbamoylpalladium species **49**, which undergoes Heck-type C–C bond formation with the 2-vinyl substituent rather than vinylic C–H activation. In 1979, Ban and coworkers reported that cyclocarbonylation of *o*-(2-bromovinyl)acetanilide produced 2-quinolone.⁵⁹ In this example, the (*Z*)-configuration of the bromostyrene moiety was highly important. Later, a Pd-catalyzed aminocarbonylation of (*Z*)-1-bromo-2-(2-bromovinyl)benzenes with primary amines leading to 2-quinolones was reported by Willis and coworkers, but only one example of 3-aryl-2-quinolone synthesis was described (Scheme 13b).⁶⁰

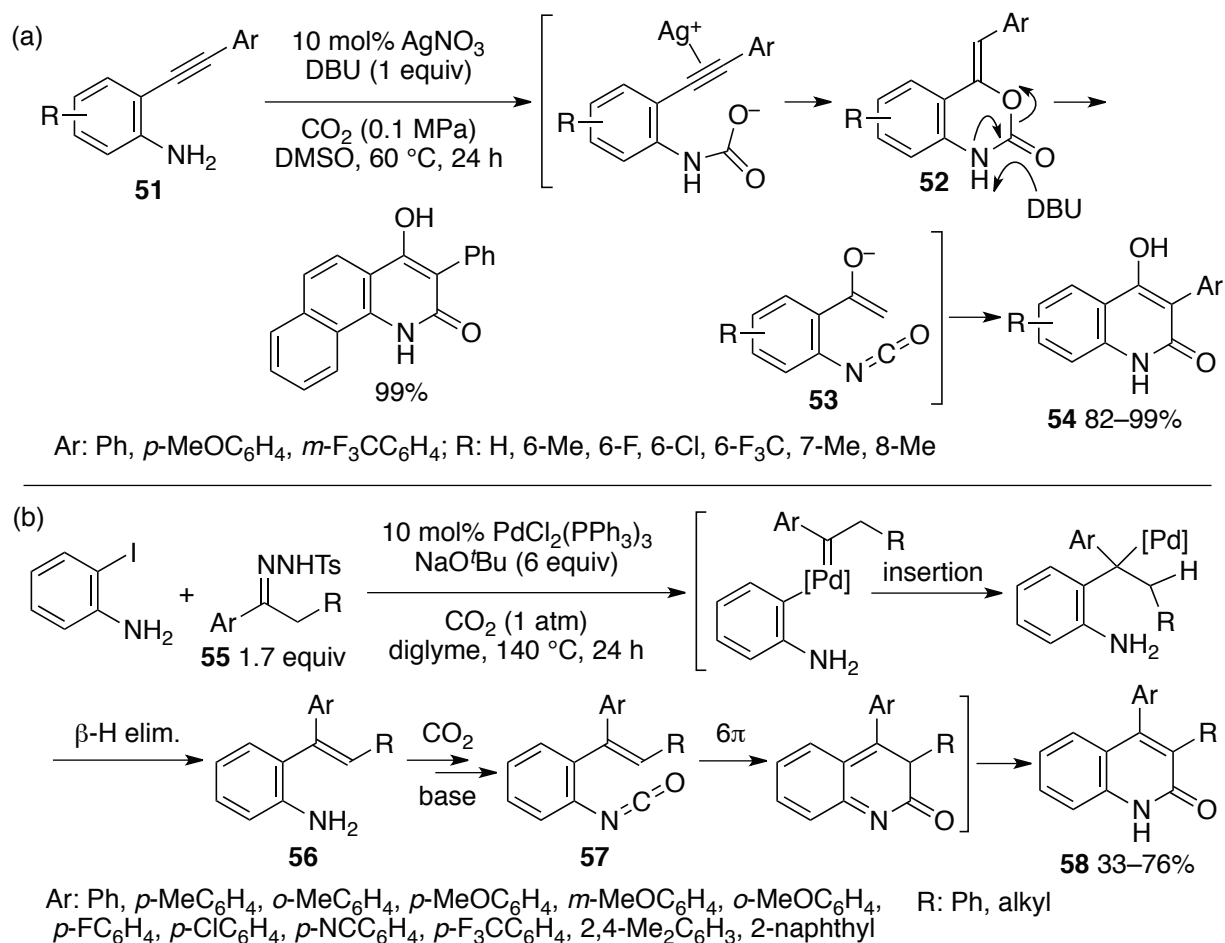


Scheme 12. Cyclocarbonylation of aniline derivatives (BQ = benzoquinone)



Scheme 13. Cyclocarbonylation of styrene derivatives

CO is a harmful gas and special equipment is required for its safety use, especially in laboratory settings. Accordingly, the development of technologies that enables the use of carbon dioxide as a CO surrogate is a highly important research objective. Yamada and coworkers reported a Ag-catalyzed synthesis of 3-aryl-4-hydroxy-2-quinolones **54** from *o*-alkynylanilines **51** and CO₂ (Scheme 14a).⁶¹ It was proposed that this reaction proceeds *via* 4-benzylidenebenzoxazin-2-one intermediates **52**. Its deprotonation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) generates enolates **53** with a pendant isocyanate moiety, which undergo ring closure to afford quinolones **54**. A similar Cu-catalyzed transformation was reported by Zhang and coworkers.⁶² A three-component reaction between *o*-iodoaniline, *N*-tosylhydrazones **55**, and CO₂ was achieved using a palladium catalyst by Cheng and coworkers (Scheme 14b).⁶³ On the basis of control experiments, it was suggested that Pd-catalyzed coupling of *o*-iodoaniline with diazo compounds derived from **55** initially generates *o*-vinylaniline intermediates **56**, which are converted into isocyanates **57** through a reaction with CO₂ and a base. Finally, electrocyclicization of **57** followed by a 1,5-H shift affords 4-aryl-2-quinolones **58**. Substituted *o*-iodoanilines could also be used in this method.

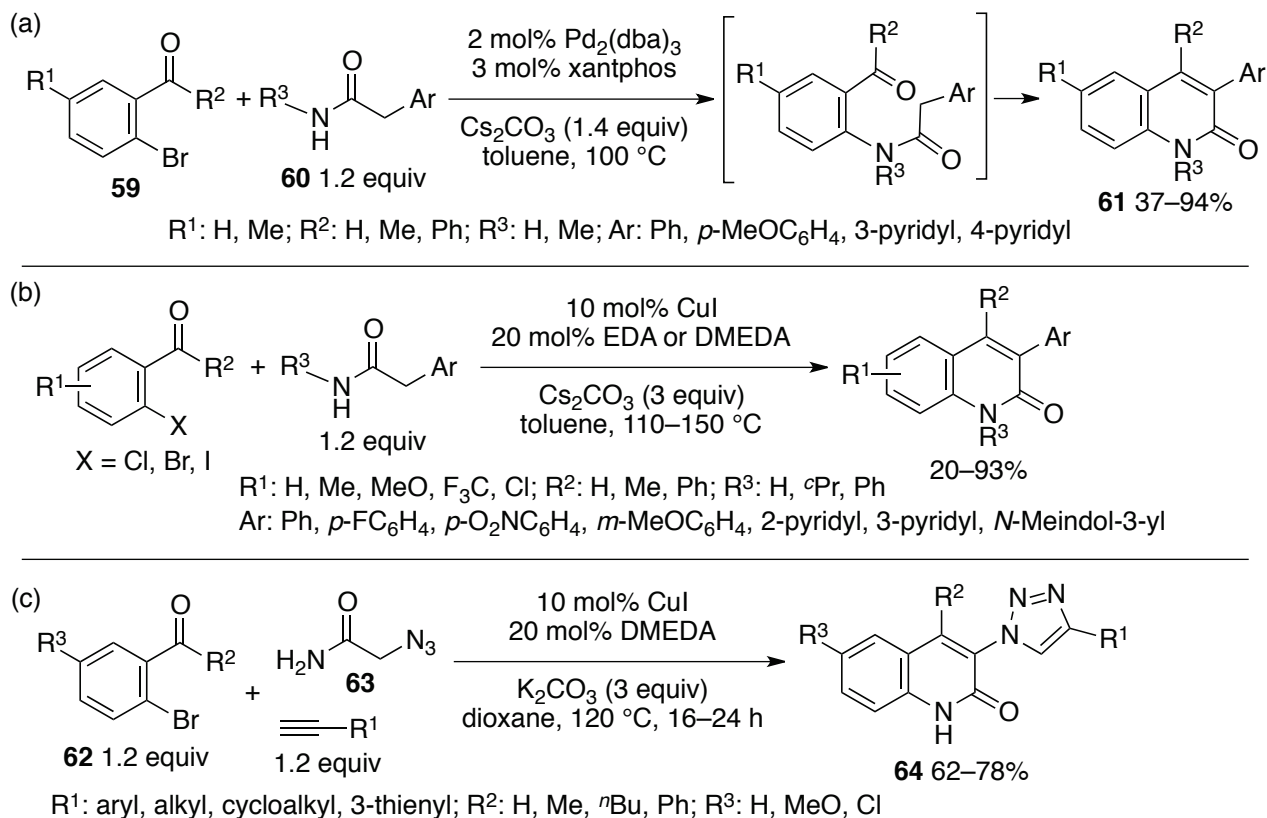


Scheme 14. Cyclocarbonylation of aniline derivatives using CO₂ as a CO surrogate

2-4. MISCELLANEOUS METHODS

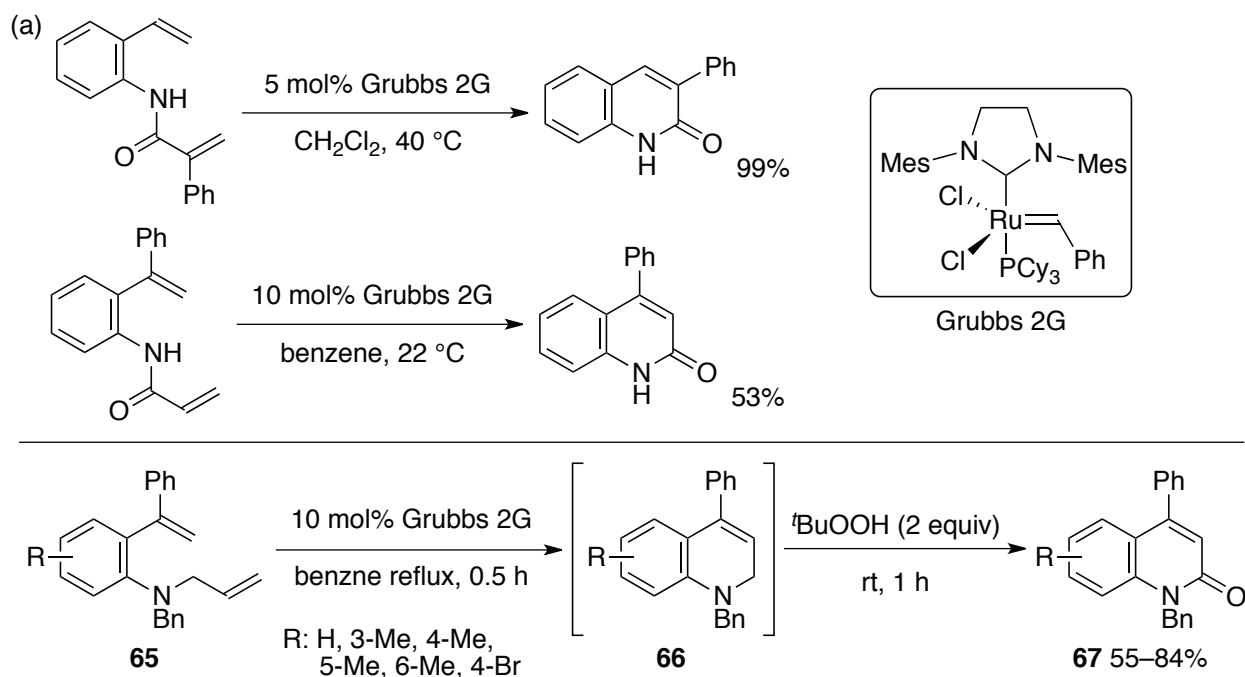
The Friedländer-type synthesis, condensation of anilines bearing an ortho carbonyl group with enolizable acids or esters, is one of the most general methods for the preparation of quinolines and quinolones.⁶ However, this method is not always efficient and selective and, thus, better methods have been developed. Manley and Bilodeau reported the Pd-catalyzed coupling of bromobenzenes **59** bearing an ortho carbonyl group with α -arylacetylacetamides **60**, affording 3-aryl-2-quinolones **61** (Scheme 15a).⁶⁴ This annulation proceeds *via* Buchwald–Hartwig amidation and subsequent Camps cyclization.⁶⁵ Notably, pyridyl moieties were compatible with this method. This method was applied to the synthesis of biologically active *N*-hydroxyquinolones.⁶⁶ The same group also briefly investigated Cu-catalyzed conditions. Because copper catalysts are less expensive and more abundant than palladium catalysts, Cu-catalyzed coupling was later revisited by Ding and coworkers.⁶⁷ They used a simple catalyst system (CuI/ethylenediamine (EDA) or *N,N'*-dimethylethylenediamine (DMEDA)) for various combinations of aryl halides and α -arylacetylacetamides to obtain a variety of 3-aryl-2-quinolones (Scheme 15b). Later, copper catalysis was extended to the three-component coupling of *o*-bromophenyl ketones or aldehydes **62**,

α -azidoacetamide **63**, and terminal alkynes by Qian and coworkers (Scheme 15c).⁶⁸ Notably, the copper catalyst promoted both azide–alkyne cycloaddition⁶⁹ and the subsequent Ullmann–Goldberg amidation.



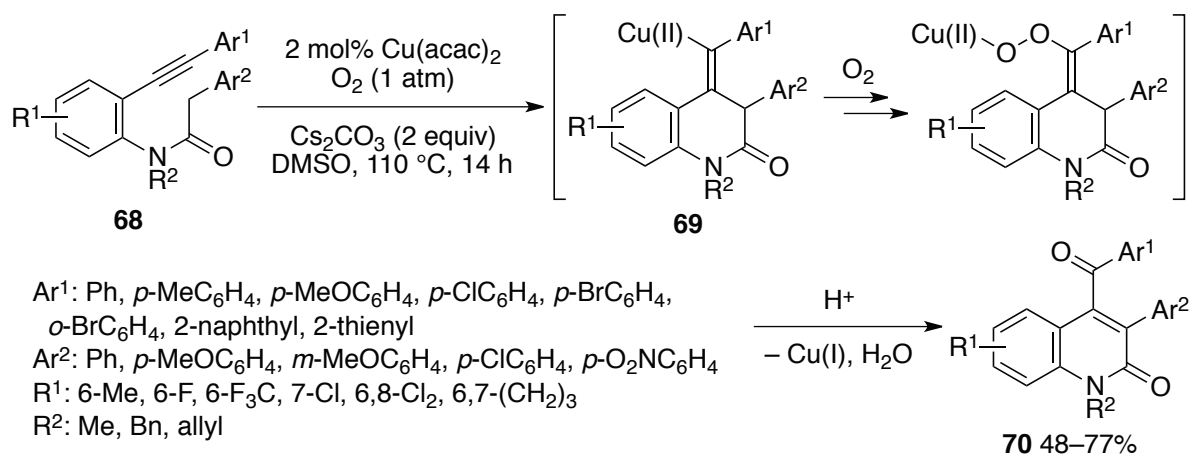
Scheme 15. Synthesis of 3-aryl-2-quinolones *via* domino Cu-catalyzed amidation/Camps cyclization

Ring-closing metathesis (RCM) enables the construction of heterocyclic frameworks *via* late-stage C–C double bond formation.⁷⁰ 2-Quinolones have been synthesized through the formation of the C3–C4 double bond *via* RCM of *N*-(2-vinylphenyl)acrylamides.⁷¹ The syntheses of 3- and 4-phenyl-2-quinolone using this strategy were described by Sturino and coworkers (Scheme 16a).⁷² In their study, 3-phenyl-2-quinolone was obtained quantitatively using Grubbs 2G catalyst (5 mol%) in CH₂Cl₂ at 40 °C, while 4-phenyl-2-quinolone was obtained in a lower yield (53%) even with a higher catalyst loading (10 mol%). Later, Arisawa, Shuto, and coworkers developed an improved two-step method for the synthesis of 4-phenyl-2-quinolones (Scheme 16b).⁷³ They conducted the RCM of *N*-allyl-2-vinylanilines **65** using Grubbs 2G catalyst (10 mol%) under benzene reflux and the resultant 1,2-dihydroquinoline intermediates **66** were subsequently subjected to oxidation conditions in the same pot. In the end, 4-phenyl-2-quinolones **67** were obtained in 55–84% yields over two steps.



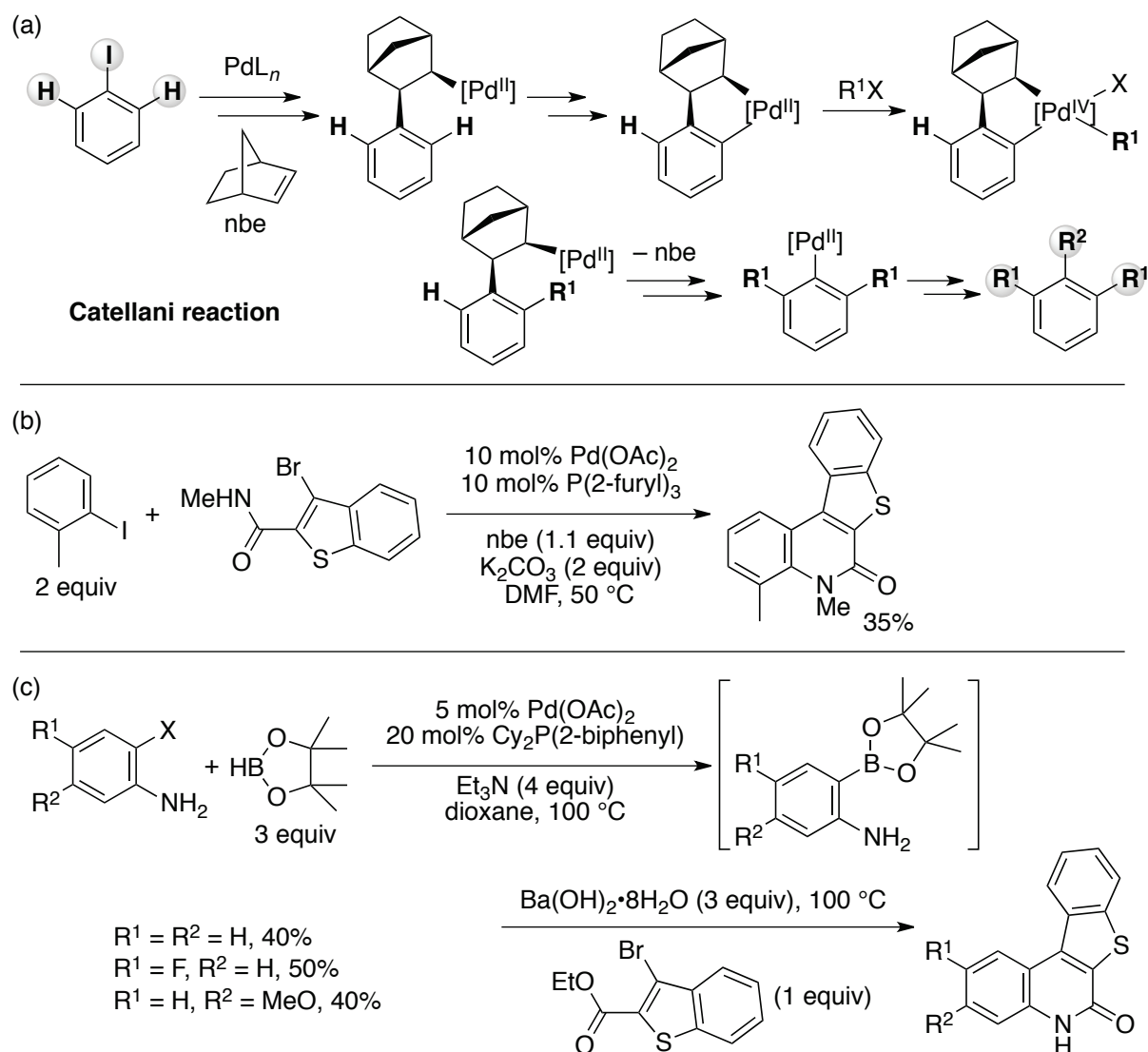
Scheme 16. Synthesis of 3- and 4-phenyl-2-quinolones *via* RCM

Cu-Catalyzed aerobic oxidative cyclization of *N*-(2-alkynylphenyl)-2-arylamides **68** was developed by Li and coworkers (Scheme 17).⁷⁴ It was proposed that this reaction begins with the anti addition of Cu(II) C-enolates to the alkyne triple bond to generate vinyl Cu(II) intermediates **69**. Subsequent aerobic oxidation finally afforded 3-aryl-4-acyl-2-quinolones **70** in 48–77% yields. This method is remarkable, as it produces functionalized 2-quinolones in an aerobic oxidative fashion. Pd-Catalyzed oxidative cyclization of *N*-(2-formylaryl)alkynamides leading to 3-acyl-2-quinolones has also been reported, but only one example of a 3-acyl-4-aryl-2-quinolone was described.⁷⁵



Scheme 17. Synthesis of 3-aryl-4-acyl-2-quinolones *via* aerobic oxidative cyclization

Benzothieno[2,3-*c*]quinolin-6(5*H*)-ones, which contain the 4-aryl-2-quinolone moiety, have been synthesized *via* Pd/norbornene-mediated multi-component coupling (Catellani reaction, Scheme 18a,b)^{76,77} and *via* Pd-catalyzed domino borylation/Suzuki–Miyaura coupling/lactamization (Scheme 18c).⁷⁸ These methods are interesting, as they enable multiple bond formations in one pot.



Scheme 18. Synthesis of benzothieno[2,3-*c*]quinolin-6(5*H*)-ones

3. ARYLATION OF 2(1*H*)-QUINOLONE SCAFFOLD

Thus far, the syntheses of 3- and/or 4-aryl-2-quinolones *via* the construction of the 2-quinolone framework have been discussed. In this section, arylations of 2-quinolone scaffolds are surveyed. Transition-metal-catalyzed cross couplings have been utilized for the syntheses of heterocycles.⁷⁹ Pd-Catalyzed cross couplings have been utilized for quinoline derivatization.⁸⁰ Thus, the first subsection (3-1) is dedicated to arylation methods that use transition-metal-catalyzed cross couplings with

prefunctionalized 2-quinolones. C–H arylations of 2-quinolones at the 3- or 4-positions are surveyed in the second subsection (3-2).

3-1. CROSS COUPLING OF PRE-FUNCTIONALIZED 2(1H)-QUINOLONES

Because 3- and/or 4-aryl-2-quinolones have been found to show diverse biological activities, as mentioned in the Introduction, divergent arylative transformations of the 2-quinolone scaffold have significant impacts on drug discovery. Along this line of thought, the Wu group developed various cross coupling protocols toward building a quinolone-based combinatorial library (Figure 3). To this end, they utilized readily available 4-hydroxy-2-quinolone **71** as the starting point since the 4-hydroxy group can be readily transformed into sulfonate leaving groups. Although aryl triflates have been used for cross coupling reactions, tosylate **72**, which is easier to handle and less expensive than the corresponding triflate, was selected as the coupling scaffold at the reaction development stage.⁸¹ The Wu group established cross coupling protocols for **72** such as Ni-catalyzed coupling with arylzinc reagents,⁸¹ Pd-catalyzed coupling with potassium aryltrifluoroborates,⁸² and Rh-catalyzed coupling with potassium aryltrifluoroborates.^{83,84} The same group prepared **73a** in two steps from **71** and used it in various coupling methods.⁸⁵ They identified two sets of reaction conditions for the cross coupling of **73a** with arylboronic acids; reactions with 1.1 equiv of the boronic acids at room temperature selectively afforded 4-aryl-3-bromo-2-quinolones **74**, while those with 3 equiv of the boronic acids at 60 °C resulted in diarylation. Thus, 2-quinolones bearing different aryl groups at the 3- and 4-positions could be prepared through sequential arylations of **73a**. Moreover, other Pd-catalyzed couplings such as the Buchwald–Hartwig amination and the M–H reaction can also be applied to the C–Br bond at the 3-position of **74**, enabling the diversification of 2-quinolone scaffold **73a**.⁸⁶ In addition, Sonogashira coupling of **74** with *o*-ethynylaniline and subsequent Cu-mediated cyclization afforded 3-(indol-2-yl)-2-quinolones **75**.⁸⁷ In contrast to **73a**, quinolone scaffold **73b** with a tosylate at the 4-position underwent selective arylation with arylboronic acids under Pd catalysis, affording 3-aryl-2-quinolones with the TsO group intact.⁸⁸ The subsequent arylation at the 4-position was conducted using a Pd(OAc)₂/SPhos catalyst system. Solid-phase Suzuki–Miyaura coupling was also developed using a 4-tosyloxy-2-quinolone scaffold bound to a resin at the 1-position.⁸⁹ Inamoto, Doi, and coworkers reported that an *N*-heterocyclic-carbene-derived pincer nickel complex proved to be efficient for the Suzuki–Miyaura coupling of **72**.⁹⁰

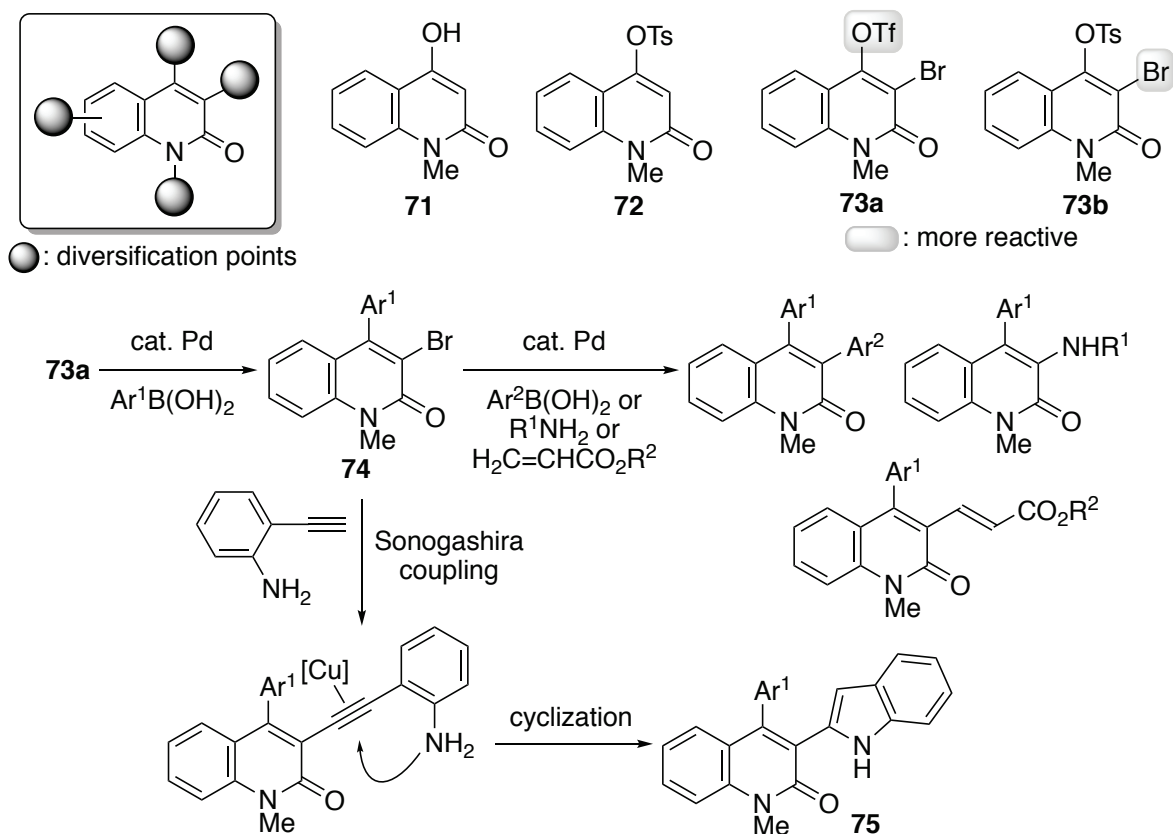
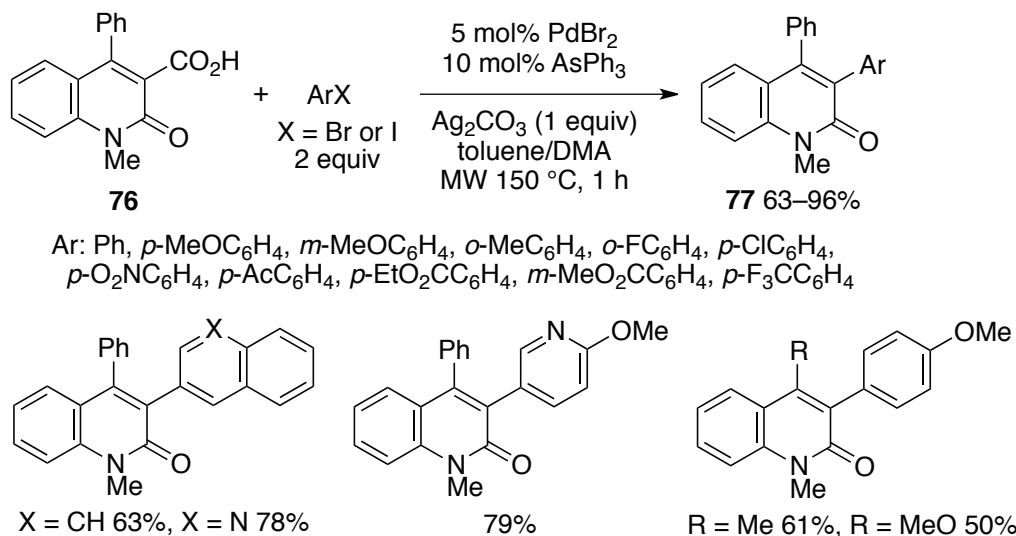


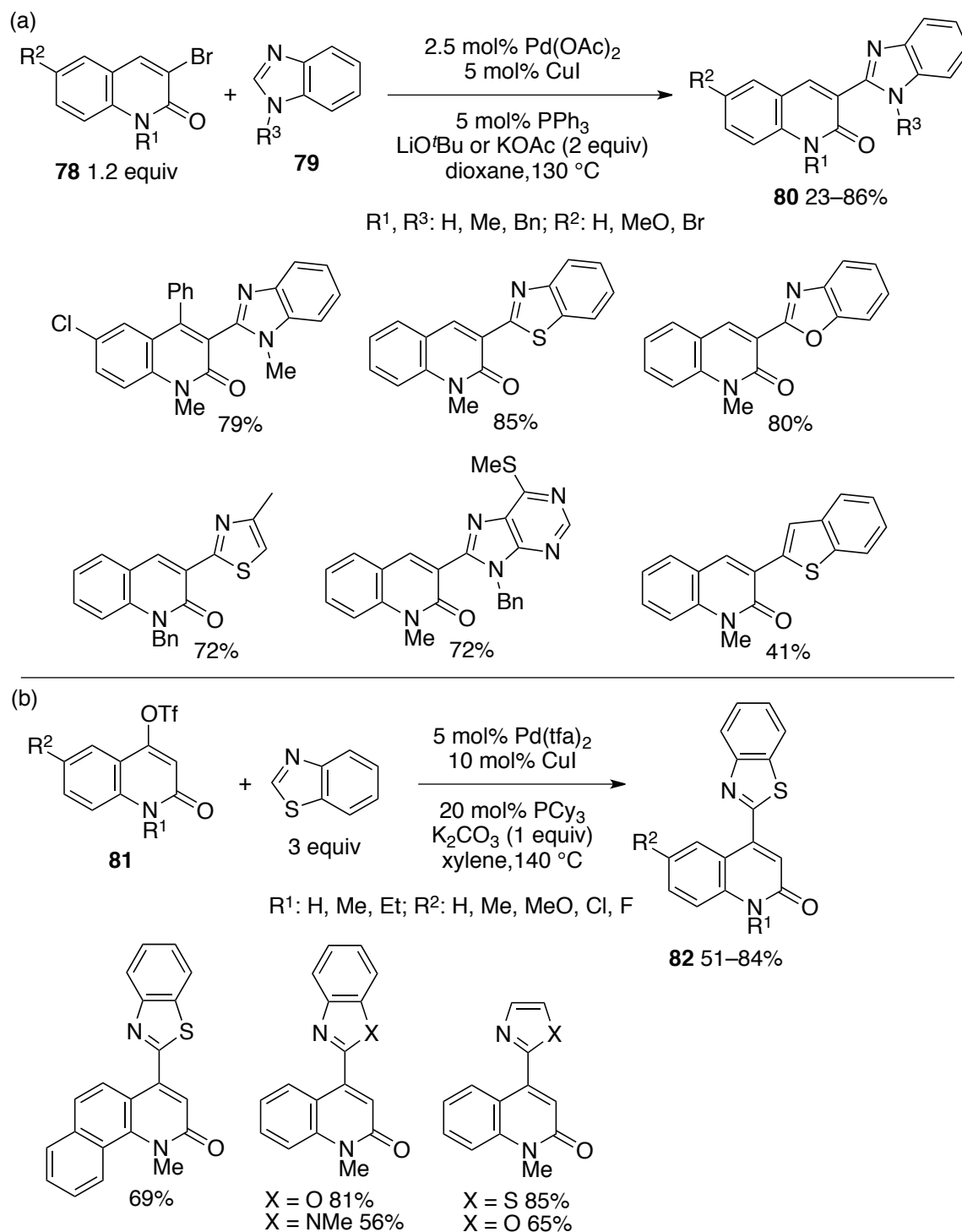
Figure 3. Diversified synthesis of 4-aryl-2-quinolones developed by the Wu group

After these seminal studies, transition-metal-catalyzed cross couplings of 2-quinolone scaffolds were applied to the synthesis of biologically active compounds and ratiometric probes.^{91–95} To further extend the applicability of cross coupling methodology, greener techniques should be developed. Carboxylic acids have attracted much attention as green coupling partners because decarboxylative couplings can minimize waste production.⁹⁶ Messaoudi, Alami, and coworkers developed the decarboxylative arylation of quinolin-2(1*H*)-one-3-carboxylic acids (Scheme 19).⁹⁷ In the presence of PdBr₂ (5 mol%) and AsPh₃ (10 mol%), carboxylic acid **76** reacted with aryl halides at 150 °C under microwave irradiation to afford various 3,4-diaryl-2-quinolones **77** in moderate to high yields. 4-Alkyl- and 4-methoxy-2-quinolone-3-carboxylic acids also participated in the decarboxylative coupling, albeit with moderate efficiency.



Scheme 19. Decarboxylative arylation of quinolin-2(1*H*)-one-3-carboxylic acids

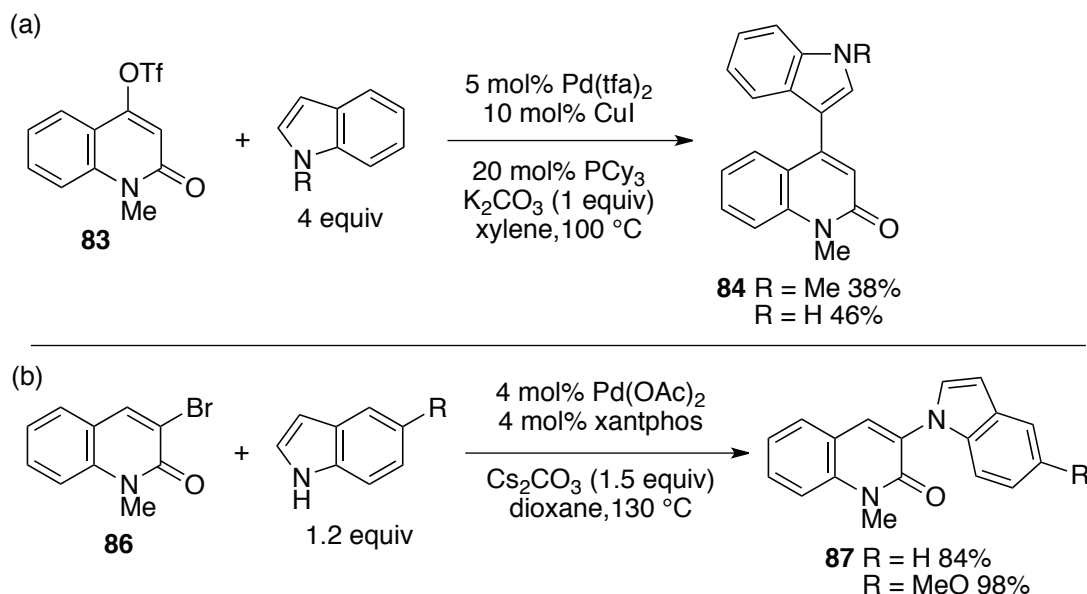
Since azoles have acidic protons that can be readily abstracted by bases such as LiO^{*t*}Bu, they can be used as nucleophilic coupling partners for cross couplings. Alami and coworkers reported a palladium/copper dual catalyst system for the coupling of 3-bromo-2-quinolones **78** with benzimidazoles **79** (Scheme 20a).⁹⁸ The expected coupling products **80** were obtained in 23–86% yields. The lowest yield of 23% was observed when both R¹ and R³ were H. A 3,4-disubstituted product was also obtained in a good yield. In addition to benzimidazoles, benzothiazole, benzoxazole, thiazole, and 6-(methylthio)-9*H*-purine derivatives could also be used as coupling partners with similar high efficiency. In contrast, benzothiophene gave the corresponding product in a modest 41% yield while indole showed no reactivity. Hong and coworkers developed a Cu-mediated coupling of iodinated quinolones with azoles.⁹⁹ In their report, one example of coupling using 1-methyl-3-iodo-2-quinolone and benzothiazole was described, but excess amounts of CuI were required. 4-Heteroaryl-2-quinolones have been synthesized *via* the coupling of triflate **81** independently by the Wu group and Gao. Wu and coworkers used a palladium/copper dual catalyst system to achieve the coupling of **81** (R² = H) with benzoxazoles.¹⁰⁰ In Gao's study, **81** reacted with benzothiazole under a different palladium/copper dual catalysis with PCy₃ as the ligand to afford the desired products **82** in 51–84% yields (Scheme 20b).¹⁰¹ Benzothiazoles bearing a substituent on the benzene ring were also used to obtain coupling products in lower yields. Other azoles such as benzoxazole, benzimidazole, thiazole, and oxazole gave similar results.



Scheme 20. Pd/Cu-Catalyzed coupling of 3-bromo-2-quinolones and 2-quinolone-3-yl triflates with azoles

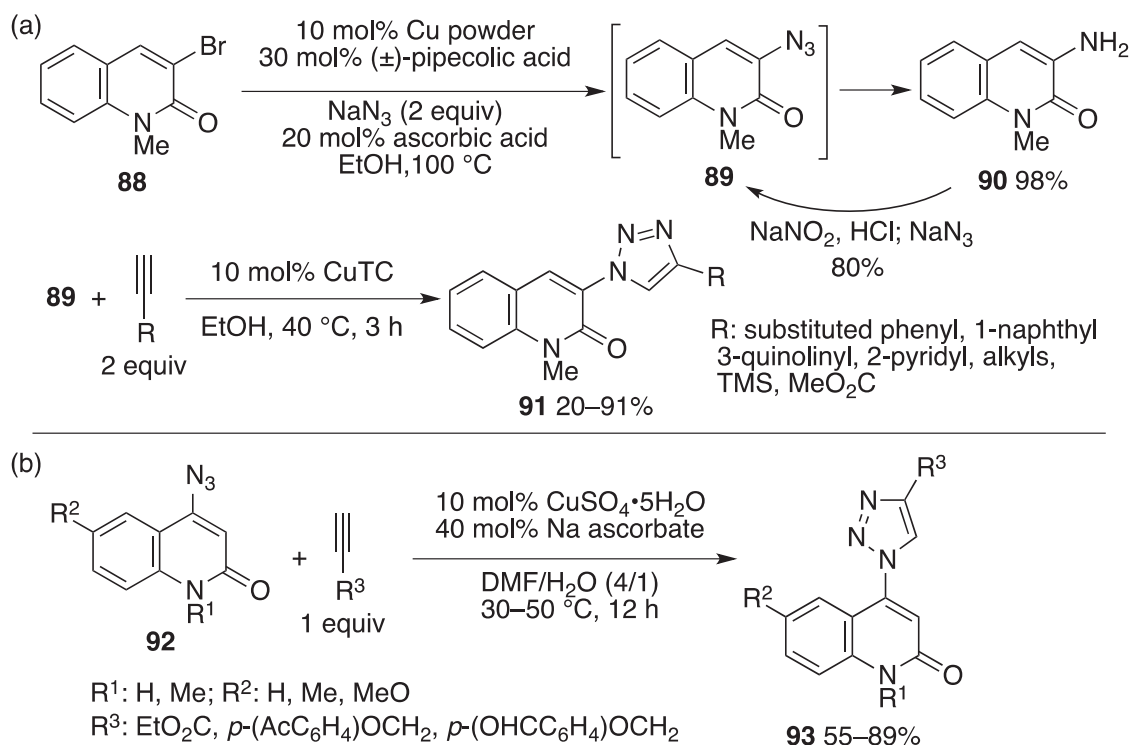
A more challenging coupling with indoles was investigated by Gao and coworkers (Scheme 21a).¹⁰² The reaction of triflate **83** with *N*-methylindole under similar catalytic conditions afforded 4-(indol-3-yl)-2-quinolone **84**, albeit in a low yield (38%). The yield was slightly higher (46%) when unprotected indole was used. Thus, further development is required to improve efficiency for the coupling of less reactive indoles. As reported by Messaoudi, Alami, and coworkers, the reaction of

3-bromo-2-quinolone **86** with indoles using a Pd(OAc)₂/xantphos catalyst system afforded C–N coupling products **87** in high yields (Scheme 21b).¹⁰³



Scheme 21. Pd-Catalyzed C–N coupling of 2-quinolone-3-yl triflate and 3-bromo-2-quinolone with indoles

For C–N coupling on 2-quinolone rings, Messaoudi, Alami, and coworkers investigated the Cu-catalyzed coupling of 3-bromo-2-quinolone **88** with NaN₃ (Scheme 22a).¹⁰⁴ However, 3-amino-2-quinolone **90** was obtained quantitatively instead of 3-azido-2-quinolone **89**. Nevertheless, **89** was prepared through the Sandmeyer reaction of **90**. Thus-obtained **89** was subjected to Cu-catalyzed azide–alkyne cycloaddition, affording various 3-triazolyl-2-quinolones **91** in 20–91% yields.^{104–106} The antileishmanial activity of 3-triazolyl-2-quinolones was investigated, but no significant effect was observed against *Leishmania* parasites.¹⁰⁵ This result was ascribed to poor solubility of 3-triazolyl-2-quinolones in aqueous solutions. Similarly, 4-triazolyl-2-quinolones **93** were produced in 55–89% yields *via* Cu-catalyzed azide–alkyne cycloaddition of 4-azido-2-quinolones **92** (Scheme 22b).¹⁰⁷ Because 4-azido-2-quinolone can be prepared by the reaction of readily available 4-hydroxy-2-quinolone with diphenylphosphoryl azide,¹⁰⁸ the azidation/cycloaddition sequence provides a short-step access to 4-triazolyl-2-quinolones.

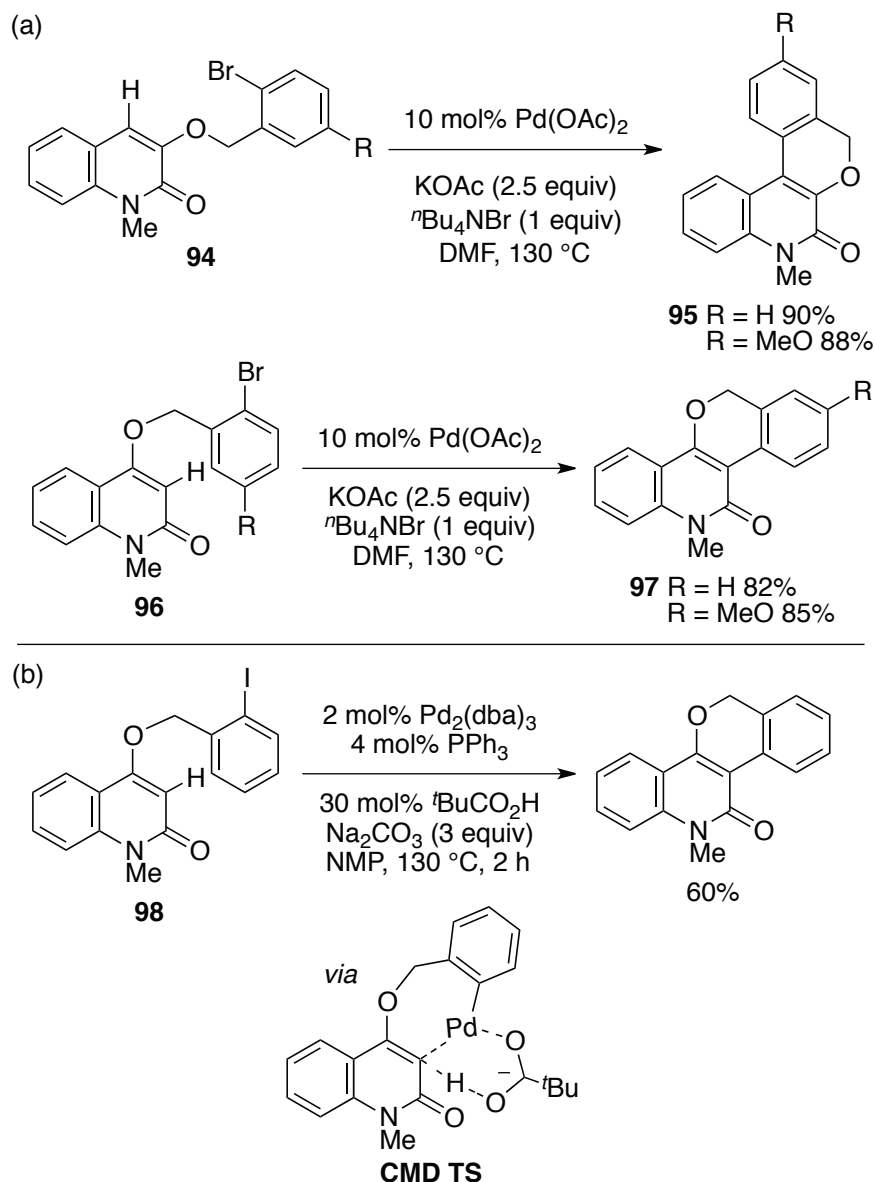


Scheme 22. Syntheses of 3- and 4-triazolyl-2-quinolones *via* Cu-catalyzed azide–alkyne cycloaddition (TC = thiophene-2-carboxylate)

3-2. ARYLATION OF 2(1*H*)-QUINOLONE C–H BONDS

In the previous subsection, transition-metal-catalyzed arylations *via* cross couplings were outlined. Those cross couplings generally require reactive functional moieties, such as halides, sulfonates, or carboxylic acids, at the 3- or 4-positions of 2-quinolone scaffolds. However, direct arylations on vinylic C–H bonds are more ideal, as they are straightforward and reduce waste production.¹⁰⁹ Hence, arylation of 2-quinolones *via* vinylic C–H arylations is discussed in this section.

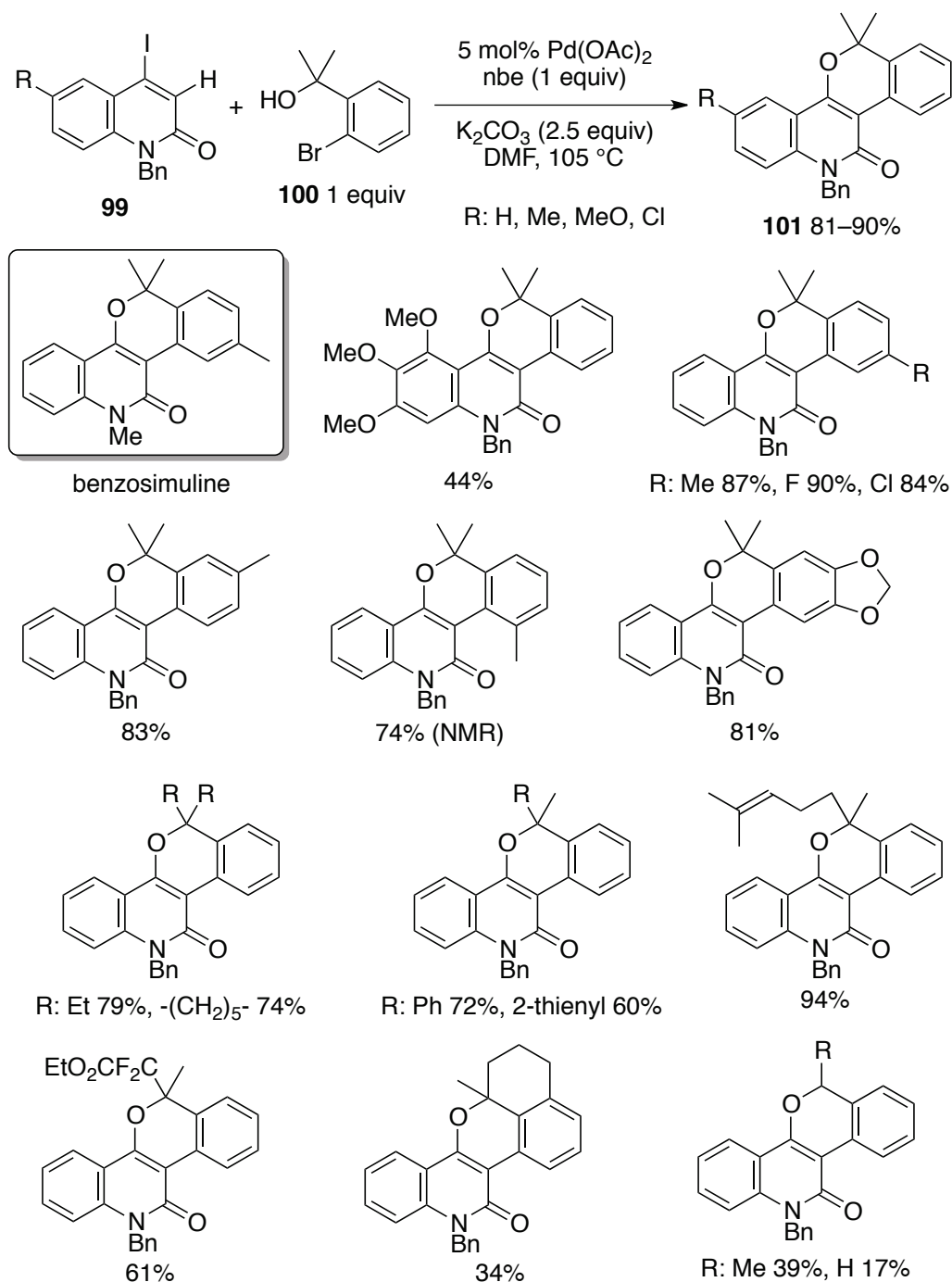
Majumdar and coworkers prepared quinolone substrates **94** and **96** from readily available 3- and 4-hydroxyquinolones, respectively, *via* alkylation with 2-bromobenzyl bromides (Scheme 23a).¹¹⁰ They subjected these substrates to Jeffery's conditions¹¹¹ (Pd(OAc)₂, KOAc, tetrabutylammonium bromide, DMF) to obtain benzopyran-fused products **95** and **97** in high yields. Thus, M–H-type intramolecular arylation at the 3- and 4-positions of 2-quinolones proved to be feasible. Later, this intramolecular approach was revisited by McGlacken and coworkers (Scheme 23b).¹¹² They used a different palladium catalyst system and iodide substrate **98** to reduce the catalyst loading, but the yield was moderate. It was suggested that the arylation proceeds *via* a concerted metalation-deprotonation (CMD) mechanism.¹¹³



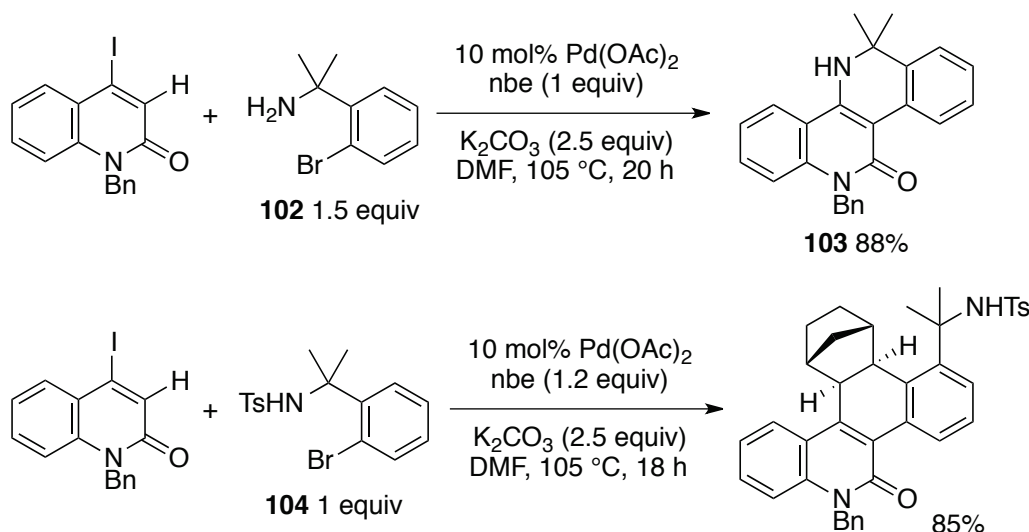
Scheme 23. Synthesis of benzopyran-fused 2-quinolones *via* intramolecular C–H arylation (NMP = *N*-methyl-2-pyrrolidone)

Benzopyran-fused 2-quinolones are fascinating because their structures are similar to that of natural product benzosimuline, which has anti-platelet aggregation activity.¹¹⁴ However, the abovementioned methods require pre-installation of 2-halobenzyl moieties before cyclization (Scheme 23). In addition, no substrate bearing a tertiary benzylic carbon was examined. Thus, an alternative approach is required for the construction of benzosimuline-type compounds *via* C–H arylation. Yamamoto and coworkers developed a Catellani-type cyclocoupling of 4-iodo-2-quinolones **99** with *o*-bromobenzyl alcohol **100** (Scheme 24).¹¹⁵ Pd(OAc)₂ (5 mol%) and 1 equiv of norbornene (nbe) mediated the cyclocoupling efficiently to produce benzopyran-fused 2-quinolones **101** with tertiary benzylic centers in high yields. This method enables the modular synthesis of benzosimuline-type products by combining various

4-iodo-2-quinolones and *o*-bromobenzyl alcohols. Unlike in the above intramolecular arylations (Scheme 23), benzyl alcohols with secondary and primary benzylic carbons resulted in lower product yields in this method, showing the importance of the tertiary alcohol moieties. The reaction with benzylamine **102** afforded dihydroquinoline-fused 2-quinolone **103** in 88% yield (Scheme 25). Moreover, an unexpected three-component coupling involving norbornene occurred when tosylamide **104** was used instead of **102**.

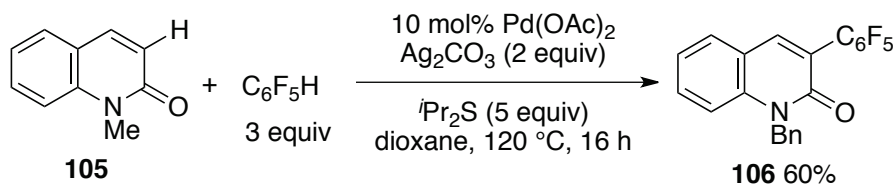


Scheme 24. Synthesis of benzosimuline analogs *via* Catellani-type cyclocoupling (nbe = norbornene)



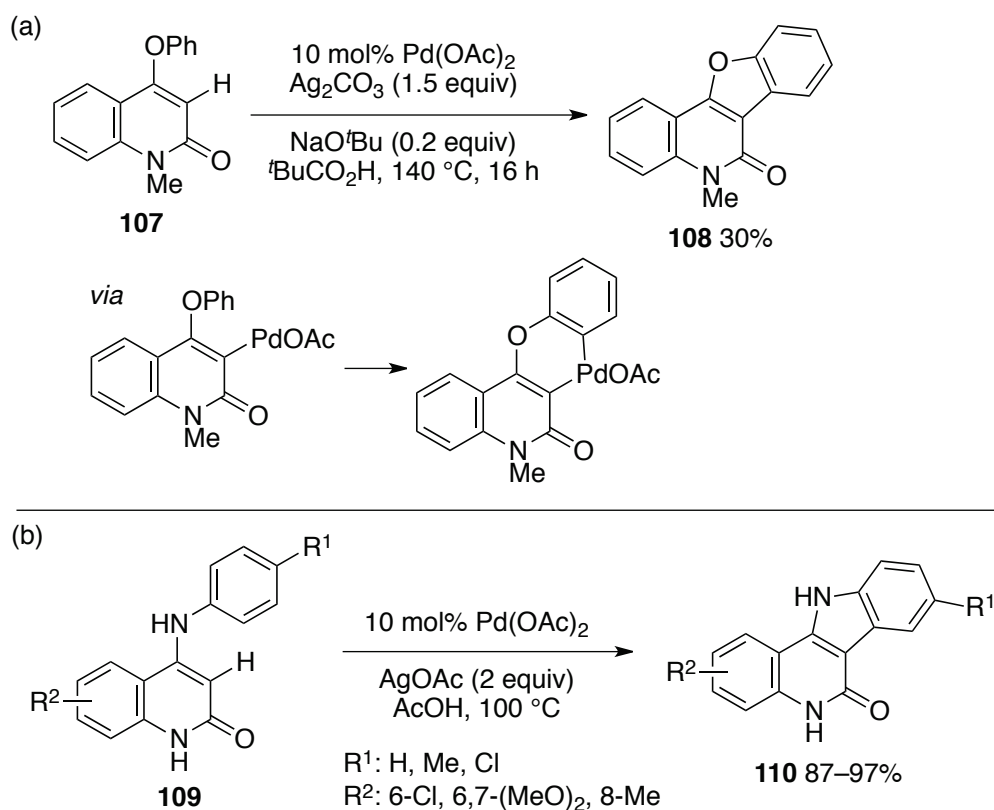
Scheme 25. Reactions of 4-iodo-2-quinolone with benzylamines under Catellani conditions

Dehydrogenative coupling is more ideal as it obviates the requirement for haloarenes as arylating agents. Li and coworkers reported the Pd-catalyzed dehydrogenative coupling of 2-quinolone **105** with pentafluorobenzene (Scheme 26).¹¹⁶ They used Pd(OAc)₂ (10 mol%) as the catalyst and Ag₂CO₃ as the oxidant in dioxane at 120 °C to obtain 3-arylated product **106** in 60% yield. This is fascinating, as it is a rare example of intermolecular quinolone C–H arylation, but the scope was not established.



Scheme 26. Synthesis of 3-aryl-2-quinolones *via* intermolecular dehydrogenative arylation

Intramolecular dehydrogenative arylation has also been investigated. The McGlacken group reported the cyclization of 4-phenoxy-2-quinolone **107** using a similar palladium catalyst in pivalic acid at 140 °C, which led to benzofuran-fused 2-quinolone **108** in 30% yield (Scheme 27a).¹¹⁷ In this report, only one 2-quinolone substrate was presented and the yield was poor. They proposed that the reaction begins with the quinolone C–H bond activation at the 3-position and subsequent intramolecular electrophilic palladation of the phenyl ring follows. Chen, Xu, and coworkers developed the dehydrogenative cyclization of 2-quinolones **109** bearing an aniline moiety at the 4-position (Scheme 27b).¹¹⁸ They employed base-free conditions with AgOAc as the oxidant to obtain indoloquinolones **110** in high yields.



Scheme 27. Synthesis of 3-aryl-2-quinolones *via* intramolecular dehydrogenative arylation

4. SUMMARY

In the past decade, various transition-metal-catalyzed methods for the construction of 3- and/or 4-aryl-2-quinolones have been developed extensively, because arylated quinolones display diverse biological activities. The new catalytic methods are not only more straightforward, but also greener than conventional condensation methods such as the Friedländer-type synthesis. Moreover, transition-metal-catalyzed methods also contribute significantly to drug discovery by enabling the synthesis of conventionally inaccessible 2-quinolones. For these reasons, these new methods have attracted great attention from the pharmaceutical science community. In addition to 2-quinolone assembly methods, arylations of 2-quinolone scaffolds have also been investigated extensively. Transition-metal-catalyzed cross couplings enable site-selective and efficient introduction of aryl groups on prefunctionalized 2-quinolones. Thus, the combination of cross coupling methods with other transformations provides efficient access to divergent and highly substituted 2-quinolones. Moreover, greener direct C–H arylations have also been applied to 2-quinolones. Although efficient C–H arylations must be intramolecular, interesting polycyclic 2-quinolones have been synthesized in a straightforward manner. In the future, superior catalytic systems that enable intermolecular C–H arylations of 2-quinolones will be identified.

ACKNOWLEDGEMENTS

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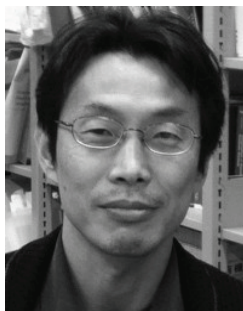
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