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INTRODUCTION

Nitrogen-containing heterocyclic compounds, particularly those in the quinazoline group, have shown a wide range of applications in both organic synthesis and medicinal chemistry. The oxidized form of quinazoline – quinazolin-4(3*H*)-one or quinazolinone for short – is among the most important heterocyclic scaffolds in drug discovery. There have been numerous methodologies developed for the synthesis quinazolinone derivatives, especially 2,3-substituted ones, many of which have been patented due to their broad applicability, high efficiency, and the diversity of structures they yield.

Despite these advancements, current synthetic methodologies often encounter several limitations. These include the use of commercially unavailable reagents, the necessity of multiple reaction steps, stability issues of the staring materials or the reagents used, or reliance on hazardous halogen-containing derivatives. Additionally, some synthesis techniques require transition metal-based catalysts such as palladium, iridium, ruthenium, and expensive, moisture- and air-sensitive phosphine-based or multidentate nitrogen-based ligands. Synthesis methods based on ring-closure condensation reactions frequently need extra external oxidizing agents, with condensation reagents typically being aromatic amines derived from nitroarene derivatives through various reduction processes. As a result, the synthesis pathway, including the isolation and purification of intermediates or final products, tends to generate significant amount of waste from the reagents and solvents being used.

Given these challenges, there is a growing need to develop quinazoline derivative synthesis methods that utilize readily available organic materials and employ heterogeneous catalyst systems. These systems should be designed for recovery and reuse, and the byproducts of these processes should be non-toxic and easily manageable to align with environmental and practical demands.

CHAPTER 1. LITERATURE REVIEWS

1.1. Introduction to quinazolinone and related derivatives

1.1.1. Structures, natural occurrence, and biological reactivities

Quinazolinones represent a significant category of N-heterocyclic compounds, commonly found across a diverse spectrum of pharmaceutical natural products, prospective drug candidates, agrochemicals, and functionalized organic materials. Among numerous natural and synthetic quinazolinone derivatives, 2- or 3-monosubstituted, 2,3-disubstituted and fused quinazolin-4(3*H*)-ones play essential roles in drug discovery and development due to their versatile biological and pharmacological reactivities. Representative quinazolinone-containing organic compounds in natural products and drug candidates are demonstrated in
Figure 1.1.

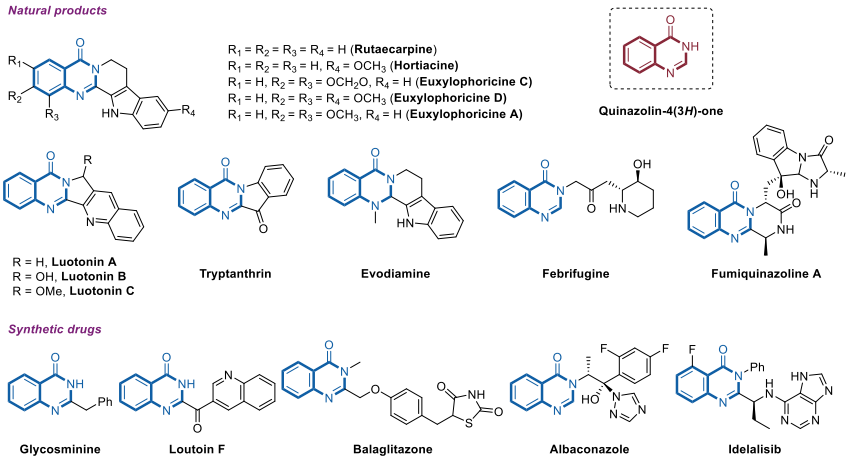


Figure 1.1. Quinazolin-4(3*H*)-one with some naturally occurring compounds and synthetic drugs containing the quinazolinone structure.

1.1.2. General approaches for the synthesis of quinazolinone derivatives

In this review, recent developments in the synthesis of variably substituted quinazolin-4(3*H*)-one analogs are highlighted, specifically those with mono-substitutions at the 2- or 3-position and 2,3-disubstituted quinazolin-4(3*H*)-ones.

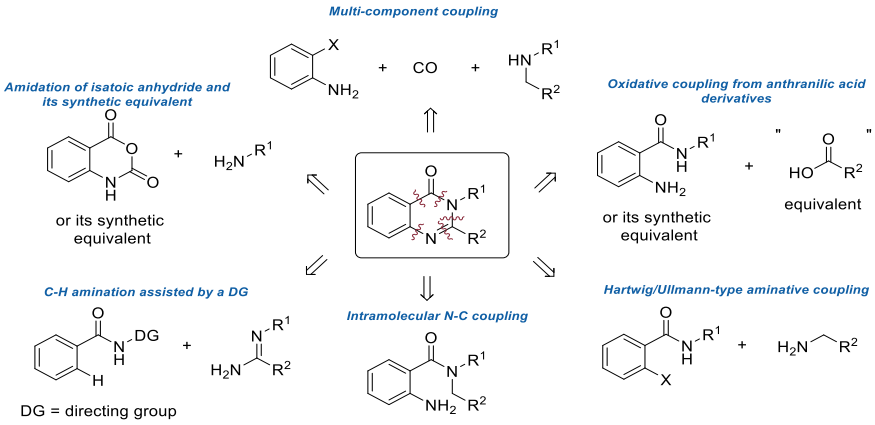


Figure 1.2. Retrosynthesis analysis for the construction of the quinazolinone structure.

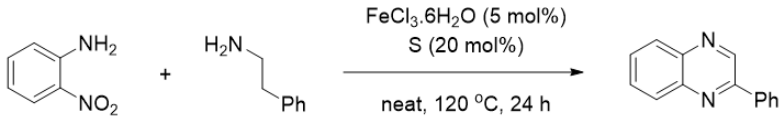
This review categorizes them into six primary methodologies. Each method is distinct, grounded in a tailored retrosynthetic analysis of the pyrimidine ring and often influenced by the commercial availability of starting materials. However, it's important to note that this review does not encompass post-synthetic modifications of these heterocycles. These include: (*i*) oxidative coupling of anthranilic acids or their amide derivatives with carboxylic acid equivalents; (*ii*) reactions between isatoic anhydride or related compounds with amines; (*iii*) intramolecular dehydrogenative N–C coupling in pre-functionalized anthranilamides; (*iv*) Ullmann-type coupling of 2-halobenzamides with amines or their

substitutes; (*v*) metal-catalyzed C–H activation in the coupling of benzamides with amidine equivalents; and (*vi*) multicomponent coupling reactions utilizing small, readily available molecules.

1.2. Nitroarenes in the synthesis of *N*-containing heterocyclic compounds

The oxidative-reductive balance using the Fe/S catalytic system was also extended to the synthesis of quinoxaline derivatives from 2-nitroaniline and phenethylamine using a mixture of 5 mol% $FeCl_3.6H_2O$ and 20 mol% S as the catalyst for the transformation (

Scheme 1.1). In this reaction, 2-nitroaniline acts as a 6-electron acceptor, and the phenethylamine derivative as a 6-electron donor, achieving an oxidative-reductive balance with water and ammonia as the only byproducts.

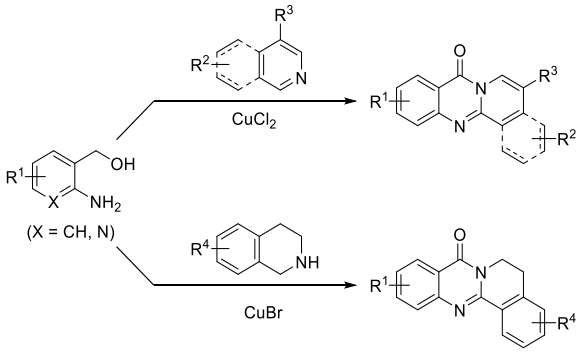


Scheme 1.1. Redox condensation between 2-nitroanilines and phenethylamines for the synthesis of quinoxaline utilizing the Fe/S system.

1.3. Aims and Objectives

The primary aim of this doctoral thesis is to explore and develop new and sustainable synthetic routes for quinazolinone derivatives, with a particular focus on 2,3-disubstituted quinazolinones, which bear structural similarities to the naturally occurring COX-2 inhibitor, rutaecarpine. The research aims to address the challenges and limitations of current synthesis methods while exploring sustainable and efficient alternatives.

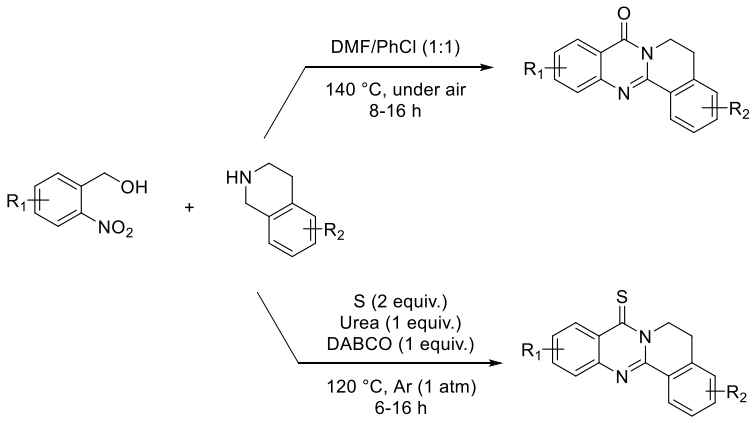
The first objective of the study was to focus on synthesizing pyrido-fused quinazolinones, starting from the condensation of 2-aminoarylmethanols with isoquinolines. The reaction's scope was expanded to include tetrahydroisoquinoline, leading to the synthesis of a series of fused quinazolinones structurally related to the natural product rutaecarpine, with good to high yields. Compared to previous studies, this new methods highlighting the use of commercially available and accessible starting materials, mild reaction conditions, with molecular as a green terminal oxidant. This innovative approach not only broadens the scope of quinazolinone synthesis but also offers a more sustainable and accessible pathway for producing these complex molecules.



Scheme 1.2. The synthesis of fused quinazolinones by copper-catalyzed oxidative condensation starting from 2-aminoarylmethanols.

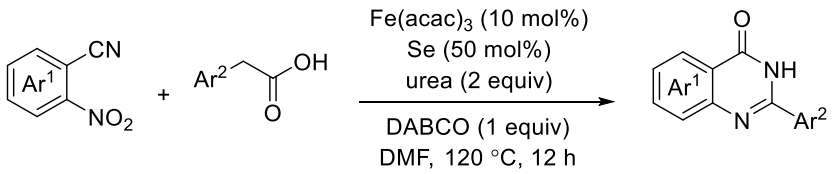
The second objective of the study was to develop a novel method for constructing tetrahydroisoquinoline-fused quinazolinone and quinazolinthione skeletons via auto-redox type coupling reaction *o*-nitrobenzyl alcohol and tetrahydroisoquinolines, with air or elemental sulfur as terminal oxidant. The study will optimize reaction conditions to

maximize yields, synthesize various quinazolin(thi)ones derivatives to demonstrate the reaction scope, and conduct a mechanistic investigation to gain more insights into the reaction pathways.



Scheme 1.3. The synthesis of quinazolinone and quinazolinthione under metal-free conditions starting from 2-nitrobenzyl alcohols.

The third objective of the research focuses on the development of a method for annulation of 2-nitrobenzonitriles and arylacetic acids to synthesize 2-arylquinazolin-4(3*H*)-one derivatives. Based on previous studies, iron(III) salt catalyst, elemental selenium promoter, and urea as a reducing agent were utilized to facilitate the reactions. Our method features a mild and convenient method to obtain 2-arylquinazolin-4(3*H*)-ones bearing a wide range of functionalities starting from the stable nitroarene-based substrates.



Scheme 1.4. The synthesis of 2-arylquinazolinons starting from the condensation reaction between 2-nitrobenzonitriles and arylacetic acids.

CHAPTER 2. EXPERIMENTAL

2.1. Materials and Instrumentations

2.1.1. Materials

All chemicals as well as materials involved in this study were obtained commercially from Sigma-Aldrich, Acros® Organic, Chemsol, and Xilong suppliers as listed in **Error! Reference source not found.**, and were used as received without further purification. The experimental procedures for the synthesis of other starting materials are described in the following sections.

2.1.2. Instrumentations

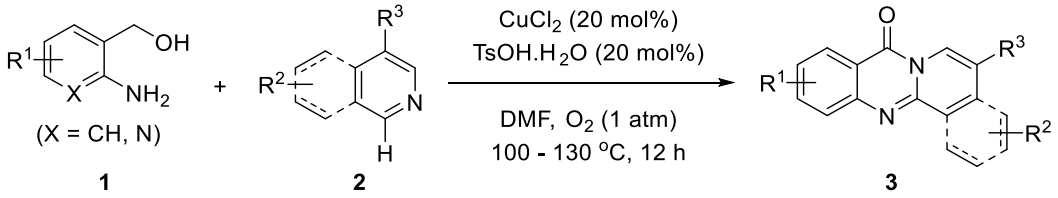
Gas chromatography (GC) analyses were performed by a Shimadzu GC 2010-Plus equipped with a flame ionization detector (FID) and an SPB-5 column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). The temperature program for GC analysis held samples at 100 °C for 1 minute, then gradually raised the temperature from 100 °C to 280 °C with an increment of 40 °C /min, which took 4.5 minutes to reach the highest temperature, and finally held them at 280 °C for another 4.5 minutes. Inlet and detector temperature were set constant at 280 °C. Diphenyl ether was used as an internal standard for GC quantification.

Gas chromatography coupled with mass spectrometry (GC-MS) analyses were performed on Shimadzu GCMS-QP2010Ultra with a ZB-5MS column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). The temperature program for the GC-MS analysis held samples at 50 °C for 2 minutes, then gradually raised the temperature from 50 °C to 280 °C with an increment of 10 °C /min, which took 23 minutes to complete, and finally held them at 280 °C for another 10 minutes. The inlet temperature was set constant at 280 °C. Mass spectroscopy used the electron ionization (EI) method to convert the samples into ions, and mass spectra were compared with those gathered from the NIST library.

The ^{1}H and ^{13}C NMR spectra were recorded on the Bruker AV 500 spectrometer or AvanceNEO 600MHz spectrometer (600 and 151 MHz, respectively) using residual solvent peak as a reference. HRMS spectra were recorded by an Agilent HPLC 1200 Series coupled to Bruker microTOF-QII.

2.2. Experimental procedures

2.2.1. Synthesis of isoquinolino-fused or pyrido-fused quinazolinones via copper-catalyzed cyclization reaction between 2-aminoarylmethanols and isoquinolines

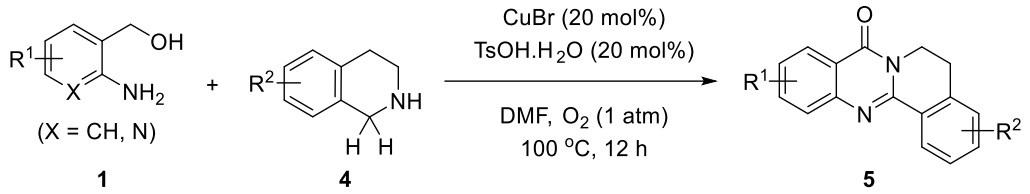


Scheme 2.1. Synthesis of fused quinazolinones via $CuCl_2$-catalyzed cyclization reaction between 2-aminoarylmethanols and isoquinolines

In a representative experiment, to a 12-mL screw-cap vial was added isoquinoline (0.3 mmol, 3.0 equiv.), $CuCl_2$ (20 mol%), $TsOH.H_2O$ (20 mol%) and DMF (1.5 mL). The reaction tube was flushed with oxygen gas, tightly capped, and stirred at room temperature for 10 min to dissolve the copper catalyst. Then, 2-aminobenzyl alcohol (0.1 mmol, 1.0 equiv.) was added in three portions and the resulting mixture was stirred at 100 °C (aluminum heating place temperature) for 12 hours. Upon completion of the reaction, the mixture was cooled to room temperature and diphenyl ether (17.2 mg, 0.1 mmol) as an internal standard was added. The organic components were subsequently extracted into ethyl acetate (2.0 mL), washed with $NaHCO_3$ solution (5% in water, 1.0 mL), brine (1.0 mL), and dried over anhydrous Na_2SO_4, and analyzed by GC with reference to diphenyl ether. To purify the quinazolinone product, the combined organic extracts were concentrated in vacuo and purified by column chromatography on silica gel with hexane/ethyl acetate solvent

system to afford pure product. The product identity was further confirmed by GC-MS, ^{1}H NMR and ^{13}C NMR. New compounds were also characterized by HRMS.

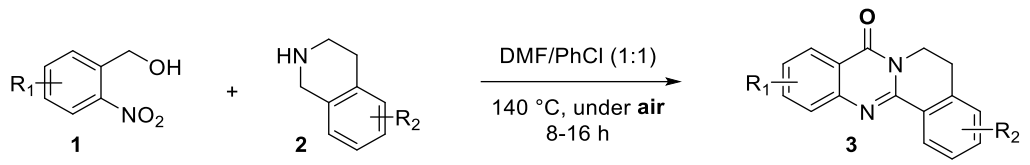
2.2.2. Synthesis of dihydroisoquinolino-fused quinazolinones via copper-catalyzed cyclization reaction between 2-aminoarylmethanols and tetrahydroisoquinolines



Scheme 2.2. Synthesis of fused quinazolinones via CuBr-catalyzed cyclization reaction between 2-aminoarylmethanols and tetrahydroisoquinolines.

In a representative experiment, to a 12-mL screw-cap vial was added tetrahydroisoquinoline (0.6 mmol, 3.0 equiv.), CuBr (20 mol%), TsOH.H_2O (20 mol%) and DMF (1.0 mL). The reaction tube was flushed with oxygen gas, tightly capped, and stirred at room temperature for 10 min to dissolve the copper catalyst. The next steps are carried out similarly to the reaction in section 2.2.1

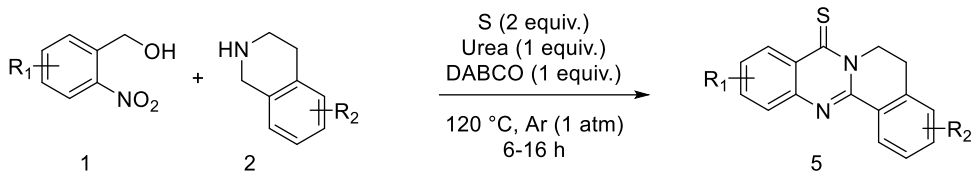
2.2.3. Metal-free synthesis of dihydroisoquinolino-fused quinazolinones via redox condensation of 2-nitrobenzyl alcohol derivatives and tetrahydroisoquinolines under air



Scheme 2.3. Synthesis of fused quinazolinones via redox condensation between 2-nitrobenzyl alcohols and tetrahydroisoquinolines under air.

To a dried 4 mL screw-capped vial equipped with a magnetic stir bar was added 2-nitrobenzyl alcohol (0.2 mmol), tetrahydroisoquinoline (0.6 mmol), DMF (0.1 mL), and chlorobenzene (0.1 mL). The mixture was stirred under air at 140 ℃ (aluminum heating plate temperature) for 8-16 h until the disappearance of 2-nitrobenzyl alcohol as monitored by TLC and/or GC. The crude mixture was then washed with brine (2 x 2 mL) and extracted with EtOAc (3 x 3 mL). Combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude product was then purified by column chromatography to yield the desired product. The product identity was further confirmed by GC-MS, ^{1}H NMR and ^{13}C NMR. New compounds were also characterized by HRMS.

2.2.4. Metal-free synthesis of dihydroisoquinolino-fused quinazolinthiones via redox condensation of 2-nitrobenzyl alcohol derivatives and tetrahydroisoquinolines in the presence of elemental sulfur

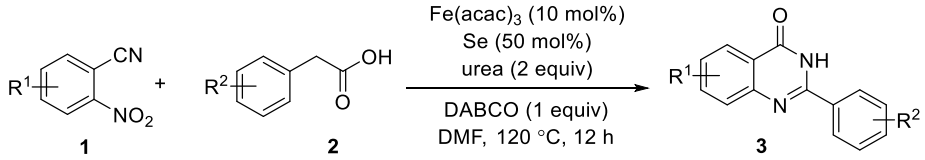


Scheme 2.4. Synthesis of fused quinazolinthiones via redox condensation between 2-nitrobenzyl alcohols and tetrahydroisoquinolines in the presence of elemental sulfur.

Two parallel, dried 4 mL screw-capped vials equipped with a magnetic stir bar was added 2-nitrobenzyl alcohol (0.1 mmol), tetrahydroisoquinoline (0.15 mmol), elemental sulfur (6.4 mg, 0.2 mmol), urea (6.1 mg, 0.1 mmol), and DABCO (11.2 mg, 0.1 mmol). Both vials were purged with argon (1 atm) then placed into a preheated bath at 120 ℃ (aluminum

heating plate temperature) for 6-16 h until the disappearance of 2-nitrobenzyl alcohol as monitored by TLC and/or GC. Upon completion, two crude mixtures were combined, then washed with brine (2 x 2 mL) and extracted with EtOAc (3 x 3 mL). Combined organic phases were dried over Na_2SO_4, filtered, and solvents removed in vacuo. The crude product was then purified by column chromatography to yield the desired product. The product identity was further confirmed by GC-MS, ^{1}H NMR and ^{13}C NMR. New compounds were also characterized by HRMS.

2.2.5. Iron-catalyzed, elemental selenium-mediated synthesis of 2-arylquinazolinones via cyclization reactions between 2-nitrobenzonitriles and phenylacetic acids



Scheme 2.5. Synthesis of 2-arylquinazolinones by reaction between 2-nitrobenzonitriles and phenylacetic acids.

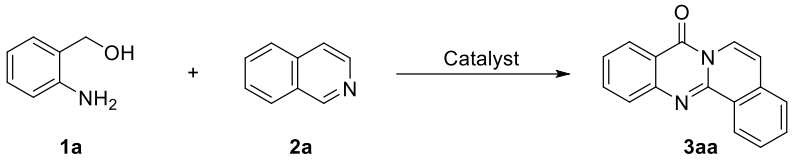
A 4-mL screw-cap vial equipped with a magnetic stir bar was added a derivative of 2-nitrobenzonitrile (0.5 mmol), an arylacetic acid (1 mmol), selenium powder (20 mg, 0.25 mmol), 1,4-diazabicyclo[2.2.2]octane (DABCO, 56 mg, 0.5 mmol), and urea (60 mg, 1 mmol). After that, a solution of anhydrous $Fe(acac)_3$ (18 mg, 0.05 mmol) in DMF (1 mL) was added. The reaction mixture was stirred at 120 °C (aluminum heating plate temperature) for 12 h. Upon completion, the vial was cooled to ambient temperature. The organic components were consequently extracted into ethyl acetate (3 × 5 mL), washed with $NaHCO_3$ (10% aqueous solution, 5 mL) and brine (5 mL). Combined organic phases were subsequently dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Purification by column chromatography on silica gel with hexanes/ethyl acetate eluent afforded the desired product. The product identity was further confirmed by GC-MS, ^{1}H NMR and ^{13}C NMR. New compounds were also characterized by HRMS.

CHAPTER 3. RESULTS AND DISCUSSION

3.1. Synthesis of pyrido-fused quinazolinones via copper-catalyzed cascade C(sp^2)-H amination and annulation of 2-aminoarylmethanols with isoquinolines

3.1.1. Screening of reaction conditions

Table 3.1. Screening of reaction conditions for the annulation of 2-aminobenzyl alcohol with isoquinoline to synthesize isoquinolino-fused quinazolinone[a].



1a 2a 3aa

Entry	Temperature (°C)	Catalyst (mol%)	**1a:2a** (mol:mol)	Additive (equiv.)	Solvent (mL)	**3aa** Yield[b] (%)
1	80	$Cu(OAc)_2$ (20%)	1:3	$TsOH.H_2O$ (1.5)	DMF (0.5 mL)	27
2	100	$Cu(OAc)_2$ (20%)	1:3	$TsOH.H_2O$ (1.5)	DMF (0.5 mL)	52
3	120	$Cu(OAc)_2$ (20%)	1:3	$TsOH.H_2O$ (1.5)	DMF (0.5 mL)	51
4	100	-	1:3	$TsOH.H_2O$ (1.5)	DMF (0.5 mL)	0
5	100	$CuCl_2$ (20%)	1:3	$TsOH.H_2O$ (1.5)	DMF (0.5 mL)	64
6	100	$CuBr_2$ (20%)	1:3	$TsOH.H_2O$ (1.5)	DMF (0.5 mL)	62
7	100	CuBr (20%)	1:3	$TsOH.H_2O$ (1.5)	DMF (0.5 mL)	61
8	100	CuCl (20%)	1:3	$TsOH.H_2O$ (1.5)	DMF (0.5 mL)	63
9	100	$CuCl_2$ (20%)	1:2.5	$TsOH.H_2O$ (1.5)	DMF (0.5 mL)	58
10	100	$CuCl_2$ (20%)	1:3	-	DMF (0.5 mL)	6
11	100	$CuCl_2$ (20%)	1:3	HCOOH (1.5)	DMF (0.5 mL)	37
12	100	$CuCl_2$ (20%)	1:3	AcOH (1.5)	DMF (0.5 mL)	46
13	100	$CuCl_2$ (20%)	1:3	CH_3SO_3H (1.5)	DMF (0.5 mL)	65
14	100	$CuCl_2$ (20%)	1:3	$TsOH.H_2O$ (0.2)	DMF (0.5 mL)	68
15	100	$CuCl_2$ (20%)	1:3	$TsOH.H_2O$ (0.2)	DMAc (0.5 mL)	67
16	100	$CuCl_2$ (20%)	1:3	$TsOH.H_2O$ (0.2)	NMP (0.5 mL)	64
17	100	$CuCl_2$ (20%)	1:3	$TsOH.H_2O$ (0.2)	DMSO (0.5 mL)	58
18	100	$CuCl_2$ (20%)	1:3	$TsOH.H_2O$ (0.2)	DMF (1.5 mL)	81

[a]Reaction conditions: 2-aminobenzyl alcohol (0.1 mmol; 12 h; reactor flushed with oxygen. TsOH: *p*-toluenesulfonic acid; DMF: *N, N*-dimethylformamide; DMSO: dimethyl sulfoxide; DMAc: *N,N*-dimethylacetamide; NMP: *N*-methyl-2-pyrrolidone. [b]GC yield.

3.1.2. Screening of the substrate scope

we further expanded our investigation to assess the versatility of our protocol in synthesizing pyrido-fused quinazolinones, as outlined in Figure 4.1. Initially, we examined a range of isoquinolines and pyridines for their reactivity with 2-aminobenzyl alcohol. Under the established standard conditions, **3aa** was synthesized with an isolated yield of 78%. Bromo-substituted isoquinolines showed good reactivity, leading to the formation of **3ab** and **3ac** with yields of 81% and 83%, respectively. Isoquinolin-5-amines and related compounds exhibited lower reactivity, yielding **3ad**, **3ae**, and **3af** at 52%, 68%, and 42%, respectively.

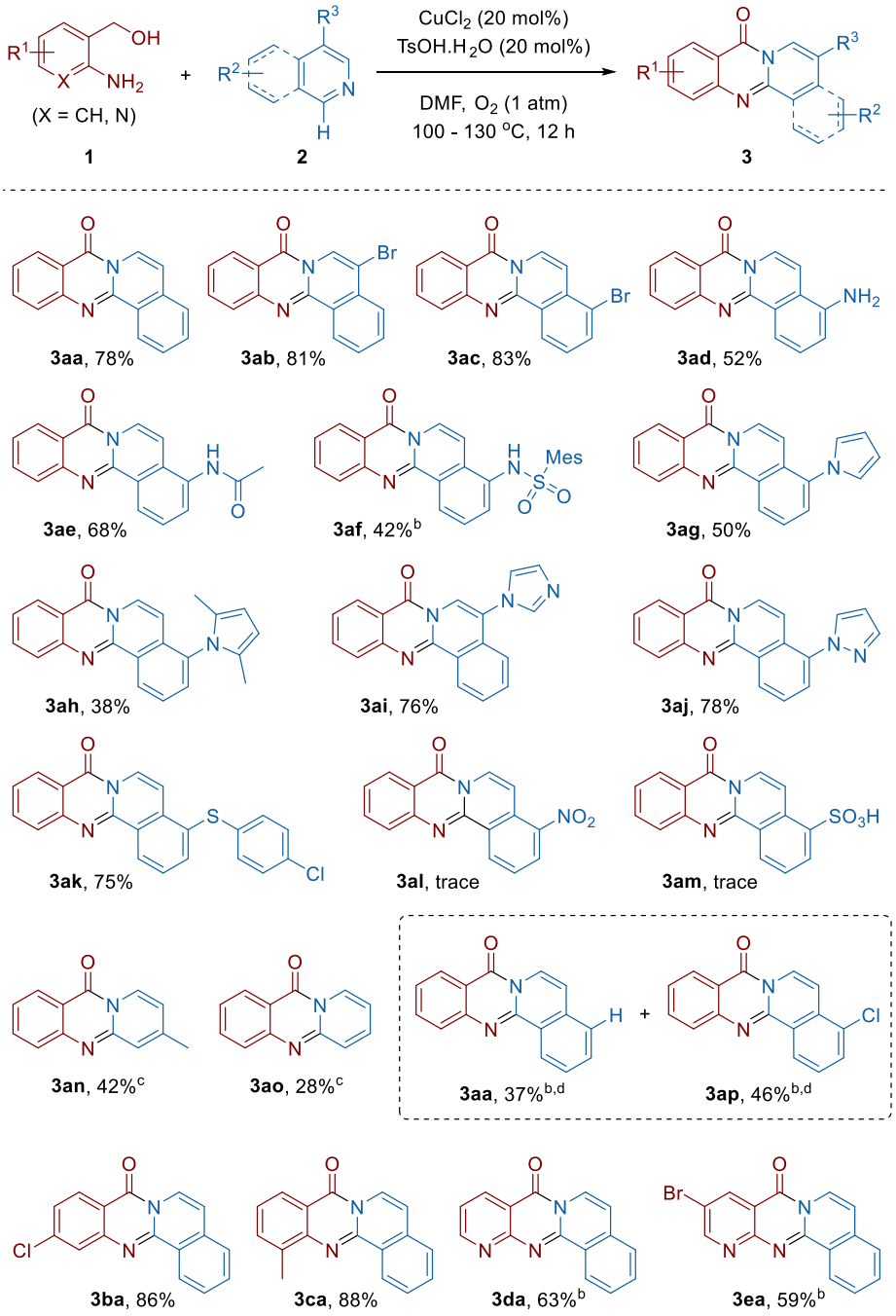


Figure 3.1. Annulation of 2-aminoarylmethanols with isoquinolines and pyridines[a].

[a] Reaction conditions: 2-aminoarylmethanols **1** (0.2 mmol, 1.0 equiv.); isoquinolines **2** (0.6 mmol, 3.0 equiv.); $CuCl_2$ (20 mol%), $TsOH.H_2O$ (20 mol%); DMF (3.0 mL), 100 °C; 12 h. Yields are isolated yields. [b] Reaction was performed at 120 °C. [c] Reaction was performed at 130 °C. [d] Isoquinoline-4-boronic acid pinacol ester (0.4 mmol, 2.0 equiv.) and $CuCl_2$ (1.2 equiv) were used.

3.1.3. Application for the reaction between 2-aminoarylmethanols and tetrahydroisoquinolines

Our initial focus was on the annulation of 2-aminobenzyl alcohol (**1a**) and tetrahydroisoquinoline (**4a**) to synthesize 5,6-dihydro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**5aa**). To optimize the yield of 5aa, various reaction parameters such as temperature, catalyst, additive, molar ratio of reactants, and solvent were systematically adjusted. A key difference from the synthesis of 3aa was the preference for CuBr over $CuCl_2$ in producing **5aa**. The most effective results were obtained by conducting the reaction in DMF at 100°C for 12 hours under an oxygen atmosphere, using 3 equiv. of tetrahydroisoquinolines, 20 mol% CuBr, and 20 mol% $TsOH.H_2O$. Under these optimized conditions, an 86% GC yield of **5aa** was observed with an isolated yield of 80% being achieved.

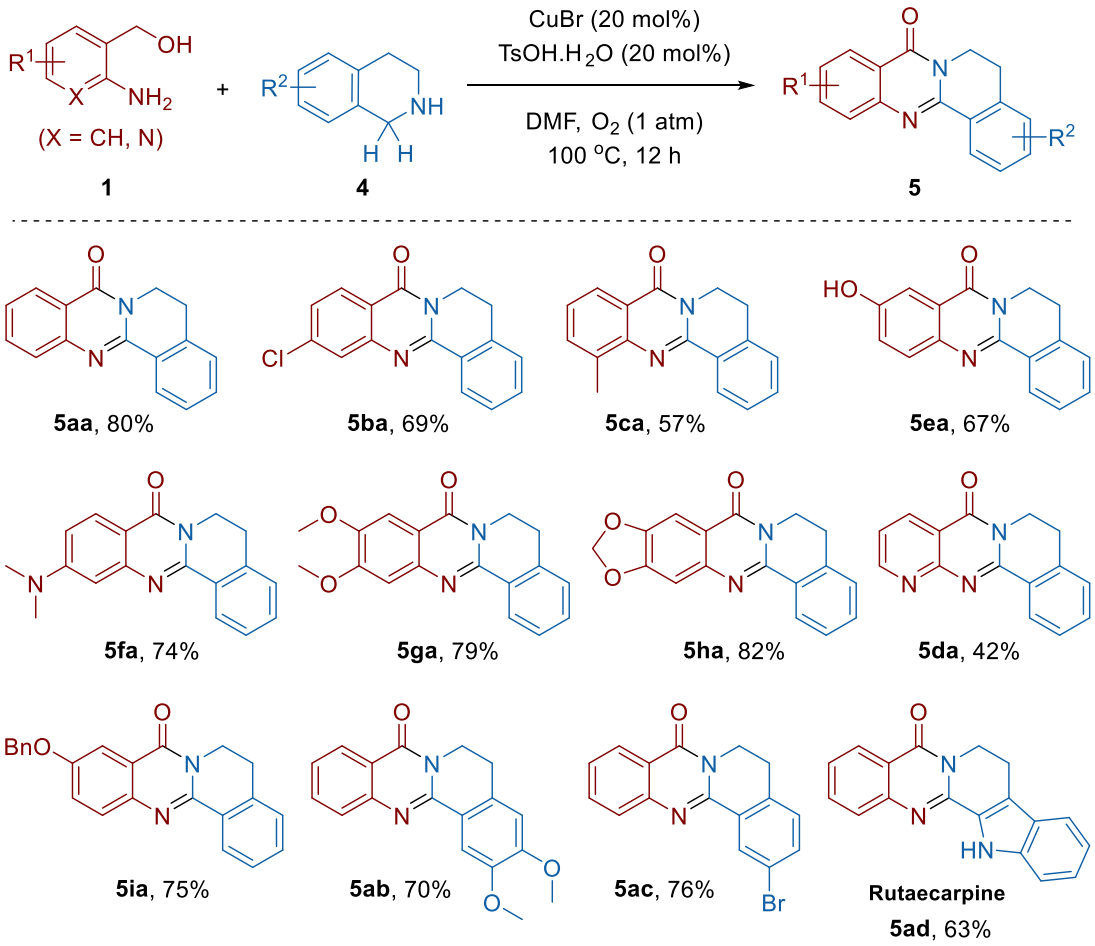


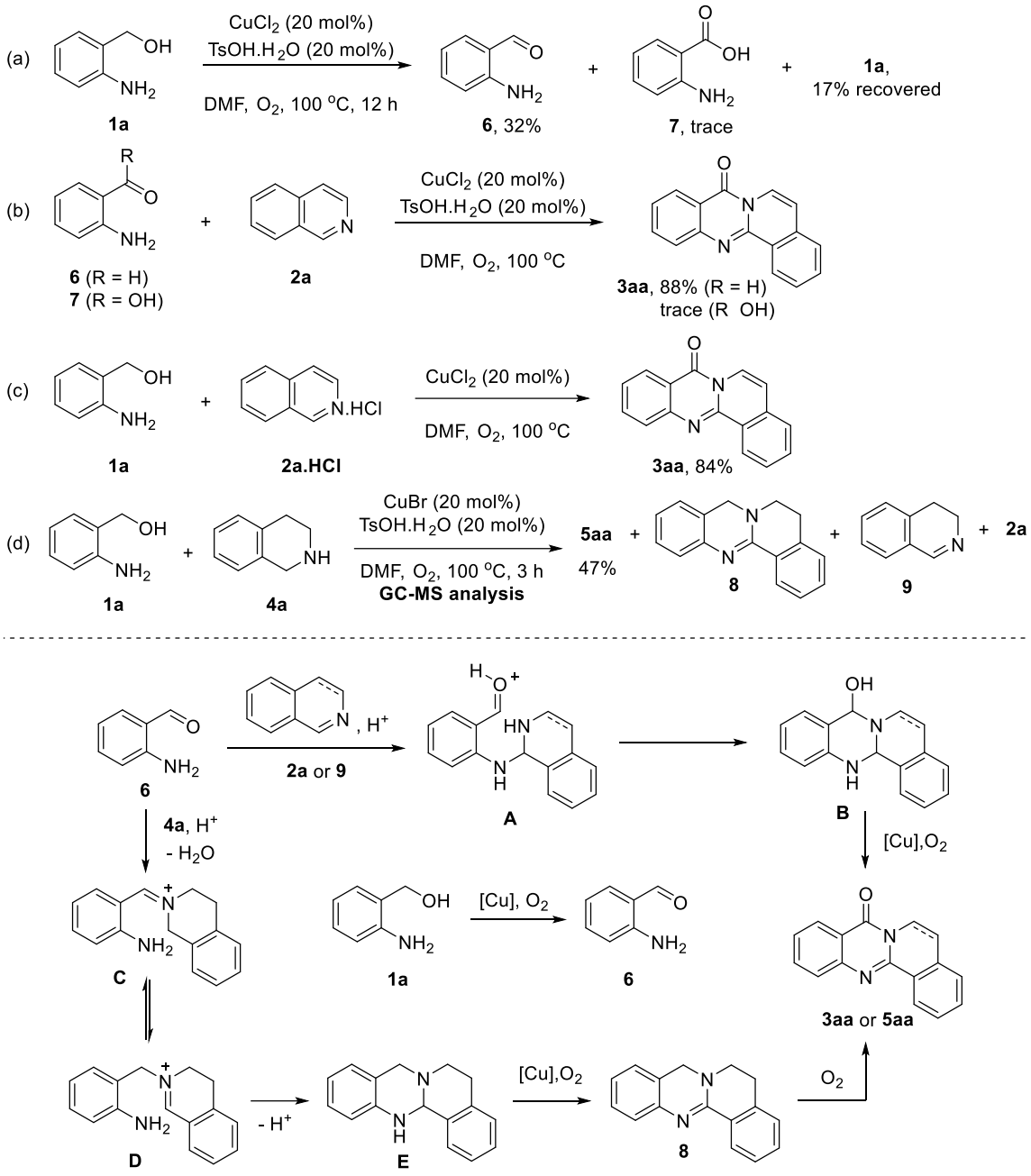
Figure 3.2. Annulation of 2-aminoarylmethanols with tetrahydroisoquinolines.

Reaction conditions: 2-aminoarylmethanols **1** (0.2 mmol, 1.0 equiv.); tetrahydroisoquinolines **4** (0.6 mmol, 3.0 equiv.); CuBr (20 mol%); TsOH.H_2O (20 mol%); DMF (1 mL); 100 °C; 12 h. Yields are isolated yields.

3.1.4. Mechanistic investigations

A potential mechanism for the synthesis of (tetrahydro)isoquinolino-fused quinazolinone is illustrated in Scheme 3.1, supported by several control experiments that explored the fundamental steps of this transformation. It is hypothesized that the key intermediate in this process is 2-aminobenzaldehyde (**6**), generated through the copper-catalyzed oxidation of the alcohol group in the presence of atmospheric oxygen. The formation of the product 3aa is then proposed to occur through an annulation reaction between 2-aminobenzaldehyde (**6**) and isoquinoline (**2a**), with subsequent oxidation leading to the formation of the quinazolinone ring.

A similar pathway for the formation of **5aa** from tetrahydroisoquinoline (**4a**) is also possible, with the cyclic imine (**9**) being the active intermediate. In both scenarios, the considerable basicity of either the isoquinoline or dihydroisoquinoline nitrogen appears to initiate the C(sp^2)-H amination step. An alternative mechanism for the formation of **5aa** is also proposed, due to the observation of an amidine intermediate by GC-MS during the reaction progress. The cyclic amidine (**8**) was susceptible to oxidation, especially under non-acidic condition, when being exposed to an oxygen atmosphere.

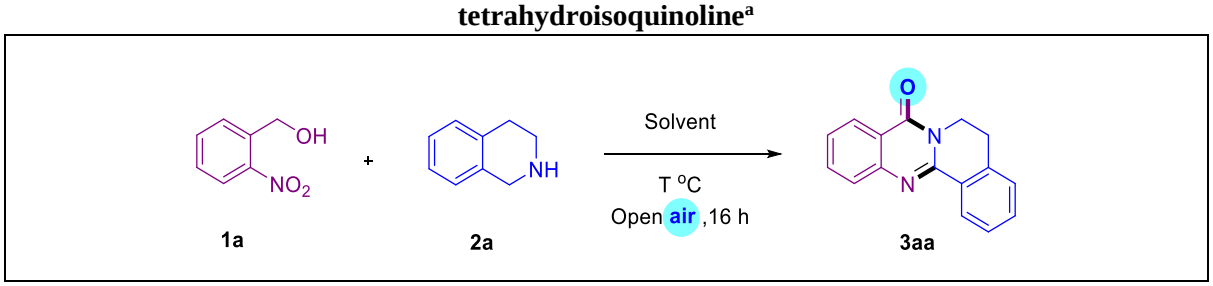


Scheme 3.1. Mechanistic consideration for the Cu-catalyzed annulation of 2-aminobenzyl alcohol with isoquinoline and tetrahydroisoquinoline.

3.2. Metal-free annulation of 2-nitrobenzyl alcohols and tetrahydroisoquinolines toward divergent synthesis of quinazolinones and quinazolinethiones

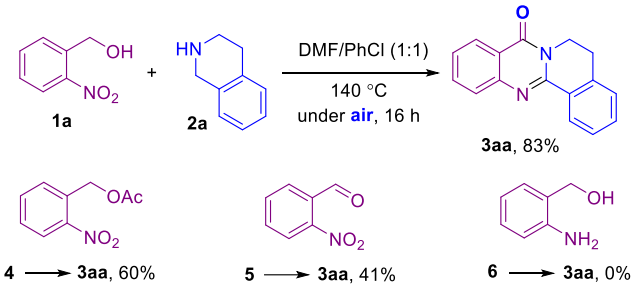
3.2.1. Screening of reaction conditions

Table 3.2. Screening of study for the redox condensation reaction between 2-nitrobenzyl alcohol and tetrahydroisoquinoline[a]



Entry	Temperature, °C	Molar ratio (1a/2a)	Solvent	3aa yield, %
1	100	1:3	-	10
2	120	1:3	-	38
3	140	1:3	-	72
4	140	1:2	-	57
5	140	1:1	-	24
6[b]	140	1:3	DMF	30
7[b]	140	1:3	PhCl	57
8[b,c]	140	1:3	DMF:PhCl	83 (81)[f]
9[b,d]	140	1:3	DMF:PhCl	81
10[b,e]	140	1:3	DMF:PhCl	82
[a]**1a** (0.1 mmol), under air for 16 h. Yields are GC yields using diphenyl ether internal standard. [b]**1a** (0.2 mmol), solvent (0.2 mL). [c]DMF:PhCl 1:1 (v/v). [d]DMF:PhCl 1: 2 (v/v). [e]DMF:PhCl 2:1 (v/v). [f]1 mmol scale.				

To examine any prevalent alternatives, different derivatives and relevant compounds with respect to 2-nitrobenzyl alcohols were investigated (Scheme 4.2). 2-Nitrobenzyl acetate **4** coupled with **2a** to afford the quinazolinone **3aa** in 60% yield. If 2-nitrobenzaldehyde **5** was used, the desired product was obtained in 41% yield. Meanwhile, 2-aminobenzyl alcohol **6** was completely inactive toward the reaction conditions. This suggests that the presence of the nitro group is crucial for this type of auto-redox coupling reaction.



Scheme 3.2. Study of 2-nitrobenzyl alcohol derivatives and relevant compounds.

Reaction conditions: **1a** or isostere (0.1 mmol), **2a** (0.3 mmol), DMF (0.1 mL), PhCl (0.1 mL), at 140 °C under air for 16 h. Yields are GC yields.

3.2.2. Screening of the substrate scope

With the reaction conditions in hand, we then turned our attention to studying the scope of the reaction system (Scheme 3.2). Generally, the annulation was tolerant of both electron-rich (**3ea**, **3ga**-**3na**) and electron-poor (**3da**) *o*-nitrobenzyl alcohols. Functionalities such as chloro (**3ba**), bromo (**3ca**, **3ad**), dimethylamino (**3ea**), and hydroxyl (**3na**) groups were compatible with reaction conditions, affording the corresponding quinazolinones in moderate to good yields. Ester (**3fa**), benzyloxy- (**3ja**), butoxy- (**3la**), and allyloxy- (**3ma**) protected alcohols groups were well compatible with the reaction conditions. The steric effect with respect to the position of NO_2 group (**3pa**) was minor. The reaction was scalable, as 71% yield of **3aa** was isolated in 1 mmol scale. In some entries of tetrahydroisoquinoline derivatives which are sold commercially as hydrochloride salt, $NaHCO_3$ were added to help obtain better yields (**3ab**-**3ad**). Lastly, rutaecarpine (**3ae**) was obtained in 47% yield if anisole solvent was employed.

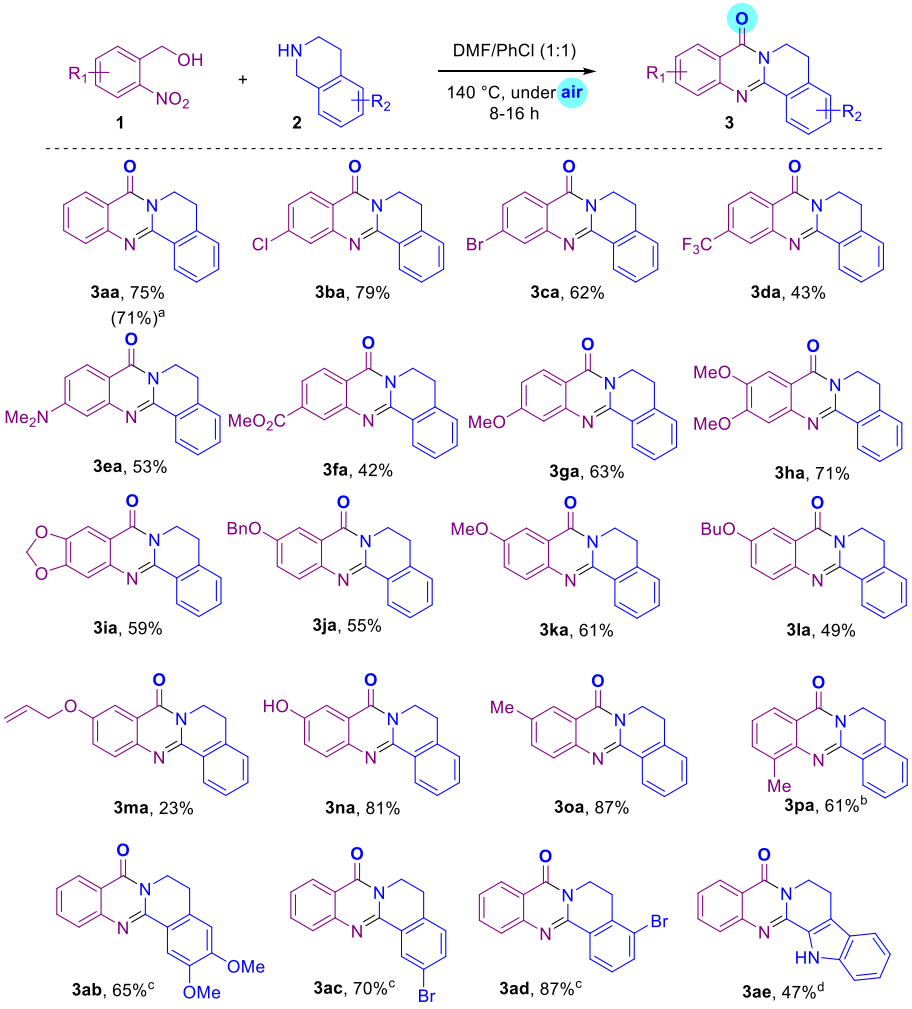
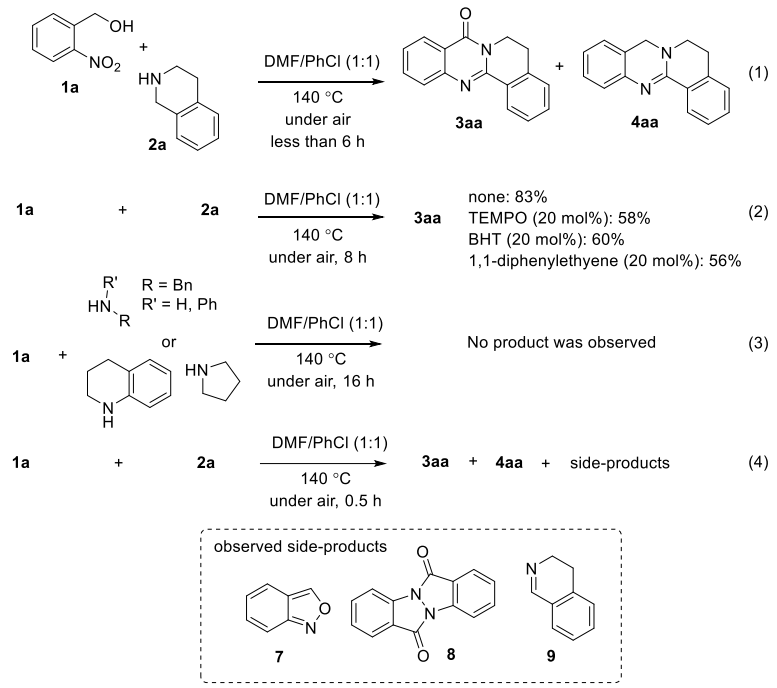


Figure 3.3. Oxidative cross coupling annulation of 2-nitrobenzylalcohols with 1,2,3,4-tetrahydroisoquinolines. Reaction conditions: **1a-1n** (0.2 mmol), **2a-2e** (0.6 mmol), DMF (0.1 mL), PhCl (0.1 mL), under air at 140 °C for 8-16 h. Yields are isolated yields. [a]1 mmol scale. [b]24 h. [c]$NaHCO_3$ (0.6 mmol) was added. [d]Anisole (0.2 mL) was used as solvent.

3.2.3. Mechanistic investigations for the condensation reaction between 2-nitrobenzyl alcohol and tetrahydroisoquinoline under air

During the course of the reaction, the formation of an amidine intermediate **4aa**, presumably a reduced precursor of **3aa**, was observed by GC-MS (eq. 1). This intermediate was gradually oxidized by atmospheric oxygen to form **3aa**, thus no longer observed after 6 hours. The result confirmed that oxidation of benzylic C−H bonds, alpha to nitrogen could occur slowly during the formation of the desired fused-quinazolinone **3aa**. Addition of radical quenchers slowed down the annulation (eq. 2). Some side-products were observed early in the reaction (eq. 4). Among them, anthranil **7** and indazoloindazole **8** were presumably obtained from 2-nitrosobenzaldehyde intermediate, while the hydride transfer of **2a** would afford dihydroisoquinoline **9**.



Scheme 3.3. Control experiments for the condensation reaction between 2-nitrobenzyl alcohol and tetrahydroisoquinoline under air.

Based on the results of control experiments, a plausible mechanism was proposed as shown in Figure 3.4. Redox-neutral decomposition of **1a** would afford a reactive intermediate 2-nitrosobenzaldehyde **10**. Condensation of **10** with **2a** followed by a deprotonation would generate the azomethine ylide **11**. The intermediate **12** would be subsequently obtained via either a 1,3-dipolar cycloaddition or an intramolecular nucleophilic addition. Ring opening followed by dehydration (from **13**) then furnished a quinazolinium ion **14**. Intermolecular hydrogen transfer of **14** and **2a** gave the amidine **4aa**, followed by oxidation to afford the desired product **3aa**. Notably, the present oxidative cross coupling was not compatible with other amine sources such as benzylamine, *N*-phenyl benzylamine, 1,2,3,4-tetrahydoquinoline, and pyrrolidine (Scheme 3.3, eq. 3). This result places emphasis on the fact that the rigid bicyclic structure of **2a** and the benzylic position of the hydrogen atoms in **2a** are incredibly important for a successive hydride transfer reaction.

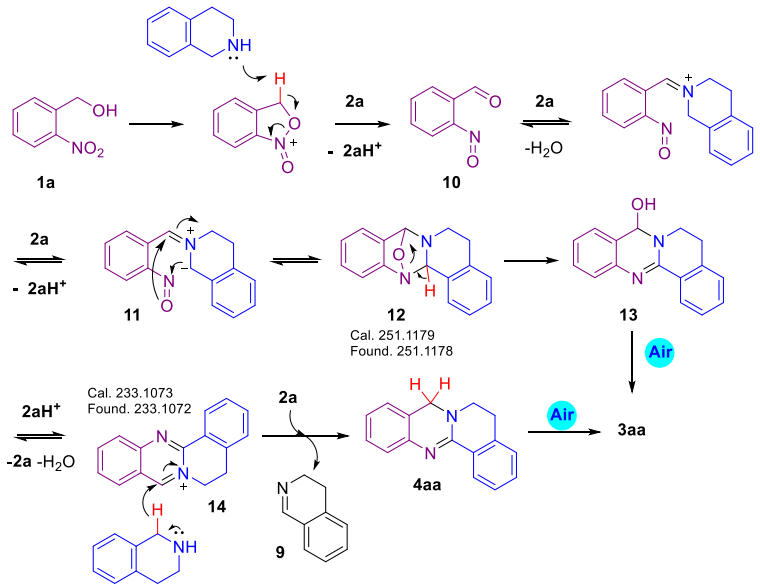


Figure 3.4. Proposed mechanism for the condensation reaction between 2-nitrobenzyl alcohol and tetrahydroisoquinoline under air.

3.2.4. Extended study for the incorporation of sulfur into the products

Based on these previous literatures, and our early observations, we hypothesized that the quinazolium ion **14** and/or amidine **4aa** (as shown in Figure 4.3) could interact with elemental sulfur in place of molecular oxygen to produce quinazolinethiones. Recently, our research group has demonstrated that 2-nitrobenzyl alcohols can be activated using elemental sulfur, DABCO, and urea. Employing this combination of reagents, we successfully achieved the annulation of 2-nitrobenzyl alcohol **1a** with tetrahydroisoquinoline (THIQ) **2a**, leading to the formation of 5,6-dihydro-8H-isoquinolino[1,2-*b*]quinazolin-8-thione **5aa**. Under the optimized conditions, a 77% GC yield of **5aa** was recorded, with an isolated yield of 70% for **5aa**. We then expanded the range of substrates to explore further possibilities, and the results are compiled in Figure 3.5. We obtained quinazolinethiones featuring dimethylamino (**5ea**), protected alcohol (**5ja**, **5ka**, **5la**), and bromo (**5ac**, **5ad**) substituents, all with moderate yields.

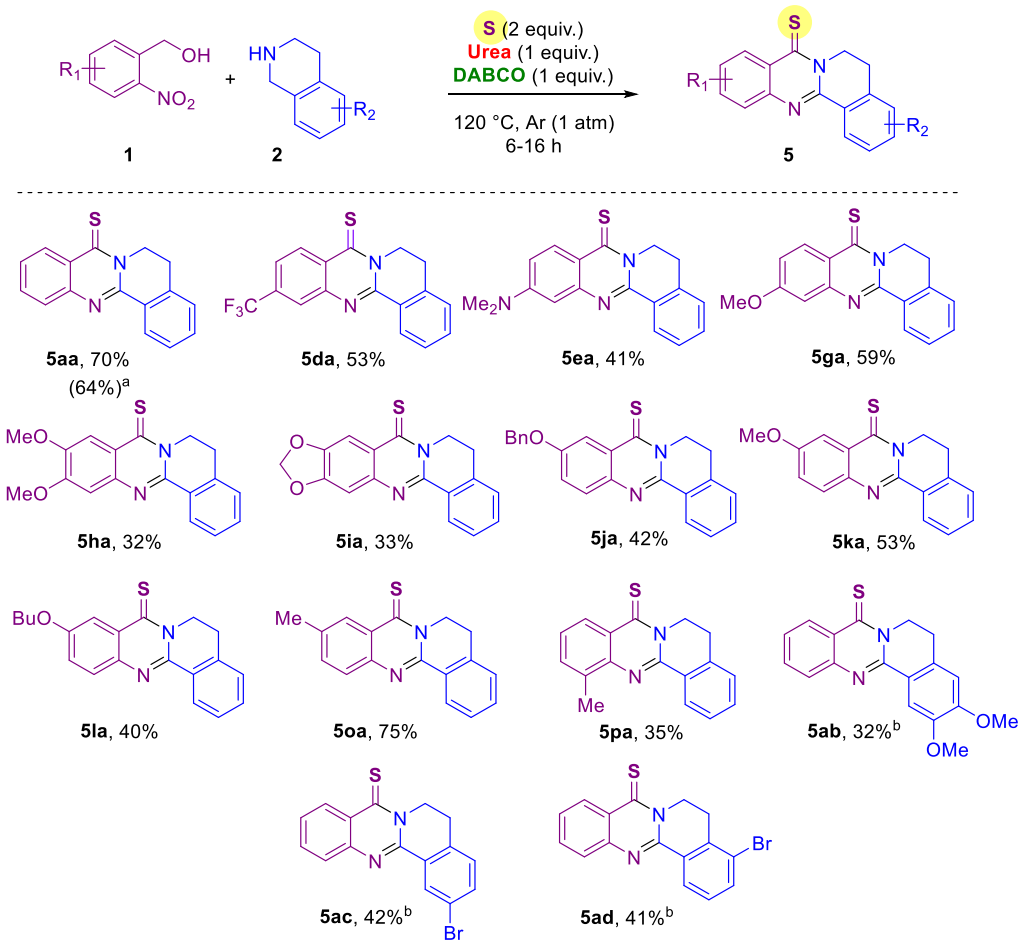
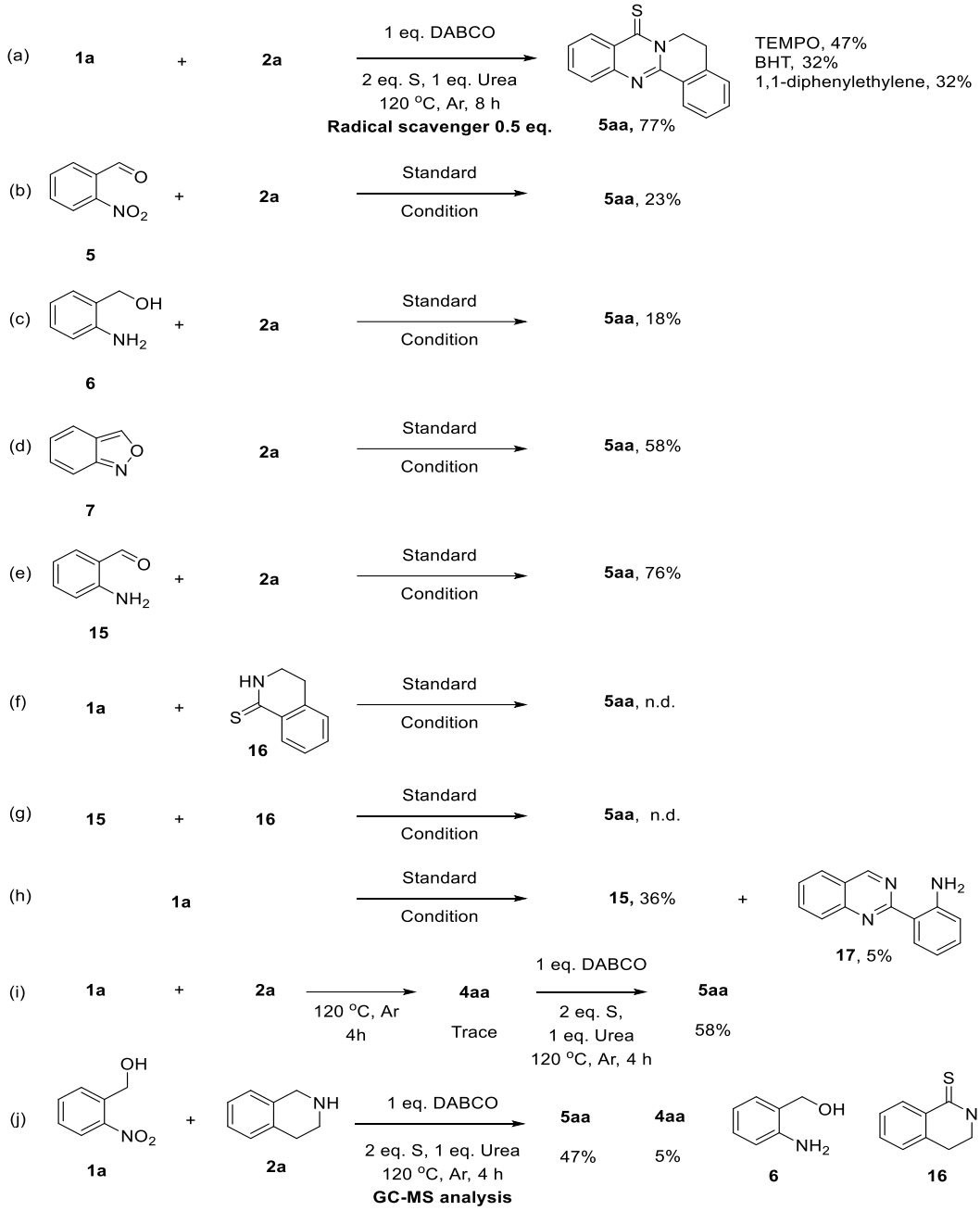


Figure 3.5. Synthesis of quinazolinethiones and possible mechanism.

Reaction conditions: *o*-nitrobenzyl alcohols (0.1 mmol), 2a-2d (0.15 mmol), elemental sulfur (0.2 mmol), DABCO (0.1 mmol), urea (0.1 mmol), at 120 ℃ under argon (1 atm) for 6-16 h. Isolation was performed from two parallel reactions. Yields are isolated yields. [a]1 mmol scale. [b]$NaHCO_3$ (0.15 mmol) was added to neutralize the starting amine.

We conducted several control experiments to understand the elementary steps involved in the transformation of **1a** into **5aa**. Considering the potential for **1a** to undergo redox decomposition to yield the nitroso intermediate **10** (as shown in Figure 3.4), or its conversion through a redox reaction with elemental sulfur to form 2-aminobenzaldehyde, various surrogates of **1a** were examined.



Scheme 3.4. Mechanistic study for the formation of quinazolinthione product.

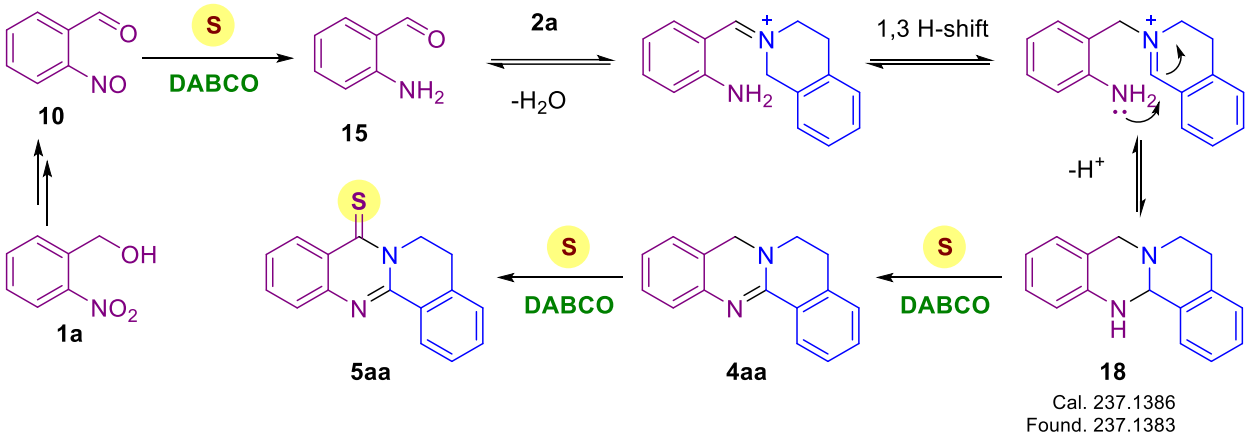


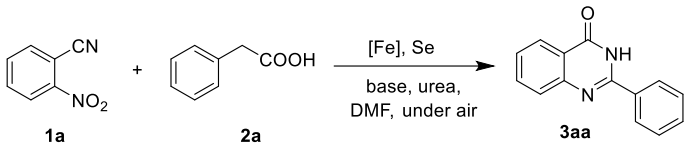
Figure 3.6. Proposed mechanism for the reaction between 2-nitrobenzyl alcohol and tetrahydroisoquinoline in the presence of sulfur and DABCO.

Based on these findings, we propose the following plausible mechanism (outlined in Figure 3.7): 2-nitrobenzyl alcohol **1a** undergoes decomposition to form nitroso benzaldehyde **10**. This intermediate, resulting from the degradation of **1a**, is then reduced by a sulfur-DABCO complex to yield 2-aminobenzaldehyde **15**. Once formed, **15** undergoes a condensation reaction followed by a 1,3-hydride shift, leading to the formation of an aminal **18**. Subsequently, **18** is oxidized by elemental sulfur, producing the amidine intermediate **4aa** and the final product **5aa**.

3.3. Iron-catalyzed, elemental selenium-promoted cyclization of 2-nitrobenzonitriles with arylacetic acids

3.3.1. Screening of reaction conditions

Table 3.3. Screening of optimal reaction conditions[a].

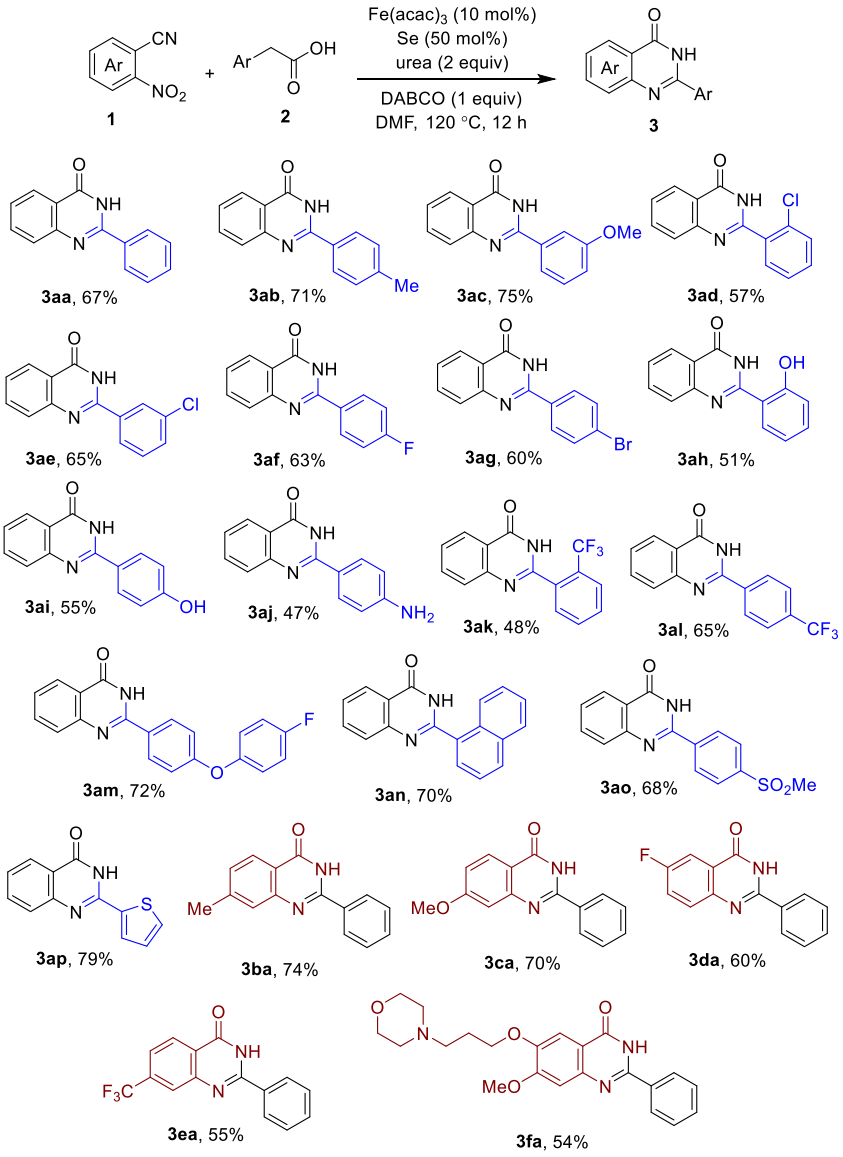


Entry	Temperature (°C)	**1a**:**2a** (molar ratio)	Catalyst (mol%)	GC Yield of **3aa** (%)
1	80	1:2	$FeCl_3$	16
2	100	1:2	$FeCl_3$	34
3	120	1:2	$FeCl_3$	54
4	140	1:2	$FeCl_3$	49
5	120	2:1	$FeCl_3$	17
6	120	1:3	$FeCl_3$	57
7	120	1:2	$Fe(acac)_3$	60
8	120	1:2	$Fe_2(SO_4)_3$	48
9[b]	120	1:2	$Fe(acac)_3$	62
10[c]	120	1:2	$Fe(acac)_3$	53
11	120	1:2	-	10
12[d]	120	1:2	$Fe(acac)_3$	58
13[e]	120	1:2	$Fe(acac)_3$	37
14[d,f]	120	1:2	$Fe(acac)_3$	65
15[d,g]	120	1:2	$Fe(acac)_3$	22

[a]Reaction conditions: **1a** (0.1 mmol), **2a**, urea (0.2 mmol), elemental selenium (0.1 mmol), iron salt (0.01 mmol), DABCO (0.2 mmol), DMF (0.1 mL), 12 h, under air. Yields are GC yields. [b]$Fe(acac)_3$ (0.015 mmol). [c]$Fe(acac)_3$ (0.005 mmol). [d]Elemental selenium (0.05 mmol). [e]No elemental selenium was added. [f]DABCO (0.1 mmol). [g]No DABCO was added. Abbreviations: acac = acetylacetonate, DABCO = 1,4-diazabicyclo[2.2.2]octane.

3.3.2. Screening of the substrate scope

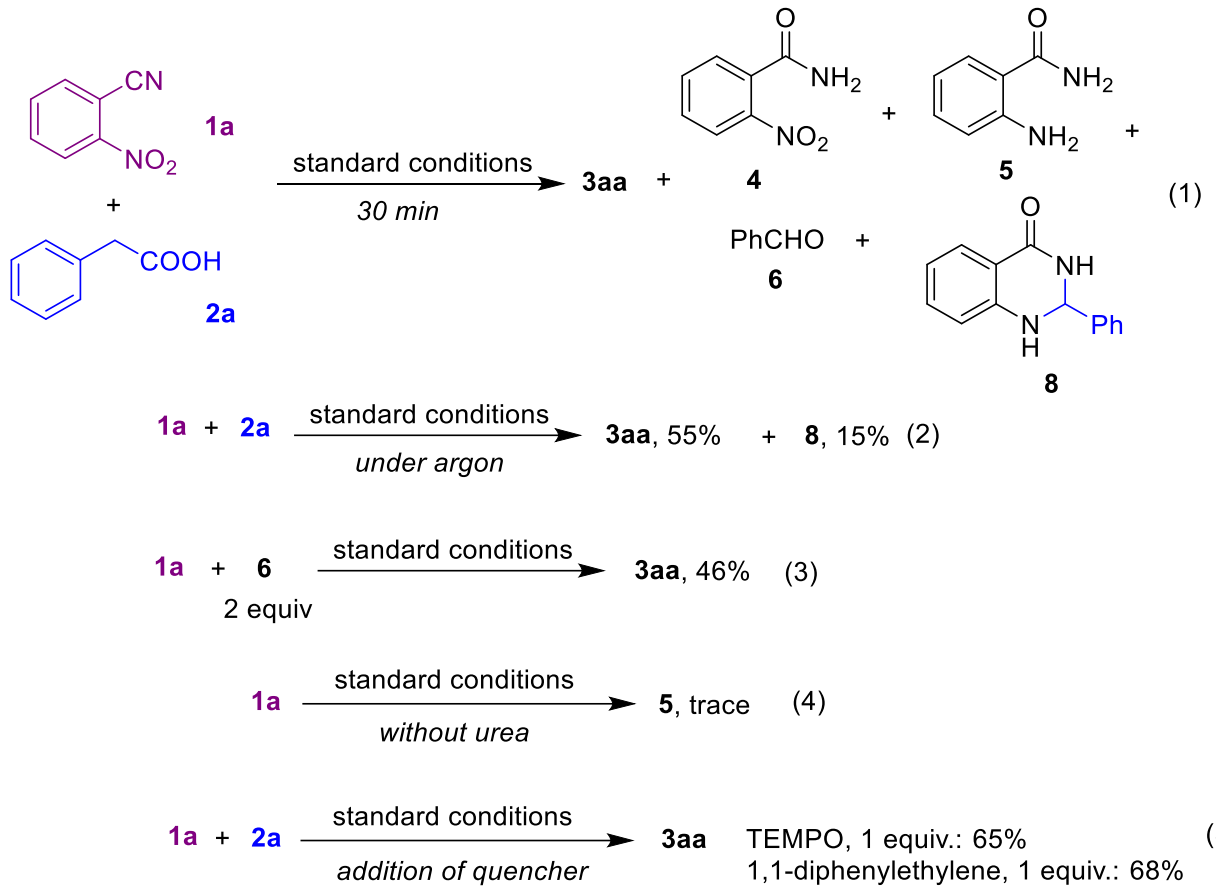
An array of arylacetic acids were successfully utilized for the reaction. Following this procedure, **3aa** was obtained in a 67% isolated yield. Fluoro (**3af**), chloro (**3ad**, **3ae**), bromo (**3ag**), phenoxy (**3am**), and methylsulfonyl (**3ao**) groups were all compatible with the reaction conditions. The annulation was somewhat affected by the steric effect on phenylacetic acids, with *ortho*-substituted substrates showed slightly lower yields of products (**3ad**, **3ah, 3ak**). Notably, the use of unprotected hydroxyl (**3ah**, **3ai**) and amino (**3aj**) substrates was feasible, affording the annulation products in moderate yields. These functional groups are known to form complexes with transition metal catalysts and, normally, this would lead to a detrimental effect to the reaction systems. Heteroarylacetic acids, such as thiophene-derived compound (**3ap**), furnished the quinazolinones in excellent yields. Successful annulation was observed if derivatives of 2-nitrobenzonitrile were attempted. Thus, the products (**3ba**-**3fa**) were obtained in moderate to good yields, including the heavily decorated nitrobenzonitrile substrate **3f**.



Scheme 3.5. Screening of substrate scope.

[a]Reaction conditions: 2-nitrobenzonitriles **1** (0.5 mmol), arylacetic acids **2** (1 mmol), $Fe(acac)_3$ (0.05 mmol), elemental selenium (0.25 mmol), DABCO (0.5 mmol), urea (1 mmol), DMF (1 mL), 120 ℃, 12 h, under air. Yields are isolated yields.

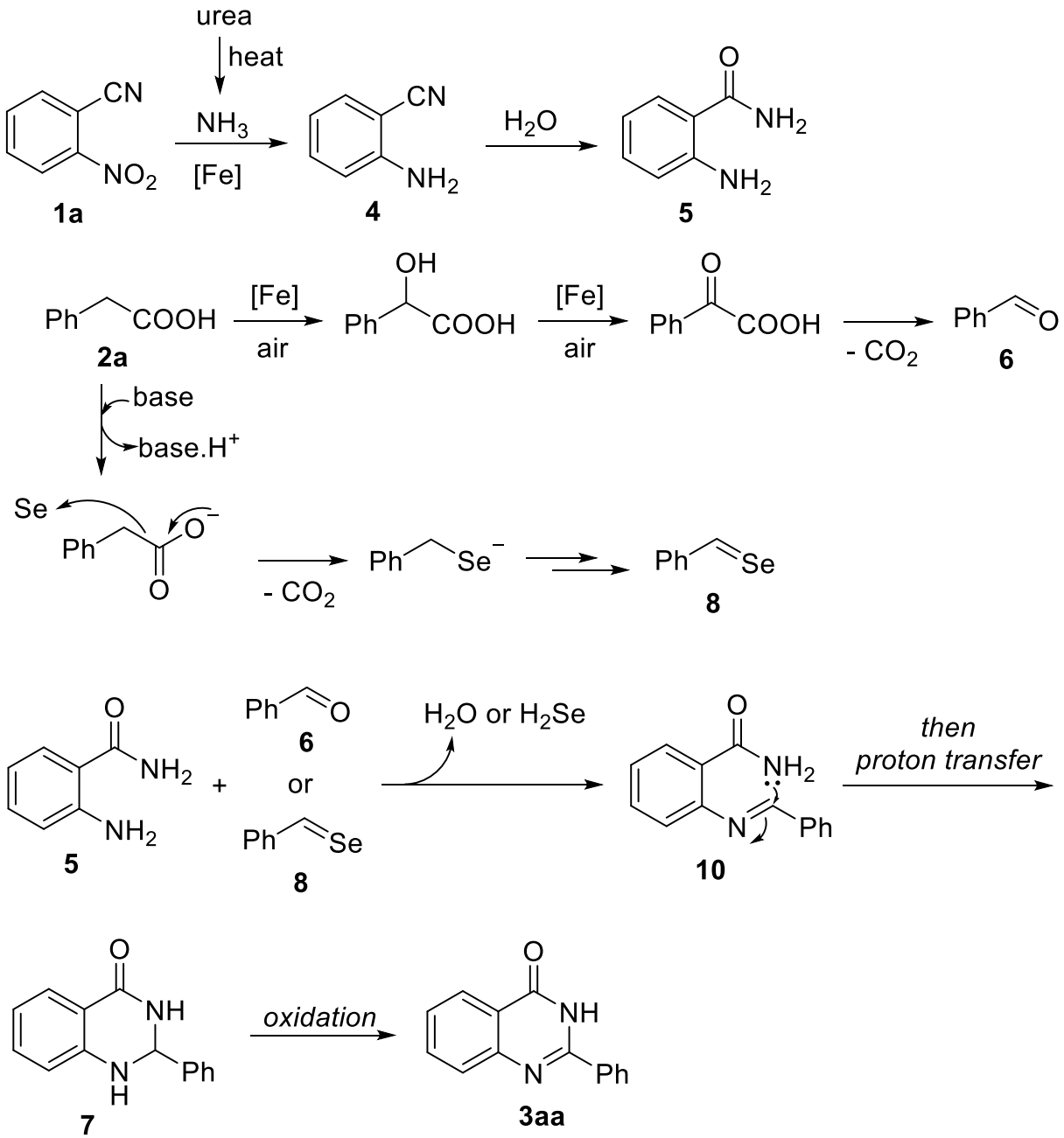
3.3.3. Mechanistic investigations



Scheme 3.6. Mechanistic consideration.

Standard conditions: 1a (0.2 mmol), 2a (0.4 mmol), $Fe(acac)_3$ (0.02 mmol), elemental selenium (0.1 mmol), DABCO (0.2 mmol), urea (0.4 mmol), DMF (0.5 mL), 120 °C, 12 h, under air. Yields are GC yields.

A proposed mechanism for these reactions is shown in Scheme 4.10. Initially, urea furnished ammonia under heat, which facilitated the ensuing iron-catalyzed reduction of 1a to afford the aniline 4. Hydrolysis of 4 under basic condition in the presence of a trace amount of water from moisture would afford 5. Meanwhile, phenylacetic acid 2a could undergo an iron-catalyzed oxidation followed by decarboxylation to yield benzaldehyde 6. Following a proposed mechanism nearly identical to that applied to elemental sulfur, an oxidative decarboxylation of 2a in the presence of elemental selenium would also afford a selenobenzaldehyde 8. Both intermediates 6 and 8 are considerably pivotal for the ensuing cyclization with 5, thus affording imine 10. Intramolecular cyclization followed by oxidation (10→7→3aa) would afford the desired quinazolinone. The last oxidation step could accelerate with the assistance of air or 2-nitrobenzonitrile 1a. In addition to the proposed mechanism mentioned above, there is another potential pathway that cannot be explicitly ruled out. This possibility involves an activation of phenylacetic acid by elemental selenium to afford an α-seleno phenylacetic acid, followed by imine condensation, cyclization, and decarboxylation.



Scheme 3.7. Proposed reaction mechanisms.

CHAPTER 4. CONCLUSION AND SUGGESTION

4.1. CONCLUSION

This dissertation has successfully explored and expanded the frontiers of the synthesis of substituted quinazolinones through the development and optimization of three novel synthetic methods, each characterized by its distinctive reaction systems, catalysts, and reaction conditions.

Copper-Catalyzed Synthesis of Pyrido-Fused Quinazolinones: The first method presented a copper-catalyzed domino C(sp^2)-H amination and annulation strategy to synthesize pyrido-fused quinazolinone derivatives. This process demonstrated the practicality of using molecular oxygen as a green terminal oxidant and showcased the efficiency of copper salts as catalysts for such reaction systems. This approach was noted for its broad substrate scope, relatively mild reaction conditions, and good tolerance of functionalities, making it a significant contribution to pharmaceutical chemistry, material science, and industrial chemistry.

Metal-Free Synthesis of Quinazolinones: The second approach highlighted a simple, metal-free method for the annulation of 2-nitrobenzyl alcohols and tetrahydroisoquinolines to afford fused quinazolinones. This process was distinguished by its tolerance of a wide array of functional groups, starting from nitro compounds as one coupling substrate in an auto-redox pathway. The simplicity and efficiency of the synthetic method, along with its applicability to synthesize quinazolinethiones with elemental sulfur as a terminal oxidant, position it as a valuable addition to the synthetic repertoire for fused quinazolines.

Iron-Catalyzed Synthesis of 2-Arylquinazolin-4(3H)-ones: The third method introduced an iron-catalyzed, elemental selenium-promoted cascade to afford 2-arylquinazolin-4(3*H*)-ones starting from 2-nitrobenzonitriles and arylacetic acids. The reaction system exhibits reasonable yields of products with notoriously challenging functional groups. This method used $Fe(acac)_3$ as the catalyst and featured likely non-radical reaction pathways. The development of this method underscored the potential of using nitro compounds with iron and selenium in quinazolinone synthesis, providing a complementary approach to existing methodologies.

In conclusion, the research presented in this dissertation not only offers new, efficient, and sustainable pathways for the synthesis of quinazolinone derivatives but also significantly contributes to the broader knowledge of catalytic reactivities and substrate combinations in organic synthesis. The methods developed in this thesis would inspire future research in the synthesis of complex organic compounds starting from simple substrates and hold great promise for applications in various fields including drug development and material science. The synergy of these methods represents profound progress in the field of organic synthesis, contributing greatly to the shift towards more sustainable and versatile synthetic methodologies.

4.2. SUGGESTION

In future studies, continuing research towards improving reaction efficiency by using greener solvents as alternatives. Continuing improve efficiency and minimize by-products in the synthesis of quinazolinones. Continue to study the stereochemical structure of reaction products and their biological activities to have sufficient scientific arguments for synthetic studies using quinazolinones as pharmaceutical precursors.