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Synthesis of Quinazoline and Quinazolinone Derivatives via Ligand-Promoted Ruthenium-Catalyzed Dehydrogenative and Deaminative Coupling Reaction of 2-Aminophenyl Ketones and 2-Aminobenzamides with Amines

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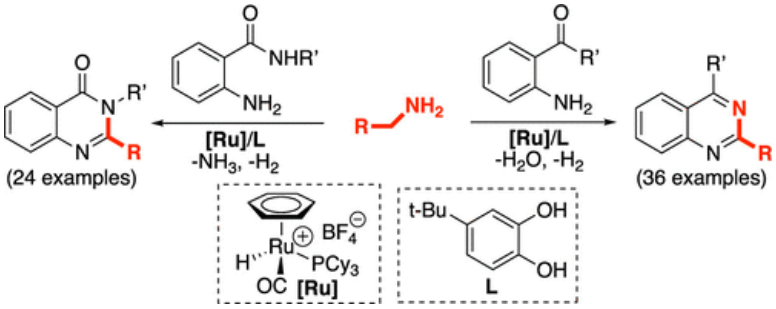
Abstract



The in situ formed ruthenium catalytic system ([Ru]/L) was found to be highly selective for the dehydrogenative coupling reaction of 2-aminophenyl ketones with amines to form quinazoline products. The deaminative coupling reaction of 2-aminobenzamides with amines led to the efficient formation of quinazolinone products. The catalytic coupling method provides an efficient synthesis of quinazoline and quinazolinone derivatives without using any reactive reagents or forming any toxic byproducts.

Quinazolines and quinazolinones are a privileged class of nitrogen heterocyclic scaffolds that have been found to exhibit a broad spectrum of pharmacological activities, including anti-inflammatory, antitubercular, and antiviral activities.(1) A number of quinazoline-based drugs such as prazocin and doxazosine have been approved to treat benign prostatic hyperplasia and post-traumatic stress disorder,(2) while both erlotinib and gefitinib have been used for the treatment of lung and pancreatic cancers (Figure 1).(3) Lapatinib, as an inhibitor for epidermal growth factor, has been shown to be effective in combination therapy for breast cancer.(4) Several quinazolinone-based drugs including idelalisib and fenquizone have been shown to exhibit a broad spectrum of antimicrobial, antitumor, antifungal, and cytotoxic activities.(5)

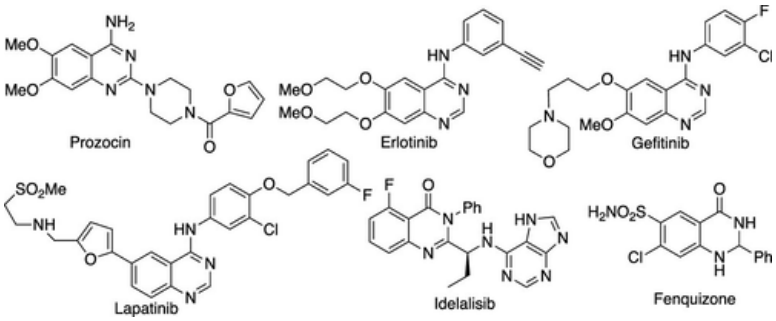


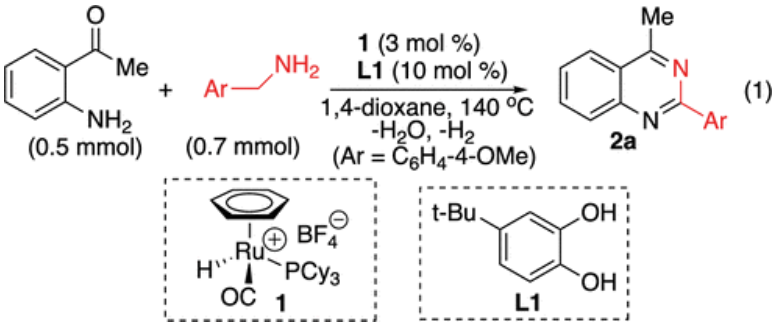
Figure 1. Selected examples of quinazoline and quinazolinone-based drugs.

A number of different synthetic strategies for quinazolines and quinazolinones have been developed over the years, in part to meet the growing needs for screening such derivatives.(6) Several research groups have successfully utilized copper-catalyzed Ullmann-type coupling methods of aryl bromides and benzamidines for the synthesis of quinazoline derivatives.(7) Similar Cu-catalyzed oxidative coupling methods of aniline derivatives with aldehydes and nitriles have also been developed for the construction of quinoline core structures.(8) Transition-metal-catalyzed oxidative C–H amination and alkylation methods have also been successfully employed to synthesize quinazoline and quinazolinone derivatives.(9) Cho and co-workers recently devised a practical synthesis of 2-arylquinazoline derivatives from the coupling of 2-aminobezylamines with halogenated toluene substrates.(10)

Since the advent of the Niementowski condensation of anthranilic acids with amides,(11) a variety of sustainable synthetic methods have also been devised for the assembly of quinazolinone core structures.(12) Much recent research effort has been devoted to the development of catalytic coupling methods to increase efficiency and

selectivity in constructing quinazolinone core structures. A number of transition-metal-catalyzed direct coupling methods of aminobenzamides with alcohols and carbonyl compounds have been successfully exploited to synthesize quinazolinone derivatives.(13) Transition-metal-catalyzed couplings of 2-aminobenzamides with alcohols and ketones(14) and three-component couplings of 2-aminobenzamides, aryl halides or equivalents, and isocyanides(15) are among the notable examples of catalytic synthesis of quinazolinones.

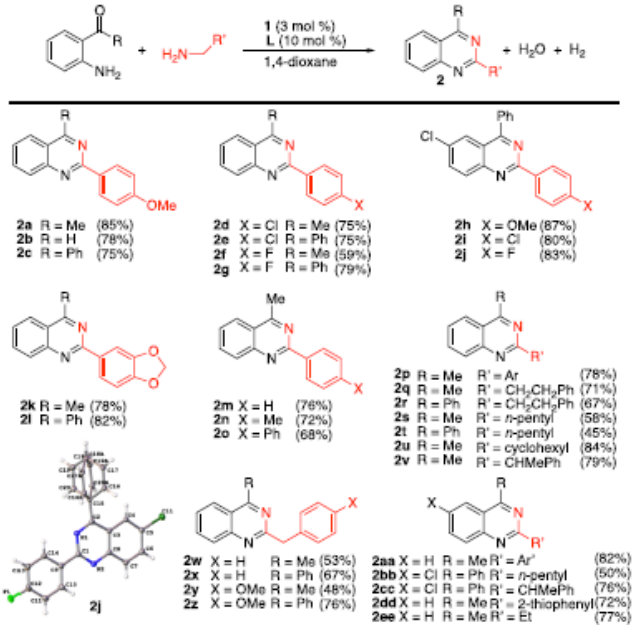
We previously reported that a phenol-coordinated cationic ruthenium–hydride complex is a highly effective catalyst for mediating the hydrogenolysis of aldehydes and ketones to give the corresponding aliphatic products.(16) We subsequently devised a catalytic system generated in situ from a tetranuclear ruthenium–hydride complex and a catechol ligand to promote a direct deaminative coupling of primary amines.(17) We have been exploring the coupling reactions of amines to further extend the synthetic utility of ligand-promoted catalysis, and herein, we disclose an efficient catalytic synthesis of quinazoline and quinazolinone derivatives from the dehydrogenative and deaminative coupling reactions of amino ketones and aminobenzamides with amines.



In an effort to extend the scope and utility of deaminative coupling methods, we initially explored the coupling reaction of 2-amino ketones with amines by employing the ligand-promoted catalysis protocol. Among the initially screened Ru catalysts and ligands, the in situ generated catalytic system from the cationic ruthenium–hydride complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ (**1**) with 4-(1,1-dimethylethyl)-1,2-benzenediol (**L1**) was found to give the highest activity and selectivity for the coupling of 2-(aminophenyl)ethanone with 4-methoxybenzylamine in yielding the quinazoline product **2a** (Table S1). After further ligand screening and optimization studies, we established the standard conditions for the quinazoline product **2a** as **1** (3 mol %) and 4-(1,1-dimethylethyl)-1,2-benzenediol (**L1**) (10 mol %) in 1,4-dioxane (2 mL) at 140 °C (eq 1).

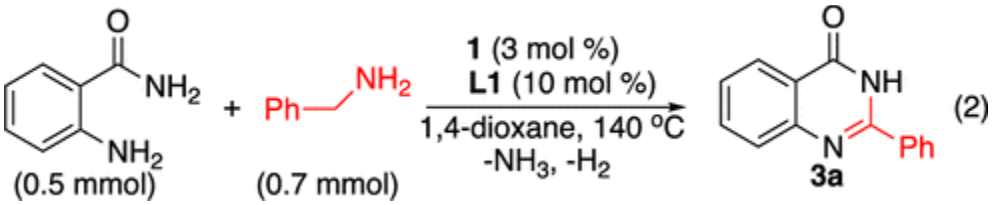
We explored the substrate scope of the coupling reaction by using the catalyst system **1**/**L1** under the standard conditions (Table1). The coupling of 2-aminophenyl ketones with a variety of benzylic amines selectively formed the quinazoline products **2a**–**o**. The coupling of 2-aminophenyl ketones with phenethylamines and with aliphatic amines also gave the selective formation of **2q**,**r** and **2s**–**u**, respectively. While the coupling reaction of 2-aminphenyl ketone substrate with a branched amine smoothly yielded the coupling products **2v** and **2cc**, coupling with sterically demanding secondary amines and branched amines generally yielded only a trace amount of the coupling products under the standard reaction conditions.

Table 1. Synthesis of Quinazolines from the Coupling of 2-Aminophenyl Ketones with Amines[a]



[a]Reaction conditions: amino ketone (0.5 mmol), amine (0.7 mmol), 1 (3 mol %), L1 (10 mol %), dioxane (2 mL), 140 °C, 20 h. Ar = 3,4,5-trimethoxyphenyl, Ar'= 3,5-methylenedioxybenzyl.

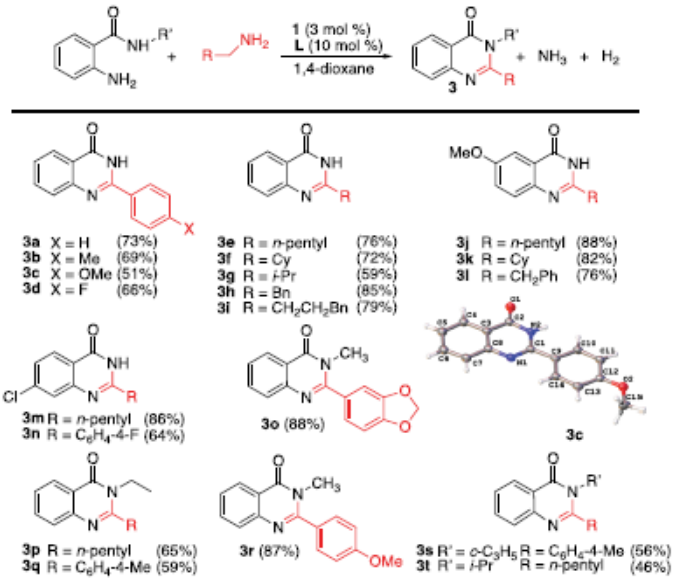
Analytically pure quinazoline products were readily isolated after silica gel column chromatographic separation, and their structures were completely established by spectroscopic methods. The structure of **2j** was also confirmed by X-ray crystallography. The coupling reaction was easily scalable to a 2–3 mmol scale reaction to yield 0.5–0.7 g of **2b**, **2l** and **2z**. The catalytic coupling method furnishes a direct synthesis of quinazoline products without resorting to employing any reactive reagents.



Adopting the previously developed deaminative coupling protocol,(17) we next sought the catalytic coupling reaction of the arylamides with amine substrates to form quinazolinone products. Thus, the treatment of 2-aminobenzamide (0.5 mmol) with benzylamine (0.7 mmol) in dioxane (2 mL) at 140 °C in the presence of the catalyst system **1** (3 mol %)/**L1** (10 mol %) led to the selective formation of the quinazolinone product **3a**, which was analyzed by both GC and NMR spectroscopic methods (eq 2).

The substrate scope of the coupling reaction was explored by using the catalyst system **1**/**L1** under the standard conditions (Table2). The coupling of 2-aminobenzamides with both benzyl- and alkyl-substituted amines led to the selective formation of the quinazolinone products **3a**–**n** with no significant amount of the quinazoline or other side products. The analogous coupling reaction of *N*-alkyl-2-benzamides with both benzylamines and alkyl-substituted amines afforded the corresponding coupling products **3o**–**t** in moderate to high yields.

Table 2. Synthesis of Quinazolinones from the Coupling of 2-Aminobenzamides with Amines[a]



[a]Reaction conditions: benzamide (0.5 mmol), amine (0.7 mmol), 1 (3 mol %), L1 (10 mol %), dioxane (2 mL), 140 °C, 20 h.

Single crystals of **3c** were obtained by slow evaporation in hexanes/EtOAc at room temperature, and its structure was determined by X-ray crystallography. The formation of quinazolinone product can be rationalized by initial deaminative coupling of amide and amine substrates followed by the cyclization dehydrogenation steps. The coupling reaction efficiently assembles synthetically valuable quinazolinone core structures by employing readily available amine and benzamide substrates.

To further demonstrate synthetic utility of the catalytic method, we next performed the couplings of both 2-aminophenyl ketones and 2-aminobenzamides with a number of biologically active amine substrates (Table3). The treatment of 2-aminophenylethanone with tryptamine under the standard conditions led to the indole-substituted product **2ff**. The analogous coupling with (−)-*cis*-myrtanylamine formed the quinazoline product **2gg** (dr = 10:1) with a minimal racemization on the benzylic carbon. The coupling of 2-aminophenylethanone with a morpholinyl-substituted amine predictively formed **2ii**. The coupling of a thiophene-substituted amino ketone with 3,4,5-trimethoxybenzylamine yielded the product **2jj** in 52% yield. The analogous treatment of 2-aminobenzamide with geranylamine formed the corresponding quinazolinone product **3u**, in which the neighboring olefinic group is selectively hydrogenated, while the treatment of a thiophene-substituted amide with 4-phenylbenzylamine formed the corresponding quinazolinone product **3v**. The coupling of 2-aminobenzamide with (−)-*cis*-myrtanylamine formed the coupling product **3w** with a modest diastereoselectivity (dr = 1.9:1). In sharp contrast, the analogous coupling with (+)-dehydroabietylamine resulted in the formation of the coupling product **3x** without any detectable racemization. The structure and stereochemistry of both **3w** (major diastereomer) and **3x** have been confirmed by X-ray crystallography.

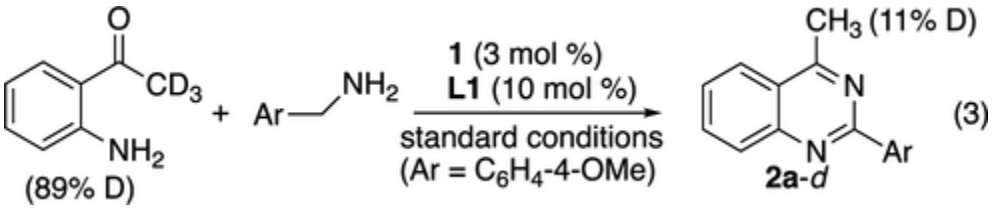
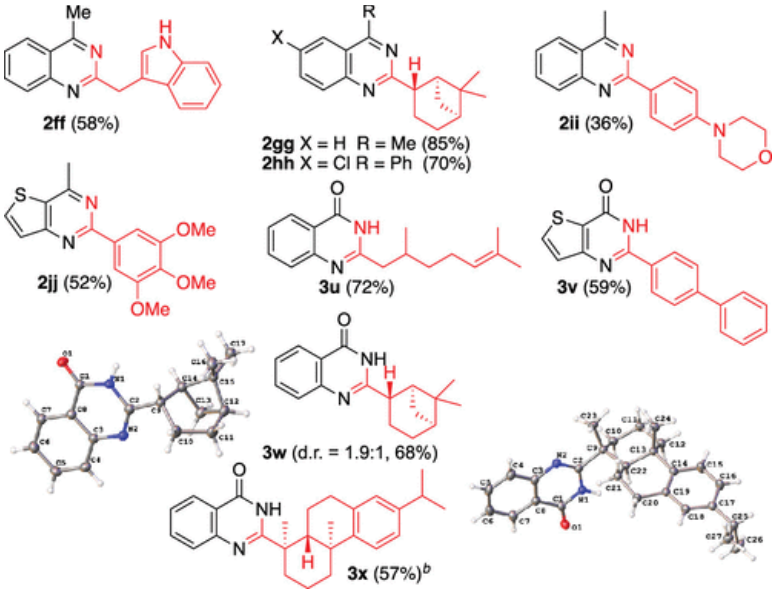


Table 3. Coupling Reaction of 2-Aminophenyl Ketones and 2-Aminobenzamides with Biologically Active Amines[a]

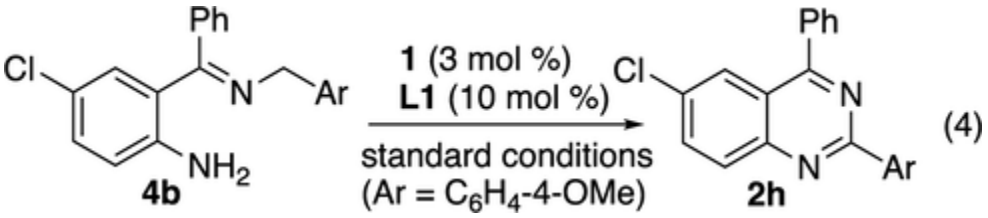


aReaction conditions: amino ketone or benzamide (0.5 mmol), amine (0.7 mmol), **1** (3 mol %), **L1** (10 mol %), dioxane (2 mL), 140 °C, 20 h.

bBenzamide (0.25 mmol), amine (0.35 mmol).

We performed the following set of experiments to probe mechanistic insights on the coupling reaction. First, we examined the deuterium-labeling pattern from the reaction of 2-aminophenylethanone-d_3 (89% D) with 4-methoxybenzylamine (eq 3). The treatment of 2-aminophenylethanone-d_3 (0.5 mmol) with 4-methoxybenzylamine (0.7 mmol) in the presence of **1** (3 mol %)/**L1** (10 mol %) in 1,4-dioxane (2 mL) was heated in an oil bath at 140 °C for 20 h. The isolated product **2a**-*d* as analyzed by ^{1}H and ^{2}H NMR contained only 11% of the deuterium on the methyl group as most of the deuterium had been washed away (Figure S1). A relatively small amount of the deuterium on **2a**-*d* suggests an extensive keto–enol tautomerization under the reaction conditions.

We next monitored the reaction progress by using NMR spectroscopy to discern intermediate species for the coupling reaction. In a resealable NMR tube, a reaction mixture of 2-aminophenylethanone (0.25 mmol), 4-methoxybenzylamine (0.25 mmol), and in situ generated catalyst **1** (3 mol %)/**L1** (10 mol %) in toluene-d_8 (0.5 mL) was immersed an oil bath set at 140 °C. The tube was taken out from the oil bath at 20 min intervals, and the reaction progress was recorded by ^{1}H NMR. The appearance of new set of peaks attributed to the imine product **4a** has been observed initially as both starting substrates are consumed. After about 100 min of reaction time, the peaks due to the quinazoline product **2a** began to appear as the imine peaks gradually disappeared. The plot of relative concentration vs time is shown in Figure 2.



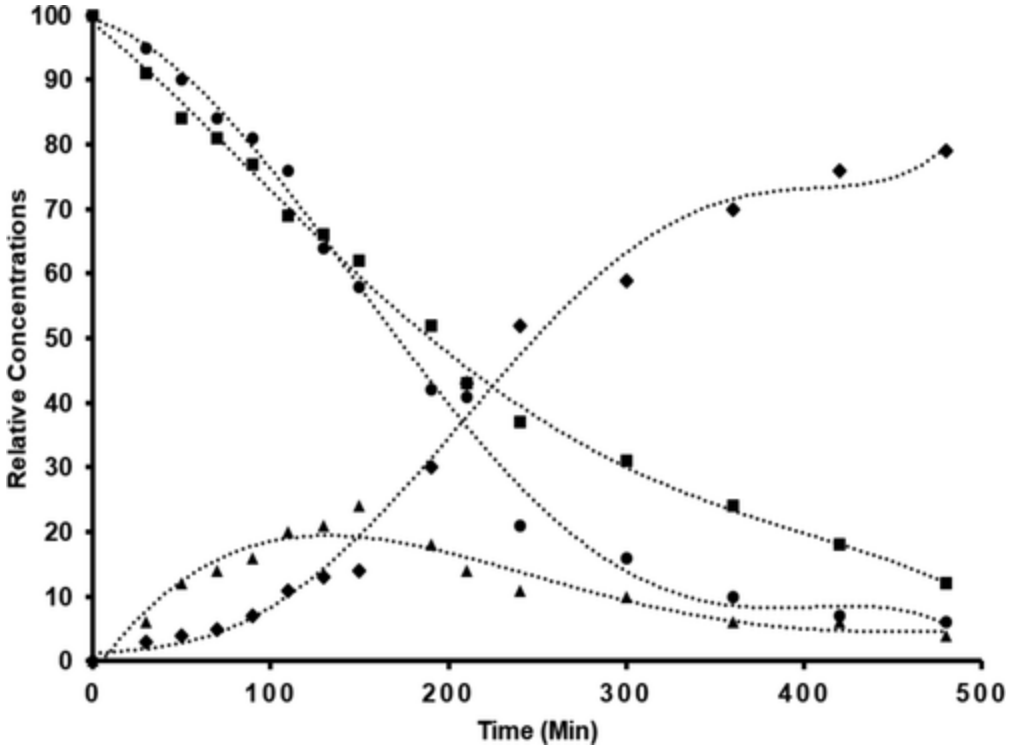
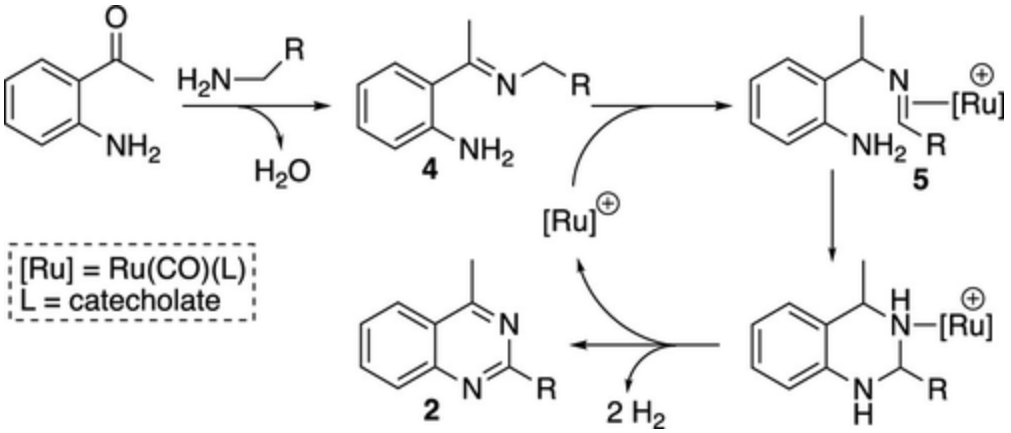


Figure 2. Plot of relative concentration vs time for the coupling reaction of 2-aminophenylethanone (■) with 4-methoxybenzylamine (●), **2a** (⧫), and **4a** (▲).

To establish the imine as a requisite intermediate for the formation of **2**, independently synthesized **4b** was treated with **1**/**L1** under the standard conditions, which proceeded smoothly to afford the quinazoline product **2h** in 87% yield (eq 4). In a control experiment, the analogous treatment of **4b** with *p*-toluenesulfonic acid (5 mol %) did not form the product **2h** under otherwise similar reaction conditions. The results showed that the ruthenium catalysis is essential for the cyclization and dehydrogenation steps of the product formation.

Although much kinetic and spectroscopic information is still needed to ascertain a detailed reaction mechanism, we offer a plausible mechanistic sequence for the formation of quinazoline products **2** on the basis of these preliminary results (Scheme 1). The reaction profile study clearly implicates that the imine intermediate **4** is generated from initial dehydrative coupling of amino ketone and amine substrates. We propose that the Ru catalyst facilitates the imine isomerization to form the imine-coordinated species **5**. The subsequent cyclization and dehydrogenation steps would yield the quinazoline product **2**. In support of this, we previously found that the ruthenium–hydride complexes are efficient catalysts for olefin isomerization reaction(18) and dehydrogenation of saturated amines and carbonyl compounds.(19) While the exact role of catechol ligand has yet to be established, we believe that a redox-active catechol ligand may be facilitating the dehydrogenation step on the catalysis.(20)



Scheme 1. Possible Mechanistic Sequence for the Formation of Quinazoline Products

In summary, we have been able to devise a catalytic protocol for the synthesis of quinazoline and quinazolinone derivatives from the dehydrogenative and deaminative couplings of 2-aminophenyl ketones and 2-aminobenzamides with amines. The in situ formed ruthenium–hydride complex with a catechol ligand (**1/L1**) was found to exhibit uniquely high catalytic activity and selectivity in forming these products. The salient features of the catalytic method are that it employs readily available substrates, exhibits a broad substrate scope while tolerating common organic functional groups, and does not require any reactive reagents or forms any wasteful byproducts. We are currently exploring synthetic utility of the deaminative coupling protocol in constructing other nitrogen heterocyclic core structures.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01082.

Experimental procedures, spectroscopic data, and NMR spectra (PDF)

pdf

ol9b01082_si_001.pdf (10.56 MB)

Accession Codes

CCDC 1906356–1906359 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

The authors declare no competing financial interest.

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