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Synthesis of Flavanone and Quinazolinone Derivatives from the Ruthenium-Catalyzed Deaminative Coupling Reaction of 2′-Hydroxyaryl Ketones and 2-Aminobenzamides with Simple Amines

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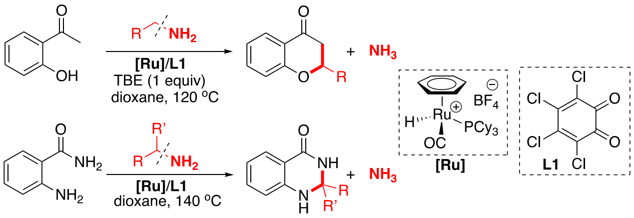
ABSTRACT: The cationic Ru−H complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ (**1**) with 3,4,5,6-tetrachloro-1,2-benzoquinone (**L1**) was found to be a highly effective catalyst for the deaminative coupling reaction of 2′-hydroxyaryl ketones with simple amines to form 3-substituted flavanone products. The analogous deaminative coupling reaction of 2-aminobenzamides with branched amines directly formed 3,3-disubstituted quinazolinone products. The catalytic method efficiently installs synthetically useful flavanone and quinazolinone core structures without employing any reactive reagents.



Transition-metal-catalyzed coupling methods via C−N bond activation have emerged as a powerful synthetic protocol for utilizing amines and related nitrogen compounds in organic synthesis.[1] Since the Garg[2] and Szostak[3] groups independently reported Ni-catalyzed coupling methods via amide C−N bond cleavage, a number of catalytic cross-coupling methods have been devised to synthesize a variety of amides and related nitrogen arene products.[4] Kakiuchi's seminal report[5] on the chelate-assisted Ru-catalyzed deaminative coupling method of arylamines has also inspired the development of Suzuki−Miyaura-type cross-coupling methods of anilines and arylamines via arene $C(sp^2)$−N bond cleavage.[6] Watson and other groups successfully employed pyridinium salts as an effective reagent to promote a variety of deaminative C−C coupling reactions.[7] The Martin group recently reported a site-selective Ni-catalyzed deaminative alkylation of unactivated olefins by using pyridinium salts.[8] Whereas a number of photocatalytic methods have been successfully developed for selective deaminative alkylation and arylation reactions,[9] the exploitation of catalytic deaminative coupling methods without the use of simple amines has been less well developed.

We recently devised a highly chemoselective Ru-catalyzed deaminative coupling method that employs a redox-active catechol/benzoquinone ligand-promoted hydrogen borrowing process to facilitate the deaminative coupling reactions.[10−12] For example, we discovered that a cationic ruthenium catalyst $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ (**1**) with a redox-active 3,4,5,6-tetrachloro-1,2-benzoquinone (**L1**) effectively promotes the deaminative coupling reaction of ketones with amines to yield α-alkylated ketone products.[10] We also found that the *in-situ*-generated catalyst from the Ru−H complex **1** and a 1,2-catechol ligand effectively promotes the deaminative coupling reaction of 2-aminophenyl ketones and 2-aminobenzamides with simple amines to form quinazoline and quinazolinone derivatives, respectively.[11] The same catalytic system was found to promote the deaminative coupling reaction of primary amines to selectively form secondary amines.[12] We have been exploring the reactions of various carbonyl compounds with simple amines to extend the scope and synthetic applicability of the deaminative coupling method. Herein we report a set of new catalytic deaminative coupling reactions of 2′-hydroxyaryl ketones and 2-aminobenzamides with simple amines that feature the chemoselective C−N bond cleavage of amine substrates in forming synthetically valuable flavanone and quinazolinone products without using reactive reagents or forming toxic byproducts.

We initially discovered that the *in-situ*-generated catalyst system **1**/**L1** is highly effective for promoting the deaminative coupling reaction of 2′-hydroxyaryl ketones with linear amines. Thus, the treatment of 2′-hydroxy-5′-methoxyacetophenone (0.50 mmol) with *n*-hexylamine (1.0 mmol) in the presence of **1** (2 mol %)/**L1** (10 mol %) and *t*-butylethylene (0.50 mmol) in 1,4-dioxane (2 mL) at 120 °C led to the selective formation of the flavanone product **2a** (eq 1). In a series of optimization studies, the cationic Ru−H catalyst **1** with **L1** was found to be the most suitable for promoting the coupling reaction among screened ruthenium catalysts and catechol/benzoquinone

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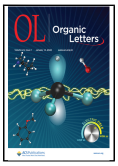

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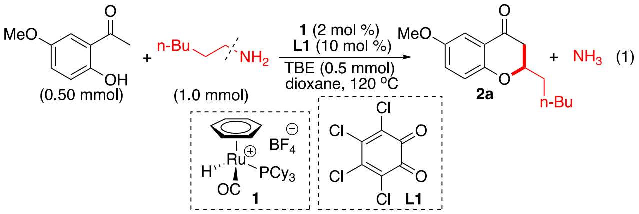
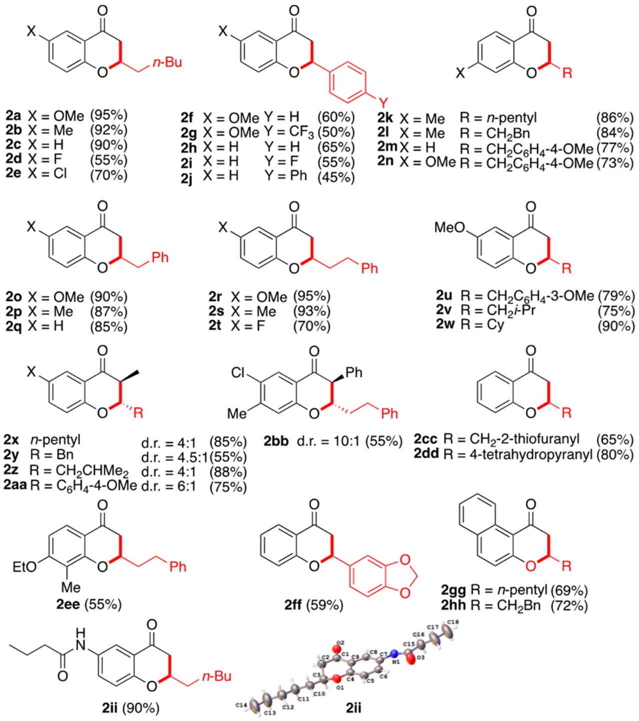


ligands (Tables S1 and S2, Supporting Information (SI)). The addition of a hydrogen scavenger *t*-butylethylene was found to substantially improve the product yield of **2a**, whereas the absence of **L1** was found to drastically decrease the product yield. The ammonia byproduct in a crude mixture was detected by gas chromatography (GC).

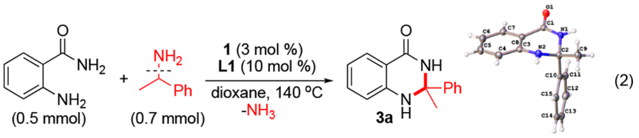
We explored the substrate scope of the deaminative coupling reaction by using the optimized procedure (Scheme 1). 2′-Hydroxyacetophenones with both electron-releasing and -withdrawing groups at the 5′-position were found to be suitable substrates for the coupling reaction with both alkyl- and aryl-substituted amines to form the 3-substituted flavanone products **2a**–**2j**. Both aliphatic and benzylic amines were found to readily react with 2′-hydroxyaryl ketones to form the products **2k**–**2n**. The analogous coupling reaction of 2′-hydroxyaryl ketones with a variety of aliphatic and benzylic amines formed the corresponding coupling products **2o**–**2w** in good to excellent yields. A diastereomeric mixture of the 2,3-disubstituted flavanone products **2x**–**2aa** was formed from the reaction of 2′-hydroxyphenylpropanone with both aliphatic and benzylic amines, favoring the formation of the anti-diastereomer in a 4:1 to 6:1 ratio. Interestingly, the coupling reaction of 5′-chloro-2′-hydroxy-4′-methyl-2-phenylacetophenone with 3-phenyl-1-propylamine formed a highly diastereoselective **2bb** (d.r. = 10:1). A number of heteroatom-containing amine substrates such as 2′-thiophenethylamine and 4-aminomethyltetrahydropyrane predictively afforded the corresponding flavanone products **2cc**–**2dd** in good yields. The coupling reaction with branched amines was quite sluggish, leading to low yields of the coupling products. Also, a scale-up coupling reaction of 2′-hydroxy-5′-methoxyacetophenone (3.0 mmol) with 2-phenylethanamine was performed, which led to the isolation of the product **2o** in 76% yield (0.61 g). The structure of the flavanone products was completely established by spectroscopic methods, and the solid-state structure of **2ii** was also determined by X-ray crystallography. The catalytic method delivered the regioselective formation of 3-substituted flavanone products **2** from the direct coupling of readily available 2′-hydroxyaryl ketones with linear amines without using any reactive reagents.

Scheme 1. Deaminative Coupling Reaction of 2′-Hydroxyaryl Ketones with Linear Amines[a]



[a] Reaction conditions: 2′-hydroxyaryl ketone (0.50 mmol), amine (1.0 mmol), *t*-butylethylene (0.5 mmol), **1** (2 mol %), **L1** (10 mol %), 1,4-dioxane (2 mL), 120 °C, 20 h.

To extend the substrate scope of deaminative coupling method, we next explored the coupling reaction of 2-aminobenzamides with branched amines. The treatment of 2-aminobenzamide (0.50 mmol) with 2-phenethylamine (0.70 mmol) in the presence of **1** (3 mol %) and **L1** (10 mol %) in 1,4-dioxane at 140 °C cleanly afforded the 3,3-disubstituted quinazolinone product **3a** along with ammonia as the only byproduct (eq 2). Once again, the optimization efforts established that the cationic Ru–H complex **1** with an electron-poor benzoquinone **L1** exhibited the highest activity among the screened Ru catalysts and benzoquinone ligands (Tables S3 and S4).



We surveyed both the benzamide and amine substrate scope by using the optimized conditions (Scheme 2). The coupling reaction of 2-aminobenzamide with *para*-substituted phenethylamines cleanly afforded the corresponding 3,3-disubstituted quinazolinone products **3a**–**3e**, whereas the coupling with both aliphatic and aryl-substituted branched amines predictively yielded the quinazolinone products **3f**–**3k**. The analogous treatment of 2-aminobenzamide with amine substrates having a cyclic group directly yielded the 3,3-*spiro*-quinazolinone products **3l**–**3u**. The coupling of six-substituted 2-aminobenzamides with *exo*-2-aminonorbornane and 2-aminoindan yielded the quinazolinone products **3v** and **3x**, respectively. The quinazolinone products were readily isolated by either crystallization or column chromatographic methods, and the solid-state structure of **3a** was also determined by X-ray crystallography.[13]

To demonstrate synthetic utility of the catalytic method, we next explored the coupling reaction of 2′-hydroxyaryl ketones and 2-aminobenzamides with a number of biologically active amine substrates (Scheme 3). The treatment of 2′-hydroxy-5′-methoxyacetophenone with geranylamine formed the coupling product **2jj** in a 1:0.8 diastereomeric mixture, which was accompanied by a regioselective hydrogenation on the proximal double bond. The coupling of 2′-hydroxy-5′-methoxyacetophenone to (−)-*cis*-myrtanylamine yielded a 1:1 diastereomeric mixture of the coupling product **2kk**. The

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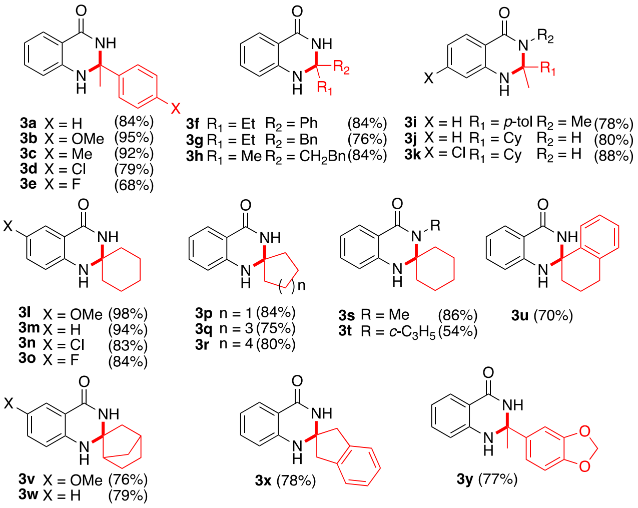
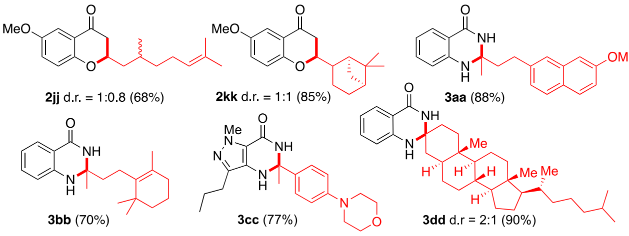
Scheme 2. Synthesis of 3,3-Disubstituted Quinazolinone Derivatives from the Coupling of 2-Aminobenzamides with Branched Amines[a]



[a]Reaction conditions: 2-aminobenzamide (0.50 mmol), amine (0.70 mmol), **1** (3 mol %), **L1** (10 mol %), 1,4-dioxane (2 mL), 140 °C, 20 h.

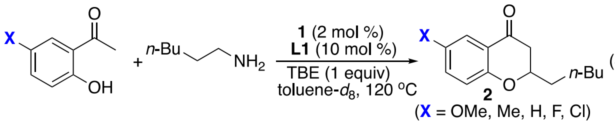
Scheme 3. Deaminative Coupling Reaction of 2′-Hydroxyaryl Ketones and 2-Aminobenzamides with Biologically Active Amines[a]



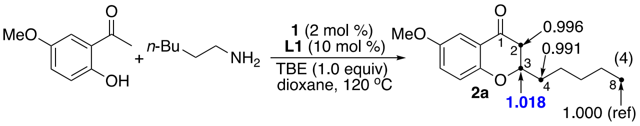
[a]Reaction conditions: 2′-hydroxyaryl ketone (0.50 mmol) or 2-aminobenzamide (0.50 mmol), amine (0.7−1.0 mmol), *t*-butylethylene (0.5 mmol), **1** (2−3 mol %), **L1** (10 mol %), 1,4-dioxane (2 mL), 120−140 °C, 20 h.

coupling reaction of 2-aminobenzamide with 1-[4-(4-morpholinyl)phenyl]ethanamine cleanly yielded the quinazolinone product **3cc**. The analogous coupling reaction of 2-aminobenzamide with the *in-situ*-generated 1-(4-(6-methoxynaphthalen-2-yl)but-2-en-2-yl)pyrrolidine formed the quinazoline product **3aa** in 70% isolated yield. The coupling of 2-aminobenzamide with 1-(4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-2-en-2-yl)pyrrolidine afforded the 3,3-disubstituted product **3bb**, whereas the coupling with a steroidal pyrrolidine derivative yielded the coupling product **3dd** in a 2:1 diastereomeric ratio. These examples clearly illustrate the synthetic versatility of the deaminative catalytic method in constructing flavanone and quinazolinone products.

To probe electronic influence of 2′-hydroxyaryl ketone substrate on the product formation, we constructed a Hammett plot from the reaction of a series of 5′-substituted 2′-hydroxyacetophenones with *n*-hexylamine (eq 3). The rate of the coupling reaction of the *para*-substituted 2′-hydroxy-5′-X-acetophenone (0.10 mmol) (X = OMe, Me, H, F, Cl) with *n*-hexylamine (0.20 mmol) and *t*-butylethylene (0.10 mmol) in the presence of **1** (2 mol %)/**L1** (10 mol %) in toluene-d_8 (1.5 mL) was measured by using NMR spectroscopy. The appearance of the product peak was recorded in 40 min intervals, and it was normalized against an internal standard (C_6Me_6). The k_{obs} of each catalytic reaction was determined from a first-order plot of $-ln([p\text{-X-}C_8H_7O_2]_t/[p\text{-X-}C_8H_7O_2]_0)$ versus time. The Hammett plot of $\log(k_X/k_H)$ versus σ_p showed a linear correlation, with a strong promotional effect from the ketone substrates with an electron-releasing group ($\rho = -0.9 \pm 0.2$) (Figure S1). A relatively high negative ρ value suggests a considerable positive charge build up in the transition state.

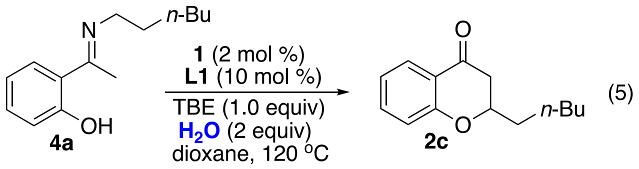


To discern the possible turnover-limiting step, we employed Singleton's NMR technique to measure the carbon kinetic isotope effect (KIE) of the coupling reaction.[14] Thus the treatment of 2′-hydroxy-5′-methoxyacetophenone (2.0 mmol), *n*-hexylamine (4.0 mmol), and *t*-butylethylene (1.0 equiv) in 1,4-dioxane (2 mL) was heated in the presence of **1** (2 mol %)/**L1** (10 mol %) to 120 °C for 20 h (eq 4). The product **2a** was isolated by column chromatography on silica gel, and the procedure was repeated two more times to provide the product sample at high conversion. The same experimental procedure was employed to provide the product **2a** at low conversion, thereby stopping the reaction after 2.5 h. The high-precision $^{13}C\{^1H\}$ NMR analysis showed the most significant carbon KIE on the C(3)-carbon of **2a** when the ^{13}C ratio of the product at high conversion was compared with the sample obtained from a low conversion (^{13}C (avg 89% conversion)/^{13}C (avg 13% conversion) at C(3) = 1.017(5); average of three runs) (Table S5). The observation of a significant KIE on the C(3) carbon of the product **2a** is consistent with an asynchronous transition state of the C−O bond formation rate-limiting step. In support of this argument, Singleton and coworkers established that the pronounced carbon KIE is definitive kinetic evidence of the coupling reactions with both C−C and C−O bond formation rate-limiting steps.[15]



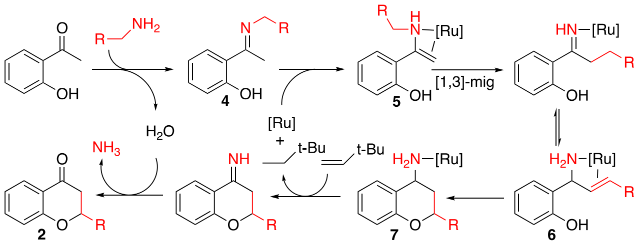
We recently reported that the Ru-catalyzed deaminative α-alkylation reaction of ketones with amines proceeds via an intramolecular [1,3]-carbon migration from an initially formed ketimine susbtrate.[10] To probe if the deaminative coupling reaction proceeds via a similar ketimine intermediate, we independently prepared and isolated the ketimine **4a** in 95% yield from the dehydrative coupling reaction of 2′-hydroxyacetophenone with *n*-hexylamine. The following treatment of the isolated imine **4a** (0.50 mmol) with **1** (2 mol %)/**L1** (10 mol %) and water (2 equiv) under otherwise standard conditions cleanly formed the product **2c** in 50% yield (eq 5). In this case, the presence of water is necessary to form the flavanone product **2c**, as water would be needed for the imine hydrolysis step.

We propose a plausible mechanistic path for the deaminative coupling reaction of 2′-hydroxyacetophenone with a linear amine on the basis of these kinetic and mechanistic data



(Scheme 4). The imine substrate **4**, which is initially formed from the dehydrative coupling of 2′-hydroxyacetophenone with an amine, would coordinate to the Ru catalyst to form a Ru−enamine complex **5**. The intramolecular [1,3]-carbon migration followed by the imine-to-allylamine isomerization would form the Ru−allylamine species **6**. We recently uncovered a similar mechanism of the deaminative alkylation reaction of ketones with amines, which was shown to occur via a stepwise [1,3]-carbon migration via a Ru(IV)−alkyl species.[10] The nucleophilic addition of the phenolic group to the allylamine moiety would form the cyclized Ru−amine complex **7**. The experimental observations of both the carbon KIE and the Hammett correlation ($\rho = -0.92 \pm 0.1$), which is promoted by an electron-releasing group of the acetophenone substrate, support the C−O bond formation as the rate-limiting step of the coupling reaction. The following transfer dehydrogenation and the imine hydrolysis steps would form the flavanone product **2** along with an ammonia byproduct.

Scheme 4. Possible Mechanism of the Deaminative Coupling Reaction of 2′-Hydroxyacetophenone with an Amine



In summary, we have successfully developed a catalytic synthesis of 3-substituted flavanone and 3,3-disubstituted quinazolinone derivatives from the deaminative coupling reaction of 2-hydroxyaryl ketones and 2′-aminobenzamides with simple amines. Both the carbon KIE and Hammett data support the catalytic reaction mechanism via an intramolecular [1,3]-carbon migration of the initially formed imine followed by the imine-to-allylamine isomerization and the cyclization (C−O bond formation) steps. Efforts toward extending the substrate scope and exploring new synthetic applications for the catalytic deaminative coupling method are currently being pursed in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c03870.

Experimental procedures, characterization data, and NMR spectra for all organic products (PDF)

Accession Codes

CCDC 2122255−2122256 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.

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Notes

The authors declare no competing financial interest.

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