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Pd-Catalyzed Benzylic C−H Amidation with Benzyl Alcohols in Water: A Strategy To Construct Quinazolinones

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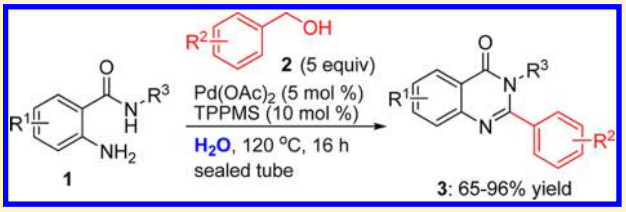
Supporting Information

ABSTRACT: A novel method for the synthesis of 4-phenylquinazolinones via a palladium-catalyzed domino reaction of *o*-aminobenzamides with benzyl alcohols is developed. This protocol involves *N*-benzylation, benzylic C−H amidation, and dehydrogenation in water, which may play an important role in the smooth generation of the (η^3-benzyl)palladium species by activation of the hydroxyl group of the benzyl alcohol.



INTRODUCTION

Palladium-catalyzed activation of carbon−hydrogen bonds for coupling reactions is a promising strategy in organic synthesis.[1] Amidation of C(sp^3)−H bonds has been particularly attractive since N-containing compounds, especially *N*-heterocycles, are ubiquitous in natural products and pharmaceuticals.[2]

We propose that a palladium-catalyzed *N*-benzylation/benzylic C−H activation of anilines substituted with directing groups should afford versatile compounds. In our previous work,[3a] *N*-benzylation of anthranilic acid with benzyl alcohol and benzylic C−H benzylation occurred simultaneously to give the dibenzylated product **A** (Scheme 1). The carboxyl group may play an important role as a directing group in the benzylic C−H activation. By replacing anthranilic acid with *o*-aminobenzamide as a starting material, we expect the *N*-benzylated product to undergo benzylic C−H amidation followed by dehydrogenation to give 2-phenylquinazolin-4(3*H*)-one (**3**; Scheme 2). Quinazolinones are key units in a wide range of relevant pharmacophores with a broad spectrum of activities.[4−11] While many methods for the synthesis of **3** have been developed,[4−13] palladium-catalyzed benzylic C−H amidation has not been described before. Herein, we report a synthesis of **3** via a palladium-catalyzed domino reaction of *o*-aminobenzamides with benzyl alcohols in water.

Palladium-catalyzed benzylation with benzylic alcohols is especially interesting because it is known that the reactivity of benzylic alcohols toward Pd(0) is poor compared with benzylic halides, esters, carbonates, or phosphates.[14] Only a few papers describe palladium-catalyzed benzylation with benzylic alcohols. For example, Sheldon and co-workers reported that the water-soluble $Pd(tppts)_3$ complex is an active catalyst for the carbonylation of benzylic alcohols in an aqueous/organic two-phase system in the presence of an acid cocatalyst.[15] Most recently, we reported the palladium-catalyzed *S*-benzylation of anthranilic acid with benzyl alcohols in water.[3b] Water may play an important role in the smooth generation of the (η^3-benzyl) palladium species by hydration of the hydroxyl group.

Furthermore, benzylic C−H activation (second step in Schemes 1 and 2) is usually achieved in organic solvents, and extrusion of moisture is essential. To the best of our knowledge, palladium-catalyzed C−H functionalization in water is extremely rare. For example, Sajiki and co-workers reported that the Pd/C-catalyzed hydrogen−deuterium (H−D) exchange reaction proceeded in D_2O in the presence of H_2 gas.[16] Li and Zhang reported Pd-catalyzed allylic C−H amination of alkenes in the presence of a catalytic amount of water.[2a]

RESULTS AND DISCUSSION

First, we heated a mixture of *o*-aminobenzamide (**1a**) and benzyl alcohol (**2a**; 5 equiv) in the presence of $Pd(OAc)_2$ (5 mol %) and sodium (diphenylphosphino)benzene-3-sulfonate (TPPMS; 10 mol %) in water at 100 °C for 16 h under air in a sealed tube. To our surprise, dehydrogenated product **3a** was obtained in 93% yield in spite of the possibility of forming the aminal **4a** (Table 1, entry 1). The reaction did not proceed in the absence of the palladium catalyst and phosphine ligand or in the presence of only TPPMS (entry 2). With regard to the palladium catalyst, the use of $PdCl_2$ also gave the product **3a** in excellent yield (entry 3, 92%). Although the use of zerovalent palladium, $Pd_2(dba)_3$, resulted in no reaction at 100 °C, improvement of the yield was observed at 120 °C (entry 4, 88%). Heating at 120 °C may be necessary to form the $Pd(tppms)_n$ complex from $Pd_2(dba)_3$ with TPPMS. Since the reaction did not occur when using $Pd(PPh_3)_4$ instead of a water-soluble ligand (entry 5) or when using DMSO, EtOH, AcOH, 1,4-dioxane, or toluene (entry 6) as a solvent, water must play an important role in the benzylation with benzyl alcohol. Indeed, the reaction in 1,4-dioxane/H_2O (1:1) proceeded in 93% yield (entry 7).

Results for the reaction of *o*-aminobenzamide (**1a**) with a number of benzyl alcohols **2** using $Pd(OAc)_2$ and TPPMS are summarized in Table 2. The benzyl alcohols with electron-

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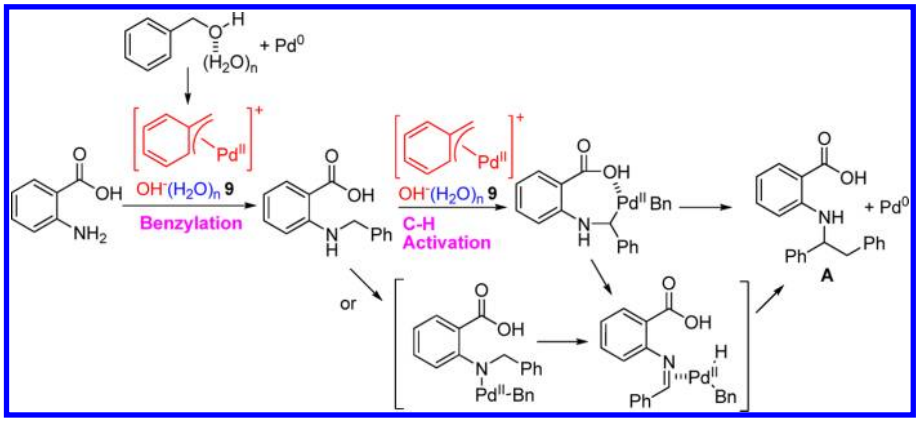
Scheme 1. Our Previous Work



Scheme 2. Our Concept of Pd-Catalyzed Benzylic C−H Amidation

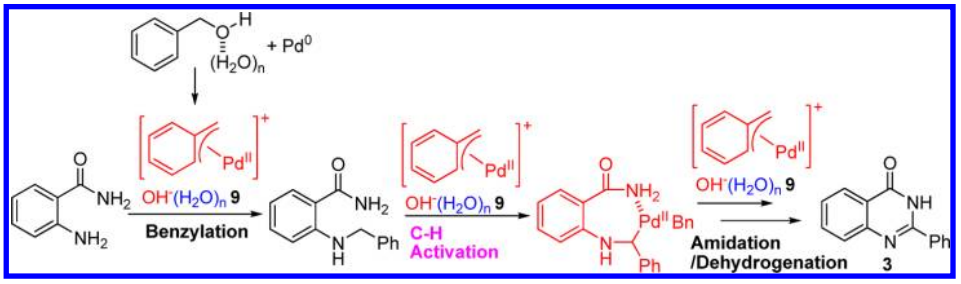
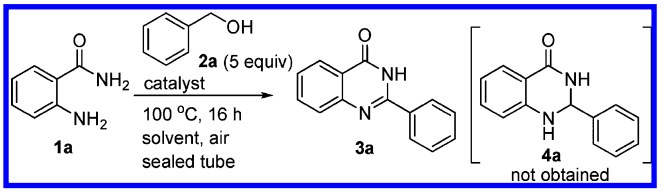


Table 1. Effect of Catalysts and Solvents[a]



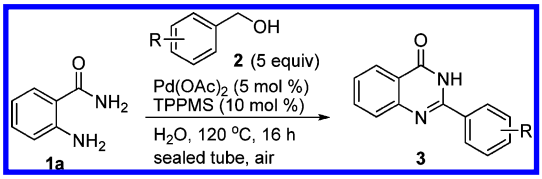
entry	catalyst	solvent	yield[b] (%)
1	$Pd(OAc)_2$/TPPMS	H_2O	93
2	none or only TPPMS	H_2O	0
3	$PdCl_2$/TPPMS	H_2O	92
4	$Pd_2(dba)_3$[c]/TPPMS	H_2O	trace (88)[d]
5	$Pd(PPh_3)_4$	H_2O	0
6	$Pd(OAc)_2$/TPPMS	DMSO, EtOH, AcOH, dioxane, or toluene	trace
7	$Pd(OAc)_2$/TPPMS	dioxane/H_2O (1:1)	93

[a]Reaction conditions: **1a** (0.5 mmol), Pd catalyst (5 mol %), ligand (10 mol %), benzyl alcohol (**2a**; 5 equiv), solvent (2 mL), 100 °C, 16 h under air in a sealed tube. [b]Yield of isolated product. [c]Concentration of 2.5 mol %. [d]The reaction was carried out at 120 °C.

donating methyl, ethyl, and methoxy groups resulted in good yields (entry 1, 90%; entry 2, 96%; entry 3, 65%, entry 4, 88%). The sterically demanding *ortho*-substituted methyl group was also tolerated in the reaction (entry 5, 89%).

Results for the reactions of several *o*-aminobenzamides **1** using $Pd(OAc)_2$ and TPPMS in water are summarized in Table 3. The 2-aminobenzamides with 4-methyl, 5-fluoro, and 6-fluoro groups resulted in good yields (entry 1, 74%; entry 2, 75%; entry 3, 77%). The reaction of 2-amino-*N*-methylbenzamide (**1e**) proceeded to give the desired products **3j−k** in good

Table 2. Reactions of 1a with Substituted Benzyl Alcohols 2[a]



entry	R	product **3**	yield[b] (%)
1	4-Me (**2b**)	**3b**	90
2	4-Et (**2c**)	**3c**	96
3	4-OMe (**2d**)	**3d**	65
4	3-OMe (**2e**)	**3e**	88
5	2-Me (**2f**)	**3f**	89

[a]Reaction conditions: **1a** (1 mmol), $Pd(OAc)_2$ (5 mol %), TPPMS (10 mol %), benzyl alcohols **2** (5 equiv), H_2O (4 mL), 120 °C, 16 h in a sealed tube. [b]Yield of isolated product.

yields (entry 4, 90%; entry 5, 86%). 2-(Methylamino)-benzamide (**1f**) also afforded the desired **3l** in good yield (entry 6, 72%). The sterically demanding *N*-methyl substituent did not influence the intramolecular cyclization.

Several control experiments were performed to exclude the possibility of other reaction pathways. First, palladium-catalyzed reaction of *N*-benzylated **6a** with benzyl alcohol (**2a**) gave the desired **3a** in quantitative yield (Scheme 3A). **2a** plays an important role in the benzylic C−H amidation step, since the reaction does not proceed in its absence. Additionally, the reaction of *o*-aminobenzamide (**1a**) with benzaldehyde (**7**) in the absence of palladium catalyst in water gave cyclic aminal **4a** in quantitative yield with no **3a** detected. Subsequent palladium-catalyzed reaction of **4a** proceeded to give the desired product **3a** in 99% yield (Scheme 3B). Under an Ar atmosphere, the reaction occurred in 90% yield (Scheme 3C).[17] These observations suggested that aerobic oxidation using

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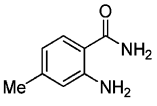
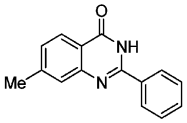
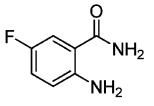
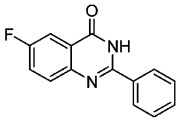
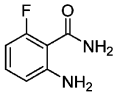
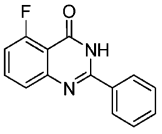
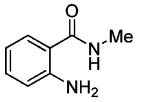
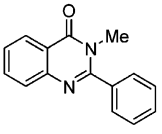
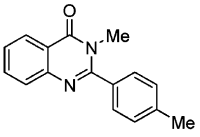
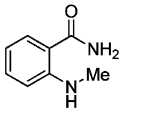
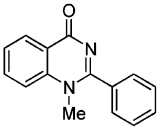
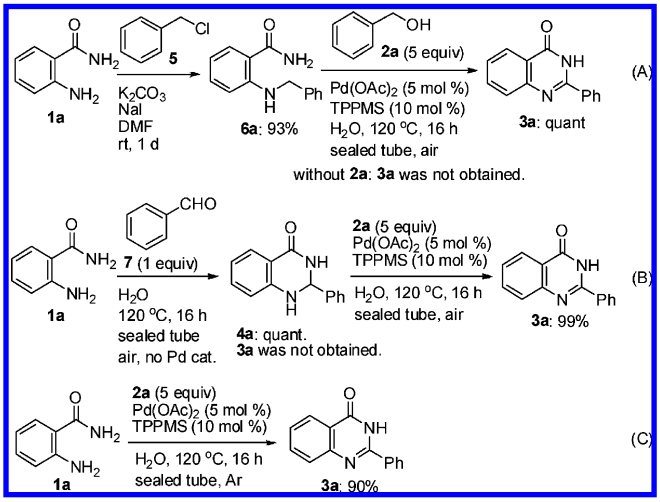
Table 3. Scope of Amide 1[a]

Entry	Amide **1**	OH **2** R=	Product **3**	Yield (%)
1	 **1b**	H (**2a**)		74 (**3g**)
2[b]	 **1c**	H (**2a**)		75 (**3h**)
3	 **1d**	H (**2a**)		77 (**3i**)
4	 **1e**	H (**2a**)		90 (**3j**)
5	**1e**	4-Me (**2b**)		86 (**3k**)
6[b]	 **1f**	H (**2a**)		72 (**3l**)

[a]Reaction conditions: **1** (1 mmol), $Pd(OAc)_2$ (5 mol %), TPPMS (10 mol %), benzyl alcohols **2** (5 equiv), H_2O (4 mL), 120 °C, 16 h in a sealed tube. The yields in column 5 are those of isolated product. [b]Time of 48 h.

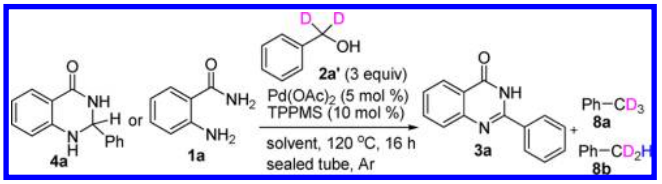
Scheme 3. (A) *N*-Benzylation with Benzyl Chloride and Pd-Catalyzed Reaction of *N*-Benzylated 6a, (B) Intramolecular Nucleophilic Addition of the Amide to the Imine and Pd-Catalyzed Dehydrogenation of Aminal 4a, and (C) Pd-Catalyzed Reaction under Ar



oxygen did not occur in our catalytic system and a palladium intermediate must play an important role in the dehydrogenation steps. Furthermore, *N*-benzylated **6a** and aminal **4a** must be intermediates in our catalytic system.

Next we utilized ^1H NMR experiments to monitor the reaction using benzyl-α,α-d_2 alcohol (**2a′**). In oxidative cyclization of **6a** and subsequent dehydrogenation steps, 2 equiv of toluene should be formed from the (η^3-benzyl)-palladium complex in our catalytic system. We were delighted to observe that indeed toluene was obtained in the reaction mixture (see the Supporting Information). Dehydrogenation of aminal **4a** with **2a′** in D_2O gave **3a** along with deuterated toluene (**8a**:**8b** = 4:1) (Table 4, entry 1), suggesting that both

Table 4. Pd-Catalyzed Reaction with Benzyl-α,α-d_2 Alcohol (2a′)[a]

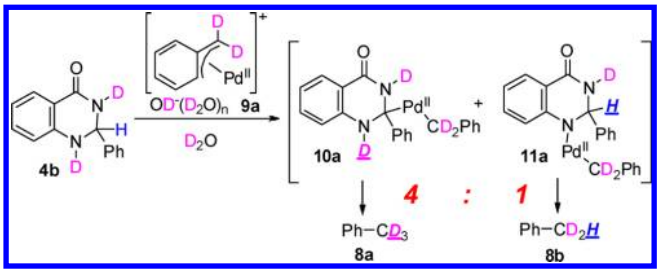


entry	**1a** or **4a**	solvent	**8a**:**8b**
1	**4a**	D_2O	4:1
2	**1a**	H_2O	1:9

[a]Reaction conditions: **1a** or **4a** (0.25 mmol), $Pd(OAc)_2$ (5 mol %), TPPMS (10 mol %), benzyl alcohol **2a′** (3 equiv), solvent (1 mL), 120 °C, 16 h in a sealed tube. After cooling, the reaction mixture was extracted with $CDCl_3$. The organic layer was analyzed by ^1H NMR.

C–H and N–H palladation of aminal **4b** occurred to form benzylic C–H activated **10a** and palladium amide **11a** (Scheme 4). In contrast, the monohydrogenated toluene **8b** was mainly

Scheme 4. Dehydrogenation of 4b in D_2O (Table 4, Entry 1)



formed (**8a**:**8b** = 1:9) from the reaction of *o*-aminobenzamide (**1a**) in H_2O (Table 4, entry 2). This result suggested that *N*-palladated intermediate **13** should not form and only amide-directed benzylic C–H activation would occur to form intermediate **12** because, as shown in Scheme 5, selective formation of **12** might only produce the dideuterated toluene **8b** with the formation of **4c** and then a 1:4 molar ratio of **8a** and **8b** might be produced by the reaction of intermediate **4c** with (η^3-benzyl)palladium complex **9b** as shown in Scheme 4. Exclusive formation of **12**, but not **13**, from *N*-benzylated **6b** with palladium complex **9b** suggested that the amide group plays an important role as a directing group in the selective benzylic C–H activation.[18] Additionally, palladation of aminal **4c**, which has no directing group, afforded both benzylic C–H activated **10b** and palladium amide **11b**, which underwent dehydrogenation to give the desired **3a** along with deuterated toluene (**8a**:**8b** = 1:4) according to the result of entry 1 in Table 4. This observation clearly explained the formation of

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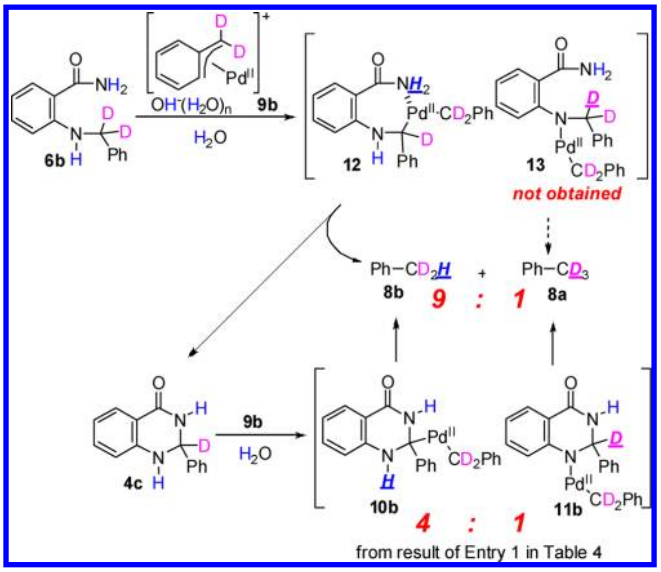
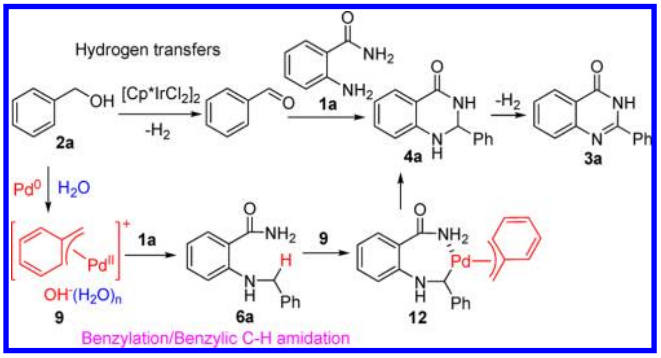
Scheme 5. C−H Amidation and Dehydrogenation Steps in H_2O (Table 4, Entry 2)



deuterated toluenes **8a** and **8b** in 10% and 90% yield (50% from **12** and 40% from **10b**), respectively.

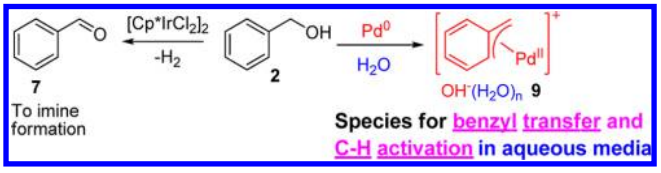
As a proof of the concept, our strategy of amide-directed benzylic C−H amidation was used to construct quinazolinones with our catalytic system. Although Zhou and co-workers recently reported the same reaction, i.e., the one-pot synthesis of 2-phenylquinazolin-4(3*H*)-one (**3**) from *o*-aminobenzamide (**1a**) with benzyl alcohols **2** via iridium-catalyzed hydrogen transfers (Scheme 6),[19] our (η^3-benzyl)palladium system works

Scheme 6. One-Pot Synthesis of Quinazolinones Starting with Benzyl Alcohols



on a mechanism quite different from the hydrogen transfer methodology. Although benzyl alcohols **2** form benzaldehyde (**7**) via iridium-catalyzed hydrogen transfers, oxidative additions of benzyl alcohols **2** to Pd^0 afford the (η^3-benzyl)palladium complex **9** in aqueous media (Scheme 7). Notably, the (η^3-benzyl)palladium system plays an important role in the *benzyl*

Scheme 7. Role of (η^3-Benzyl)palladium Species 9



transfer and *C−H activation*. Furthermore, subsequent reaction steps for C−H activation require an oxidant capable of converting palladium to a higher oxidation state, and benzyl alcohols **2** work for regeneration of Pd^{II} species to toluene in our catalytic system. Thus, our method provides a unique strategy for the benzylation and activation of a benzylic C−H bond by palladium catalyst and benzyl alcohols in water.

Importantly, the reaction of *o*-aminobenzamide **1** afforded only desired quinazolinone **3** via benzylic C−H amidation in spite of the possibility of forming dibenzylated product **14** (Scheme 8, this work). Since Pd-catalyzed reaction proceeds by intramolecular oxidative coupling of an amide NH with a C(sp^3)−H bond,[18b] amidation of intermediate **12** also might proceed smoothly. In contrast, the reaction of anthranilic acid afforded only dibenzylated product **A**, with no internal cyclized product **15** (Scheme 8, our previous work), since the oxygen nucleophilicity of the carboxyl group might be weak in neutral aqueous conditions.

CONCLUSION

In summary, we have developed a methodology for achieving a palladium-catalyzed domino reaction for the construction of 2-phenylquinazolin-4(3*H*)-one (**3**). The domino reactions achieved *N*-benzylation, benzylic C−H amidation, and dehydrogenation in water, which played an important role in the activation of the benzylic alcohols to form the corresponding palladium complexes. Water is still not commonly used as a solvent in organic synthesis despite its distinctive properties. Furthermore, the (η^3-benzyl)palladium system could be used for not only benzylation, but also C−H activation and dehydrogenation. We are currently investigating the scope of various nucleophiles on the benzylation and are developing new reactions using (η^3-benzyl)palladium from benzyl alcohols in aqueous media.

EXPERIMENTAL SECTION

General Procedure. A mixture of 2-aminobenzamide **1** (0.5−1 mmol), palladium(II) acetate (5 mol %), sodium (diphenylphosphino)benzene-3-sulfonate (TPPMS; 10 mol %), and benzyl alcohol **2** (5 equiv) in H_2O (2−4 mL) was heated at 100−120 °C for 16−48 h in a sealed tube. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc) to give desired product **3**.

*2-Phenylquinazolin-4(3H)-one (**3a**; Table 1, Entry 1).*[19] Following the general procedure, **3a** was obtained as a white solid: 103 mg (93%); mp 232−235 °C; IR (KBr) (cm^{-1}) 3078, 1667, 1606; ^1H NMR (400 MHz, DMSO-d_6) δ 7.50−7.65 (m, 4H), 7.76 (d, J = 8.0 Hz, 1H), 7.85 (dd, J = 7.2, 7.2 Hz, 1H), 8.15−8.25 (m, 3H) 12.5 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 120.9, 125.8, 126.5, 127.4, 127.7, 128.6, 131.3, 132.7, 134.5, 148.6, 152.3, 162.3; MS (EI) m/z (rel intens, %) 222 (M^+, 82.5), 119 (100).

*2-p-Tolylquinazolin-4(3H)-one (**3b**; Table 2, Entry 1).*[19] Following the general procedure, **3b** was obtained as a white solid: 213 mg (90%); mp 231−234 °C; IR (KBr) (cm^{-1}) 3075, 1662, 1605; ^1H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H), 7.36 (d, J = 8.0 Hz, 2H), 7.51 (dd, J = 8.0, 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.83 (dd, J = 8.0, 8.0 Hz, 1H), 8.11 (d, J = 8.0 Hz, 2H), 8.16 (d, J = 8.0 Hz, 1H), 12.5 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ ; 21.0, 120.9, 125.8, 126.4, 127.4, 127.7, 129.2, 129.9, 134.5, 141.4, 148.8, 152.2, 162.2; MS (EI) m/z (rel intens, %) 236 (M^+, 73.1), 119 (100).

*2-(4-Ethylphenyl)quinazolin-4(3H)-one (**3c**; Table 2, Entry 2).*[20] Following the general procedure, **3c** was obtained as a white solid: 240 mg (96%); mp 201−204 °C; IR (KBr) (cm^{-1}) 3178, 1666, 1606; ^1H

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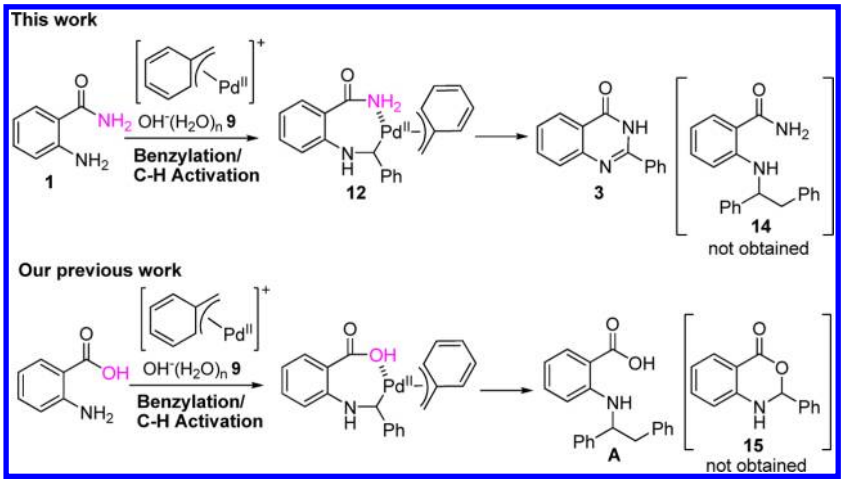
Scheme 8. Comparison between Our Previous Work and This Work



NMR (400 MHz, DMSO-d_6) δ 1.23 (t, J = 7.6 Hz, 3H), 2.70 (q, J = 7.6 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.52 (dd, J = 7.6, 7.6 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.84 (dd, J = 7.6, 7.6 Hz, 1H), 8.13 (d, J = 8.0 Hz, 2H), 8.16 (d, J = 8.4 Hz, 1H), 12.5 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 15.2, 28.0, 120.9, 125.8, 126.4, 127.4, 127.8, 128.0, 130.1, 134.5, 147.5, 148.8, 152.2, 162.2; MS (EI) m/z (rel intens, %) 250 (M^+, 100).

*2-(4-Methoxyphenyl)quinazolin-4(3H)-one (**3d**; Table 2, Entry 3).*[19] Following the general procedure, **3d** was obtained as a white solid: 163 mg (65%); mp 231−234 °C; IR (KBr) (cm^{-1}) 3091, 1680, 1608; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 2H), 7.09 (d, J = 8.8 Hz, 2H), 7.49 (dd, J = 7.6, 7.6 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.82 (dd, J = 7.6, 7.6 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8.8 Hz, 2H), 12.4 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 55.4, 113.9, 120.7, 124.8, 125.8, 126.1, 127.2, 129.4, 134.5, 148.9, 151.8, 161.8, 162.2; MS (EI) m/z (rel intens, %) 252 (M^+, 100).

*2-(3-Methoxyphenyl)quinazolin-4(3H)-one (**3e**; Table 2, Entry 4).*[19] Following the general procedure, **3e** was obtained as a white solid: 223 mg (88%); mp 204−205 °C; IR (KBr) (cm^{-1}) 3040, 1672, 1607; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.87 (s, 3H), 7.15 (d, J = 8.0 Hz, 1H), 7.46 (dt, J = 8.0, 2.0 Hz, 1H), 7.50−7.58 (m, 1H), 7.75−7.90 (m, 4H), 8.17 (d, J = 7.6 Hz, 1H), 12.5 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 55.4, 112.5, 117.6, 120.1, 121.0, 125.8, 126.6, 127.6, 129.7, 134.0, 134.6, 148.6, 152.0, 159.3, 162.2; MS (EI) m/z (rel intens, %) 252 (M^+, 100).

*2-o-Tolylquinazolin-4(3H)-one (**3f**; Table 2, Entry 5).*[12d] Following the general procedure, **3f** was obtained as a white solid: 211 mg (89%); mp 212−215 °C; IR (KBr) (cm^{-1}) 3054, 1684, 1605; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.39 (s, 3H), 7.30−7.40 (m, 2H), 7.44 (dd, J = 7.6, 7.6 Hz, 1H), 7.50−7.60 (m, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.84 (t, J = 7.2 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 12.4 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 19.5, 120.9, 125.6, 125.7, 126.6, 127.3, 129.1, 129.8, 130.5, 134.2, 134.4, 136.1, 148.7, 154.3, 161.7; MS (EI) m/z (rel intens, %) 236 (M^+, 89.5), 235 (100).

*7-Methyl-2-phenylquinazolin-4(3H)-one (**3g**; Table 3, Entry 1).*[19] Following the general procedure, **3g** was obtained as a white solid: 175 mg (74%); mp 227−230 °C; IR (KBr) (cm^{-1}) 3040, 1672, 1611; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.49 (s, 3H), 7.36 (d, J = 8.0 Hz, 1H), 7.50−7.65 (m, 4H), 8.05 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 6.8 Hz, 2H), 12.5 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 21.3, 118.6, 125.7, 127.1, 127.7, 128.0, 128.6, 131.3, 132.8, 145.0, 148.8, 152.3, 162.1; MS (EI) m/z (rel intens, %) 236 (M^+, 75.0), 133 (100).

*6-Fluoro-2-phenylquinazolin-4(3H)-one (**3h**; Table 3, Entry 2).*[21] Following the general procedure, **3h** was obtained as a white solid: 180 mg (75%); mp 229−231 °C; IR (KBr) (cm^{-1}) 3036, 1680, 1616; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50−7.65 (m, 3H), 7.30 (dt, J = 8.4, 2,4 Hz, 1H), 7.75−7.90 (m, 2H), 8.17 (d, J = 8.0 Hz, 2H), 12.7 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 110.5 (J = 92 Hz), 122.2, 123.0 (J = 92 Hz), 127.7, 128.6, 130.2, 130.3, 131.4, 132.5, 145.6, 151.8, 158.7, 161.4 (J = 188 Hz); MS (EI) m/z (rel intens, %) 240 (M^+, 77.7), 137 (100).

*5-Fluoro-2-phenylquinazolin-4(3H)-one (**3i**; Table 3, Entry 3).*[22] Following the general procedure, **3i** was obtained as a white solid: 185 mg (77%); mp 235−238 °C; IR (KBr) (cm^{-1}) 3059, 1687, 1616; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26 (dd, J = 11.2, 8.4 Hz, 1H), 7.50−7.65 (m, 4H), 7.75−7.85 (m, 1H), 8.18 (d, J = 8.0 Hz, 2H), 12.6 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 110.4, 112.9 (J = 82 Hz), 123.6, 127.9, 128.6, 131.7, 132.2, 135.1 (J = 40 Hz), 150.9, 153.3, 159.4 (J = 128 Hz), 161.8; MS (EI) m/z (rel intens, %) 240 (M^+, 82.8), 137 (100).

*3-Methyl-2-phenylquinazolin-4(3H)-one (**3j**; Table 3, Entry 4).* Following the general procedure, **3j** was obtained as a white solid: 213 mg (90%); mp 130−132 °C (lit.[23] mp 131−132 °C); IR (KBr) (cm^{-1}) 1678, 1560; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.37 (s, 3H), 7.50−7.60 (m, 4H), 7.65−7.70 (m, 3H), 7.84 (dd, J = 8.0, 8.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 33.8, 120.1, 126.1, 126.8, 127.1, 128.2, 128.4, 129.8, 134.3, 135.4, 147.0, 156.1, 161.6; MS (EI) m/z (rel intens, %) 236 (M^+, 68.7), 235 (100).

*3-Methyl-2-p-tolylquinazolin-4(3H)-one (**3k**; Table 3, Entry 5).* Following the general procedure, **3k** was obtained as a white solid: 215 mg (86%); mp 139−140 °C (lit.[24] mp 128 °C); IR (KBr) (cm^{-1}) 3023, 1672, 1596; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (s, 3H), 3.31 (s, 3H), 7.35 (d, J = 8.0 Hz, 2H), 7.55−7.57 (m, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 1H), 7.83 (ddd, J = 6.8, 6.8, 1.2 Hz, 1H), 8.18 (dd, J = 8.0, 1.2 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 20.9, 33.9, 120.0, 126.0, 126.7, 127.1, 128.2, 128.8, 132.6, 134.3, 139.5, 147.1, 156.2, 161.7; MS (EI) m/z (rel intens, %) 250 (M^+, 80.9), 249 (100).

*1-Methyl-2-phenylquinazolin-4(1H)-one (**3l**; Table 3, Entry 6).*[25] Following the general procedure, **3l** was obtained as an off-white solid: 170 mg (72%); mp 158−161 °C; IR (KBr) (cm^{-1}) 1641, 1600; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.64 (s, 3H), 7.53−7.64 (m, 4H), 7.65−7.72 (m, 2H), 7.76 (d, J = 8.4 Hz, 1H), 7.89 (dd, J = 7.6, 7.6 Hz, 1H), 8.15 (d, J = 7.6 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 37.8, 116.8, 119.7, 125.9, 127.0, 128.3, 128.6, 130.2, 133.9, 135.2, 141.7, 162.0, 167.6; MS (EI) m/z (rel intens, %) 236 (M^+, 70.0), 105 (100).

*2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (**4a**; Scheme 3B).*[19] A mixture of 2-aminobenzamide (**1a**; 136 mg, 1 mmol) and benzaldehyde (**7**; 101 μL, 1 mmol) in H_2O (4 mL) was heated at 120 °C for 16 h in a sealed tube. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc) to give desired product **4a** (224 mg, quant) as an off-white solid: mp 222−225 °C; IR (KBr) (cm^{-1}) 3302, 1660; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.75 (s, 1H), 6.60−6.70 (m, 1H), 6.74 (d, J =

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8.0 Hz, 1H), 7.09 (s, 1H), 7.20−7.30 (m, 1H), 7.30−7.45 (m, 3H), 7.45−7.55 (m, 2H), 7.60 (d, J = 7.6 Hz, 1H), 8.26 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 66.5, 114.4, 114.9, 117.1, 126.8, 127.3, 128.3, 128.4, 133.3, 141.6, 147.8, 163.5; MS (EI) m/z (rel intens, %) 224 (M^+, 31.9), 147 (100).

*2-(Benzylamino)benzamide (**6a**; Scheme 3A).*[12a] A mixture of 2-aminobenzamide (**1a**; 1.0 g, 7.4 mmol), K_2CO_3 (1.0 g, 7.4 mmol), NaI (1.1 g, 7.4 mmol), and benzyl chloride (**5**; 1.2 mL, 10 mmol) in DMF (10 mL) was stirred at rt for 1 d. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc) to give desired product **6a** (1.6 g, 93%) as a pale yellow solid: mp 166−169 °C; IR (KBr) (cm^{-1}) 3441, 3205, 1620, 1575; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.38 (s, 2H), 6.53 (dd, J = 7.6, 7.6 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 7.10−7.45 (m, 7H), 7.62 (dd, J = 8.0, 1.2 Hz, 1H), 7.85 (br s, 1H), 8.59 (br s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 46.0, 111.5, 114.2, 126.8, 127.0, 127.1, 128.4, 129.0, 132.4, 139.6, 149.5, 171.6; MS (EI) m/z (rel intens, %) 226 (M^+, 99.9), 180 (100).

■ ASSOCIATED CONTENT

Supporting Information

General procedure and ^{1}H NMR spectra (Table 4) and ^{1}H and ^{13}C NMR spectra of compounds **3a−l**, **4a**, and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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