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Direct Use of Benzylic Alcohols for Multicomponent Synthesis of 2-Aryl Quinazolinones Utilizing the π-Benzylpalladium(II) System in Water

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Abstract: We demonstrate the direct use of benzylic alcohols for a multicomponent reaction of readily available isatoic anhydrides with amines in water, which is a synthetic route for the direct construction of a series of 2-aryl quinazolinones. This one-pot synthetic method involves the dehydrative N-benzylation of in situ generated anthranilamides followed by an amide-directed benzylic C–H amination process utilizing the π-benzylPd(II) system. Comparison of independent rate measurements using benzyl alcohol and its deuterated form gave a kinetic isotope effect of 3.5. Therefore, the benzylic C–H bond is cleaved in the rate-determining step. We successfully carried out a gram-scale reaction in 85% yield with simplified product isolation.

Keywords: C–H activation; isatoic anhydride; palladium; water; benzyl alcohol

Introduction

Multicomponent reactions (MCRs) are recognized as an atom-economic synthetic strategy allowing the straightforward and efficient transformation of novel fine chemicals directly from easily available starting materials.[1] This system has many advantages such as high atom economy and less waste generation compared to stepwise reactions involving multistep and hazardous processes. The first report of MCRs was in 1850 by Strecker, in the well-known Strecker reaction, for the synthesis of α-amino acids using aldehydes, hydrogen cyanide and ammonia as substrates.[2] In 1881, Hantzsch reported the three-component synthesis of 1,4-dihydropyridines.[3] A calcium channel blocker, Nifedipine, was prepared by this method.[4] Furthermore, the Ugi reaction is a four-component condensation, where the coupling between a ketone (or aldehyde), amine, isocyanide and carboxylic acid affords a bis-amide.[5] Therefore, performing MCRs enables the rapid construction of diverse molecular skeletons through highly convergent one-pot processes, which can be applied to the library synthesis of drug candidates.

Quinazolinones are well represented in medicinally relevant molecules, since the substrate scaffolds act as key structural units in a wide range of relevant pharmacophores exhibiting a broad spectrum of biological and pharmaceutical activities (Figure 1).[6] Therefore, the development of efficient synthetic protocols for accessing such motifs has attracted a great deal of effort. Recently, multicomponent synthesis of quinazolinones involving condensation between *in situ* generated anthranilamides and aldehydes or orthoesters followed by dehydrogenation of the aminal has been successfully developed (Scheme 1A).[7] Despite these elegant protocols, stoi-

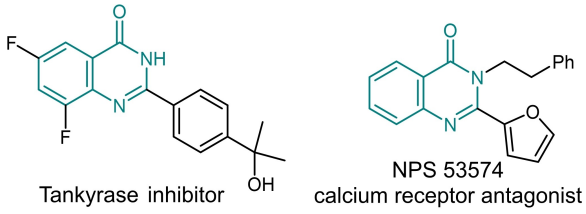
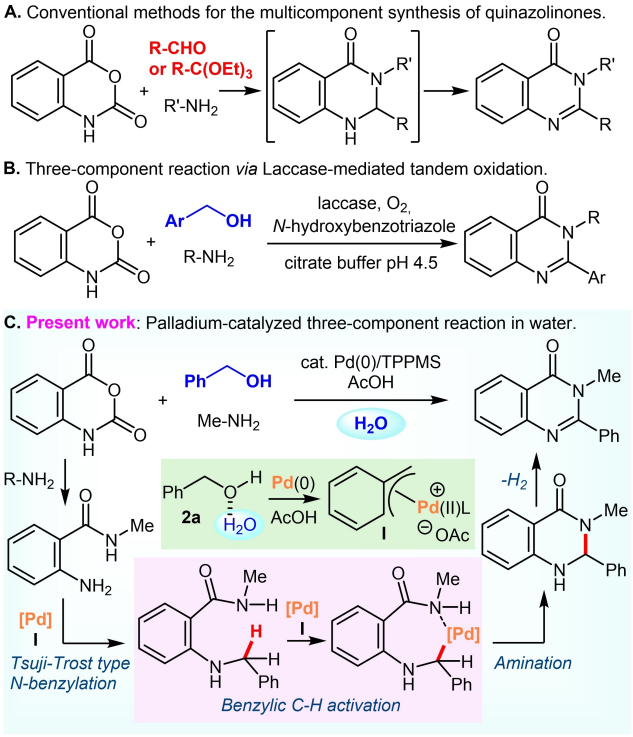


Figure 1. Representative biologically active quinazolinones.



Scheme 1. Multicomponent synthesis of quinazolinones.

chiometric amounts of toxic oxidants such as DDQ or I_2 are generally needed for the oxidation step. Furthermore, benzaldehydes are unstable and their preparation requires oxidation from readily available alcohols. Therefore, a more efficient approach utilizing non-activated coupling partners such as readily available alcohols is highly desirable.[8] In 2014, Habibi and Faramarzi *et al.* developed a MCR *via* the laccase-mediated tandem oxidation of alcohols to aldehydes followed by cyclocondensation under an O_2 atmosphere in a citrate buffer solution (Scheme 1B).[8d] Despite this important advance, the direct use of simple benzylic alcohols for an efficient MCR remains a great challenge.

We have been developing environmentally benign benzylic C–H functionalizations at sites adjacent to heteroatoms utilizing the π-benzylpalladium system in water.[9] The catalytic amination of C–H bonds is recognized as an atom-economic, straightforward and efficient method that can incorporate nitrogen into molecular frameworks without pre-activation of starting materials.[10] Herein, we present the first example of the direct use of benzylic alcohols for MCR of isatoic anhydrides with amines catalyzed by Pd(0)/TPPMS in water, furnishing a series of 2-aryl quinazolinone derivatives (Scheme 1C). Our π-benzylpalladium(II) system shows water tolerance and enables the key intramolecular C–N bond formation at the benzylic position. Additionally, water accelerates the three-component coupling reaction due to its unusual chemical and physical properties such as formation of an extensive hydrogen bonding network.

Results and Discussion

Reaction Optimization

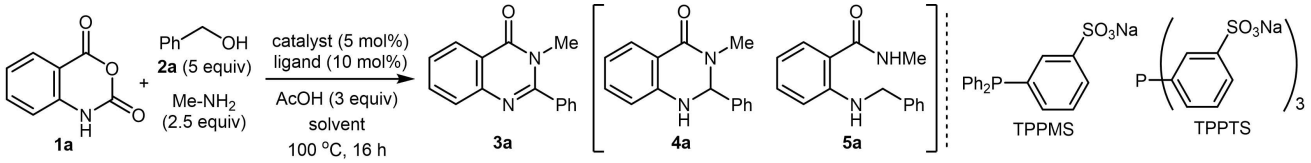
We selected commercially available isatoic anhydride (**1a**) and benzyl alcohol (**2a**) as model substrates to optimize the MCR conditions. In the presence of palladium(II) acetate (5 mol%) and sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 10 mol%), the reaction was performed employing $MeNH_2$ (40% in water) as an amine source to give the corresponding quinazoline product **3a** in only 3% yield along with dihydroquinazolinone product **4a** in 15% yield (Table 1, entry 1). We speculated that the palladium catalyst was poisoned by methylamine. To test our hypothesis, addition of several acids was examined. As expected, the use of $MeNH_2 \cdot AcOH$ was found to significantly improve the yields of cyclized products **3a** and **4a** to 29% and 38%, respectively (entry 2). Additionally, N-benzylated intermediate **5a** was observed in 22% yield. To our delight, the three-component synthesis of the quinazolinone **3a** could be achieved by fine-tuning the mol ratio of $MeNH_2$ (2.5 mmol) and AcOH (3 mmol) (entry 3). The yield of **3a** decreased from 90% to 60% when the temperature was reduced from 100 °C to 80 °C (entry 4). Replacing AcOH with strong Brønsted acids such as HCl, TFA and $TsOH \cdot H_2O$ was not effective (entries 5–7). When using $Pd(TFA)_2$, $PdCl_2$ $PdBr_2$ or $Pd_2(dba)_3 \cdot CHCl_3$, almost the same or lower yields of desired product **3a** were observed (entry 3 vs. entries 8–11). Furthermore, $[Cp^*IrCl_2]_2$, which is often used for borrowing hydrogen reactions, showed poor catalytic performance (entry 12). With regard to the phosphine ligand, the absence of TPPMS or replacing TPPMS with TPPTS significantly diminished the reactivity (entries 13–14). The catalyst system was tested in several organic solvents such as toluene, 1,4-dioxane, dimethyl sulfoxide and ethanol, but all afforded inferior results compared to the reaction in water (entries 15–18). Furthermore, an aqueous biphasic system using cyclopentyl methyl ether (CPME) resulted in lower yields (entry 19). These results suggested that water plays an important role in the Pd-catalyzed reaction.

Reaction Scope

To expand the substrate scope, we examined the MCR of isatoic anhydrides **1** using various amines and alcohols **2** under optimized conditions (Figure 2).

We first tested the scope of benzylic alcohols. Electron-donating groups (OMe and Me) at the *meta* or *para* positions were effective, furnishing the

Table 1. Effects of catalysts and solvents.[a]



Entry	Catalyst/Ligand	Amine (equiv.)	Acid (equiv.)	Solvent	NMR yield (%)[b] 3a	4a	5a
1	$Pd(OAc)_2$/TPPMS	$MeNH_2$ (2.5)	none	H_2O	3	15	0
2	$Pd(OAc)_2$/TPPMS	$MeNH_2 \cdot AcOH$ (3)		H_2O	29	38	22
3	$Pd(OAc)_2$/TPPMS	$MeNH_2$ (2.5)	AcOH (3)	H_2O	90 (89)[d]	5	0
4	$Pd(OAc)_2$/TPPMS	$MeNH_2$ (2.5)	AcOH (3)	H_2O (at 80 °C)	60	22	0
5	$Pd(OAc)_2$/TPPMS	$MeNH_2$ (2.5)	HCl (3)	H_2O	15	0	0
6	$Pd(OAc)_2$/TPPMS	$MeNH_2$ (2.5)	TFA (3)	H_2O	8	0	0
7	$Pd(OAc)_2$/TPPMS	$MeNH_2$ (2.5)	$TsOH \cdot H_2O$ (3)	H_2O	7	0	0
8	$Pd(TFA)_2$/TPPMS	$MeNH_2$ (2.5)	AcOH (3)	H_2O	77	22	0
9	$PdCl_2$/TPPMS	$MeNH_2$ (2.5)	AcOH (3)	H_2O	80	13	0
10	$PdBr_2$/TPPMS	$MeNH_2$ (2.5)	AcOH (3)	H_2O	39	50	0
11	$Pd_2(dba)_3 \cdot CHCl_3$[c]/TPPMS	$MeNH_2$ (2.5)	AcOH (3)	H_2O	84 (79)[d]	12	0
12	$[Cp^*IrCl_2]_2$[c]/TPPMS	$MeNH_2$ (2.5)	AcOH (3)	H_2O	16	8	0
13	$Pd(OAc)_2$	$MeNH_2$ (2.5)	AcOH (3)	H_2O	7	32	0
14	$Pd(OAc)_2$/TPPTS[e]	$MeNH_2$ (2.5)	AcOH (3)	H_2O	3	0	0
15	$Pd(OAc)_2$/TPPMS	$MeNH_2$ (2.5)	AcOH (3)	Toluene	17	51	0
16	$Pd(OAc)_2$/TPPMS	$MeNH_2$ (2.5)	AcOH (3)	1,4-dioxane	16	0	0
17	$Pd(OAc)_2$/TPPMS	$MeNH_2$ (2.5)	AcOH (3)	DMSO	19	0	0
18	$Pd(OAc)_2$/TPPMS	$MeNH_2$ (2.5)	AcOH (3)	EtOH (at 80 °C)	(7)[d]	0	0
19	$Pd(OAc)_2$/TPPMS	$MeNH_2$ (2.5)	AcOH (3)	CPME/H_2O (1:1)	2	29	0

[a] Optimal conditions: isatoic anhydride **1a** (1 mmol), $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), benzyl alcohol **2a** (5 equiv.), 40% $MeNH_2$aq. (2.5 mmol), AcOH (3 mmol), H_2O (4 mL), 100 °C, 16 h in a sealed tube under air;
[b] The conversion was determined by ^1H NMR analysis of the crude product using 4-nitroanisole as an internal standard;
[c] 2.5 mol%;
[d] Yield of the isolated product in parenthesis;
[e] Trisodium 3,3′,3-phosphinetriyltribenzenesulfonate.

quinazoline products **3b–d** in moderate to excellent yields (60–92%). To our delight, 2-naphthalenemethanol could be converted to the product **3e**. The loss of resonance energy for the formation of the η^3-naphthalenemethylpalladium intermediate was less important than for the η^3-benzylpalladium intermediate reported by Fiaud.[11] The reaction of 1-naphthalenemethanol afforded the cyclized products (quinazolinone **3f**, 14%; aminal **4f**, 67%), and the dehydrogenation of **4f** proceeded slowly, probably due to steric reasons. The use of a benzyl alcohol with an electron-withdrawing fluoro group resulted in excellent yield (**3g**, 85%). In contrast, no reaction occurred when using 4-nitrobenzyl alcohol or 2-phenylethyl alcohol, likely because the corresponding π-benzyl Pd(II) cation species was not generated.

To further expand the substrate scope, various substituted isatoic anhydrides were employed as substrates to examine the catalytic tandem reactions in water. Isatoic anhydrides with electron-donating groups (OMe and Me) were effective, affording the quinazoline products **3h–j** in excellent yields (79–90%). Sterically demanding 3-methylisatoic anhydride (**1k**) and *N*-methylisatoic anhydride (**1l**) were tolerated in the tandem coupling reaction (**3l**, 86%; **4m**, 69%). 4-Chloroisatoic anhydride **1n** was converted into the corresponding dehalogenated product **3a** in 68% yield, which suggested that the water-tolerant Pd(0)/TPPMS catalyst system could be formed in water.

We next tested the alkylamine scope. Ethyl and *n*-butylamines were capable coupling partners for the MCR, furnishing the quinazolinone products (**3o**, 71%; **3p**, 48%). Aniline was converted to the corresponding dihydroquinazolinone **3q** in 47% yield. When utilizing the ammonia solution (28% in water), the tandem reaction proceeded smoothly to give the desired quinazolinones **3r–v** (65–77%).[12]

Reaction Progress

To explore the full reaction profile for the MCR system, the reaction of isatoic anhydride with meth-

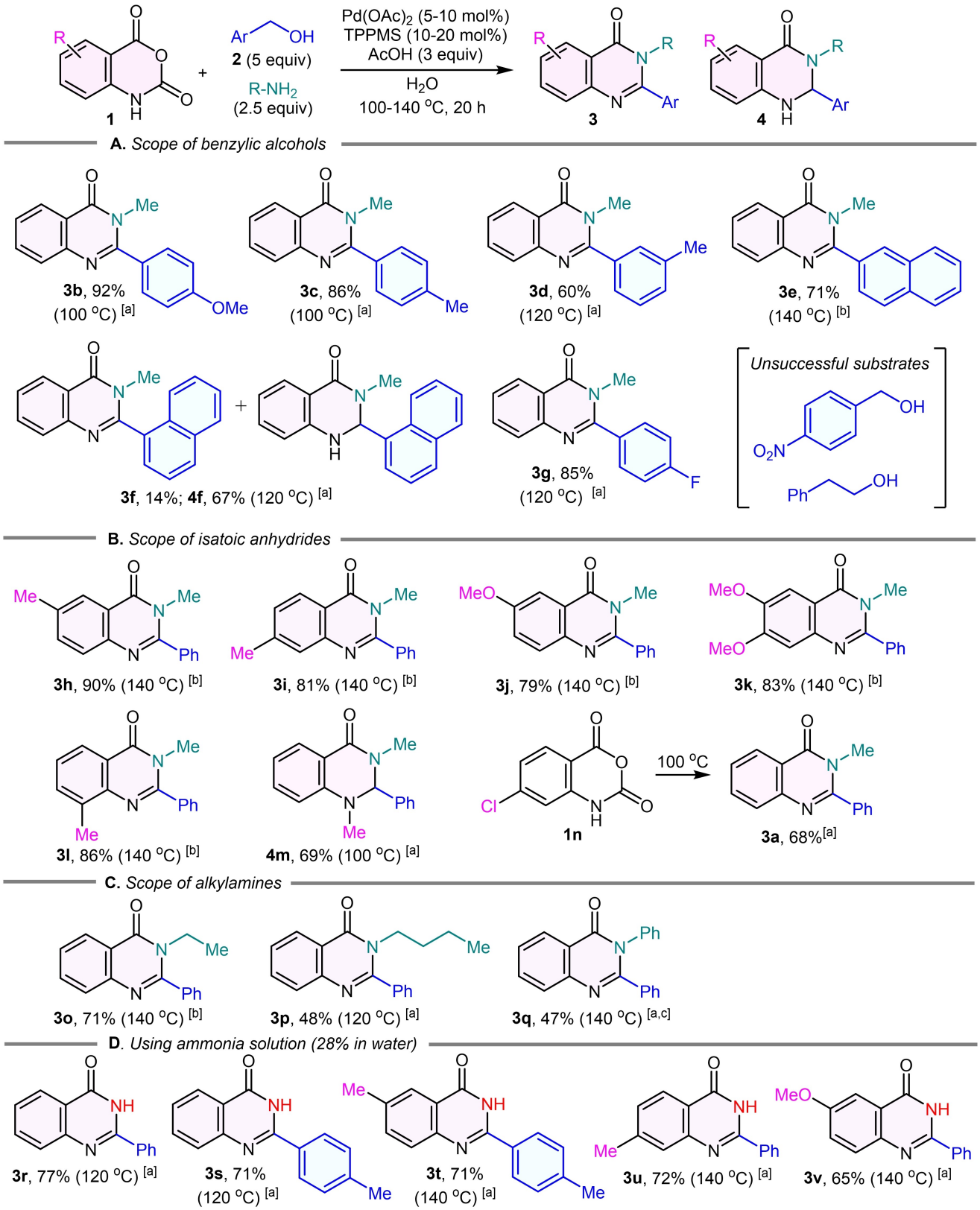
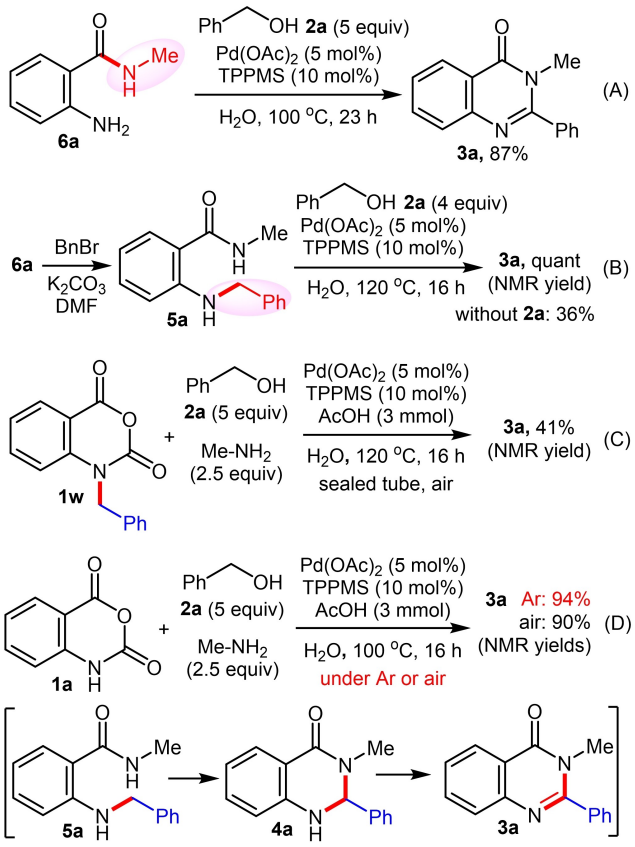


Figure 2. Substrate scope of coupling reaction and isolated yields of **3** and **4**.

ylamine and benzyl alcohol was monitored over time. The conversion yield was determined by ^{1}H NMR analysis. After 1 h, *N*-benzylated product **5a** and cyclized product **4a** as key intermediates were generated, which were smoothly transformed into quinazolinone **3a** (Figure 3A). Furthermore, a decrease of alcohol **2a** was observed as the catalytic reaction progressed (Figure 3B).

Control Experiments

To gain preliminary mechanistic insights into this catalytic system, we performed several control experiments. First, starting from 2-amino-*N*-methylbenzamide (**6a**), the corresponding quinazolinone **3a** was formed (Scheme 2A). Next, *N*-benzyl substrate **5a** was prepared by benzylation of **6a** with benzyl bromide, and subjected to the standard reaction conditions, furnishing the cyclized product **3a** in quantitative yield (Scheme 2B).[13] In contrast, a lower yield of **3a** was observed in the absence of alcohol **2a** ($Pd(OAc)_2$-catalyzed oxidation of **5a** occurred to give product **3a** in 36% yield). The reaction of *N*-benzylisatoic anhydride (**1w**) also gave **3a** (Scheme 2C), suggesting that the oxidative cyclization of *N*-benzylated **5a** proceeds smoothly in the benzylic C–H amination step, which is consistent with the observation of **5a** over the time course of the reaction (see Figure 3). The NMR determined yield of 94% for a reaction conducted under an Ar atmosphere was almost the same as that for a reaction conducted under air (see entry 3 in Table 1), suggesting that oxygen is not essential for either oxidative cyclization of *N*-benzylated **5a** or dehydrogenation of aminal **4a** (Scheme 2D).



Scheme 2. Control experiments.

Deuterium-Labeling Studies

We next performed deuterium-labeling studies using D_2O, while monitoring the reaction by ^{1}H NMR spectroscopy. If Pd-catalyzed intramolecular amination of *N*-benzylated anthranilamide **5a** followed by a subsequent cascade of dehydrogenation occurs, 2 equiv. of toluene would be generated through the π-benzylpalladium system along with desired product **3a**.

First, the yield of **3a** was found to be dependent on the concentration of benzyl alcohol (**2a**) in the examined range (0.5–2.5 mmol) (Scheme 3A). We were delighted to observe deuterium-labeled toluene (79% D incorporation of one H on the methyl group)

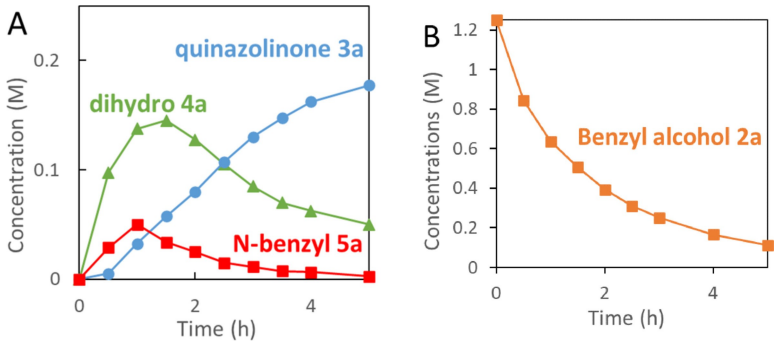
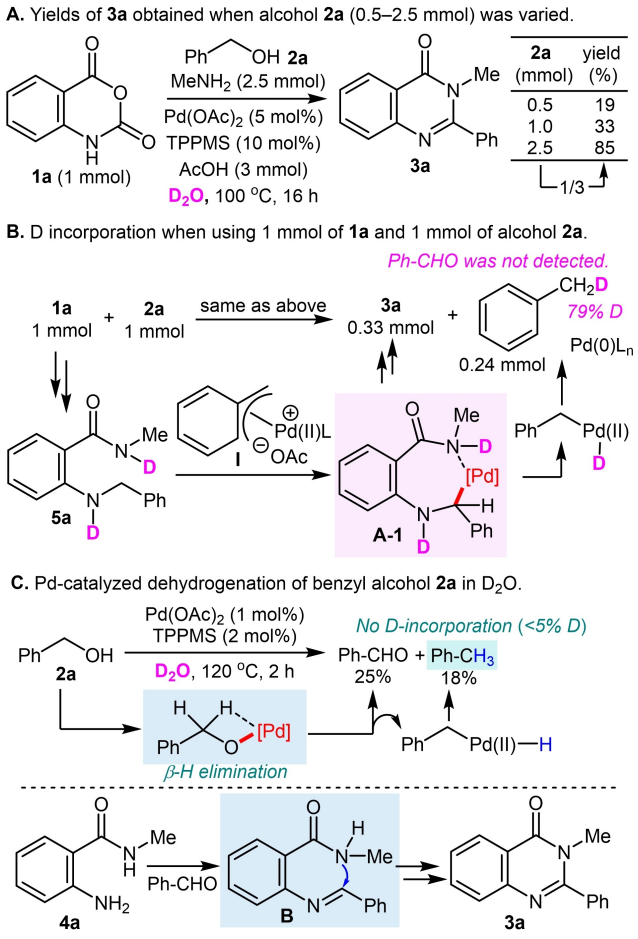


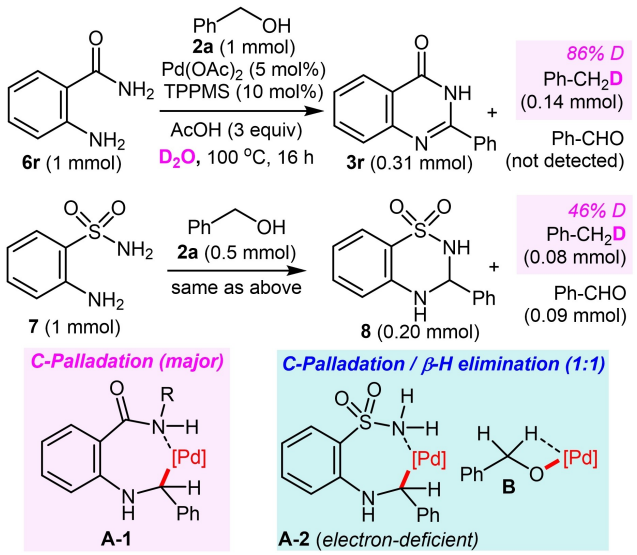
Figure 3. Monitoring of reaction progress. Conditions: isatoic anhydride **1a** (1 mmol), $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), $MeNH_2$ (2.5 mmol), AcOH (3 mmol), alcohol **2a** (5 mmol), H_2O (4 mL), 100 °C.



Scheme 3. Deuterium-labeling experiments.

and no formation of benzaldehyde in the reaction mixture, when the reaction between 1 mmol of substrate **1a** and 1 mmol of alcohol **2a** was conducted (Scheme 3B). This observation revealed that benzylic C–H amination product **3a** is formed from *N*-benzylated intermediate **5a** with π-benzylPd complex **I** via C-palladated species **A-1**. In contrast, Pd-catalyzed disproportionation of **2a** leads to the corresponding non-deuterated toluene via dehydrogenation (Scheme 3C), suggesting that the minor pathway for the construction of quinazolinone **3a** involves the condensation of *in situ* generated amine with benzaldehyde to form the imine intermediate **B**.

Next, the same technique was used to determine the influence of the amide groups on the key benzylic C–H amination step (Scheme 4). The reaction of anthranilamide (**6r**) afforded the quinazolinone **3r** with deuterium-labeled toluene (86% D incorporation).[9b] In contrast, the reaction of sulfonamide substrate **7** showed significant diminishment of deuterium incorporation (46% D incorporation in toluene) and benzaldehyde was detected by ^{1}H NMR.[9a] These observed intramolecular reactivity



Scheme 4. Catalytic reaction of benzamide and benzenesulfonamide in D_2O.

trends suggest that the anthranilamide complexes **A-1** would be stable compared with electron deficient sulfonamide complex **A-2**, and therefore the C–H amination can proceed preferentially at electron-rich benzylic C–H bonds.

Kinetic Isotope Effect

Next, we performed kinetic isotope effect (KIE) experiments to study the reaction mechanism by identifying the rate-determining step. Comparison of independent rate measurements using alcohol **2a** and benzyl-d_7 alcohol **2a**–***d*** showed a KIE of 3.5,[14] suggesting that the benzylic C–H bond in the **TS** is cleaved in the rate-determining step (Figure 4).

When the reaction rates in H_2O and in D_2O were compared, the conversion to cyclized products **3a** and **4a** was clearly faster in H_2O than in D_2O (Figure 5A). Furthermore, the pseudo first-order plot for the reaction of alcohol **2a** gave a KSIE (kinetic solvent isotope effect) of 1.6 (Figure 5B). These results suggest that hydrogen bonding between water molecules plays an important role in our catalytic system.

Mechanistic Considerations

Following our previous proposals on Pd-catalyzed benzylic C–H amination and considering the results of several mechanistic studies, we propose a plausible catalytic cycle for the direct use of benzyl alcohol in the multicomponent synthesis of quinazolinones (Scheme 5).

Step 1: Initially, the reaction of $Pd(OAc)_2$/TPPMS with alcohol **2a** generates an active Pd(0) species with

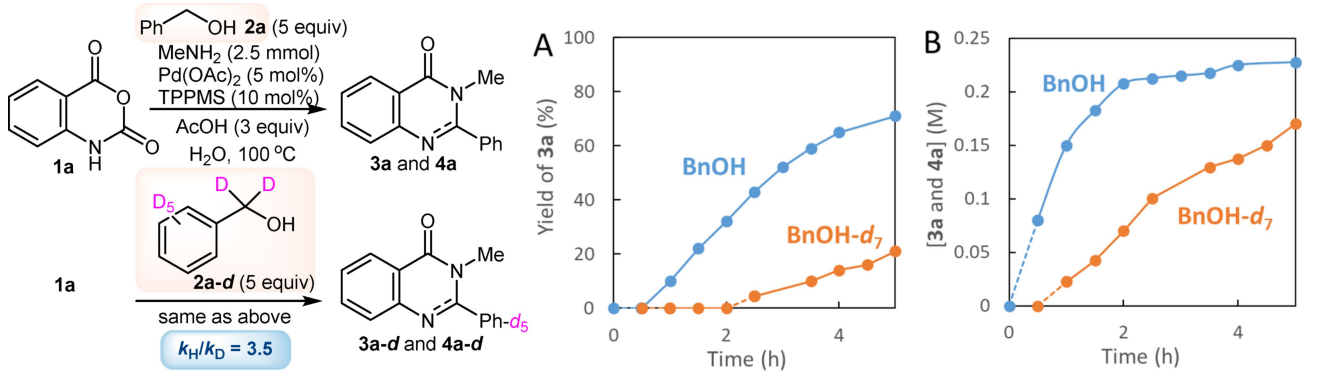


Figure 4. KIE determined from two parallel reactions using alcohol **2a** and benzyl-d_7 alcohol **2a**–***d***. Reaction conditions: **1a** (1 mmol), $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), $MeNH_2$ (2.5 equiv.), AcOH (3 equiv.), **2a** or **2a**–***d*** (5 equiv.), H_2O (4 mL), 100 °C. (A) Reaction time course for conversion to product **3a**, and (B) cyclized products **3a** and **4a**.

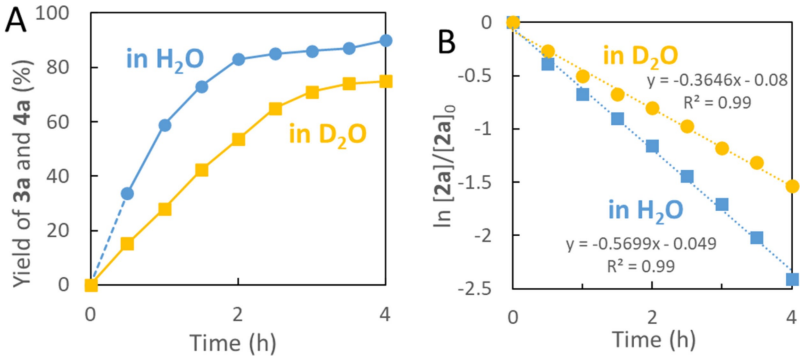
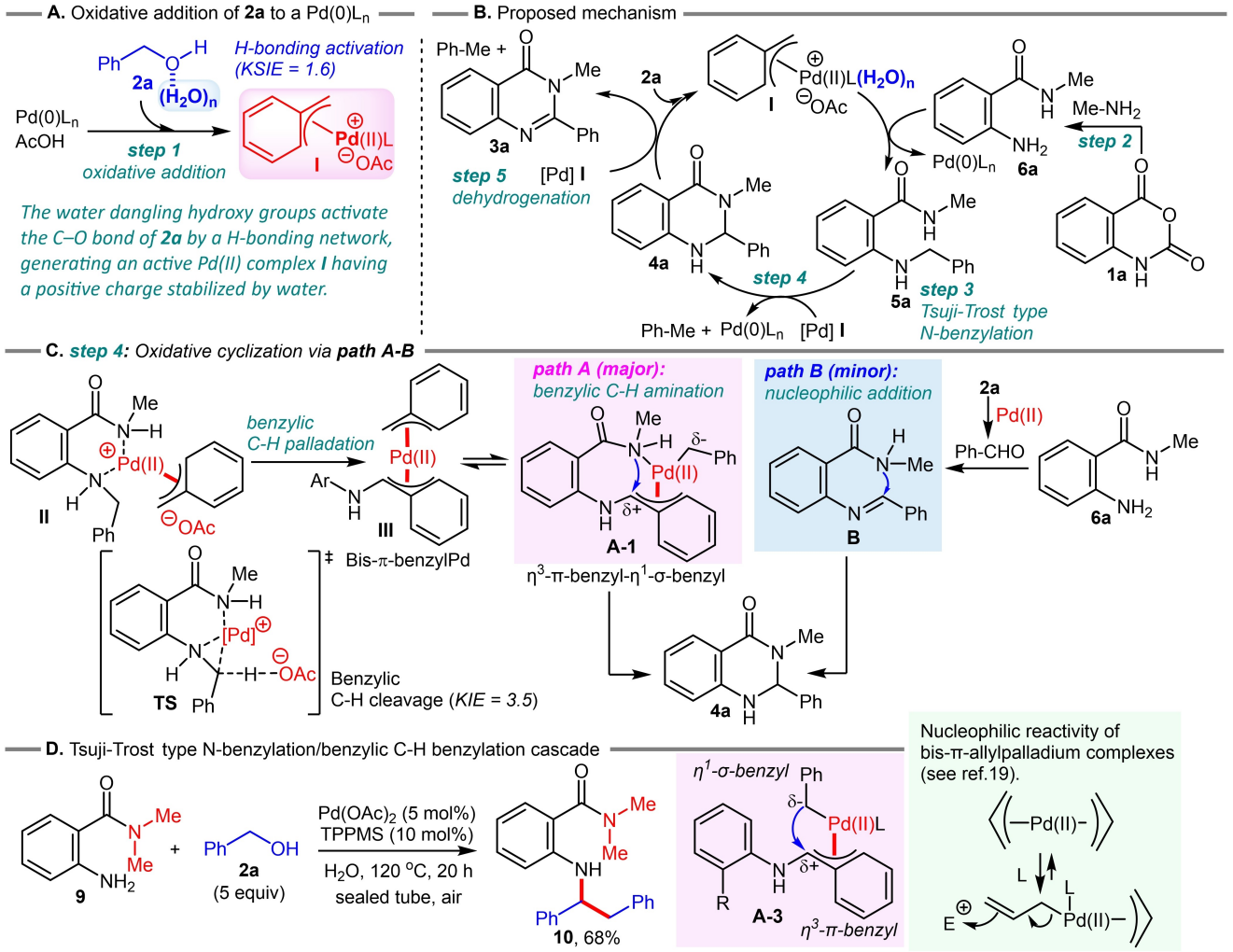


Figure 5. (A) Reaction time course for conversion to cyclized products **3a** and **4a** in H_2O and D_2O. (B) Pseudo-first-order kinetic plot in H_2O and D_2O. $kH_2O/kD_2O = 1.6$. Reaction conditions: isatoic anhydride **1a** (1 mmol), $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), $MeNH_2$ (2.5 equiv.), AcOH (3 equiv.), benzyl alcohol (**2a**, 5 equiv.), H_2O or D_2O (4 mL), 100 °C.

an aldehyde via Uemura type oxidation in water.[15] Subsequently, oxidative addition of **2a** to the $Pd(0)L_n$ complex generates the π-benzylPd(II) cation intermediate **I** (Scheme 5A).[16] The water dangling hydroxy groups activate the carbon-oxygen bond of **2a** by a hydrogen bonding network, generating an active Pd(II) complex **I** having a positive charge stabilized by water.[17] This proposed mechanism is consistent with the observed KSIE ($kH_2O/kD_2O = 1.6$). Furthermore, the use of acetic acid is the key to the success of the catalyst system, since it accelerates the formation of the π-benzylPd(II) species.[18–19]

Steps 2–3: Decarboxylative amide formation of isatoic anhydride (**1a**) with methyl amine generates 2-amino-*N*-methylbenzamide (**6a**), which attacks the cationic π-benzylpalladium(II) intermediate **I** via dehydrative Tsuji-Trost type N-benzylation to form the *N*-benzylated anthranilamide **5a** and regenerate $Pd(0)L_n$ (Scheme 5B).[20]

Step 4: Anthranilamide **5a** coordinates to the cationic Pd(II) complex **I** to form an activated complex **II**, whose positive charge is stabilized by the chelating amine and amide ligands (Scheme 5C). Consequently, C–H cleavage of complex **II** occurs to generate the bis-π-benzyl species **III** since the positive charge of cationic palladium(II) increases the acidity of the benzylic proton in the transition state **TS**. Additionally, the resulting acetoxy anion (conjugate base) acts as a base for the deprotonation of the amine and amide nucleophiles. Indeed, the use of a strong acid such as TFA is not effective for the Pd-catalyzed tandem reaction. The observed KIE of 3.5 supports the notion that the rate-determining step is C–H activation in the **TS**. The bis-π-benzyl species **III** is in equilibrium with η^3-π-benzyl-η^1-σ-benzyl Pd(II) **A-1**, whose δ^+ charge is stabilized due to proximity to the nitrogen atom. Consequently, an intramolecular nucleophilic substitution reaction to the π-benzyl ligand of **A-1** generates a C–N bond, since the complex **A-1** involves a nucleophilic σ-benzyl ligand with an electrophilic π-benzyl ligand (path A). Indeed, dehydrative tandem benzylation of 2-amino-*N*,*N*-dimethylbenzamide **9** affords the corresponding dibenzylated product **10**, suggesting that the η^1-σ-benzyl ligand attacks the η^3-π-



Scheme 5. (A)-(C) Proposed mechanism. (D) Control experiment for benzylic C–H activation.

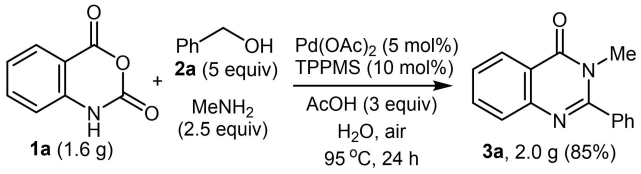
benzyl ligand of intermediate **A-3** (Scheme 5D). Yamamoto *et al.* proposed nucleophilic reactivity of bis-π-allylpalladium complexes, whereas mono-(π-allyl)PdCl complexes with an electron-withdrawing chloro group exhibited electrophilic reactivity.[19]

As a route to generate the dihydroquinazolinone intermediate **4a**, the control experiments (see Scheme 4) revealed that there was a minor route through nucleophilic addition to imine intermediate **B** (path **B** in Scheme 5C).

Step 5: Finally, Pd-catalyzed dehydrogenation of aminal intermediate **4a** generates the quinazoline product **3a** along with toluene and regenerated Pd(0).

Scale-Up Experiment

Finally, to demonstrate the applicability of the multi-component synthesis of quinazolinones, a gram scale reaction of isatoic anhydride (**1a**) with benzyl alcohol (**2a**) was performed in water (Scheme 6). Recrystallization of the resulting crude product from *n*-hexane/EtOAc provided the desired product **3a** in 85% isolated yield. Notably, this method is operationally facile and can be applied to gram-scale synthesis without purification by column chromatography. Furthermore, a key advantage for the direct utilization of alcohols rather than the corresponding aldehydes is that the use of toxic and unstable reagents can be avoided.



Scheme 6. Gram-scale synthesis of **3a**.

Conclusion

In summary, we have developed a palladium-catalyzed three-component reaction of isatoic anhydrides in water. This method enables the synthesis of a wide range of 2-aryl quinazolinone derivatives from readily available benzylic alcohols while avoiding the use of unstable aldehydes. Several control experiments and kinetic investigations revealed that C–H bond cleavage is the rate-determining step. Notably, the water-tolerant π-benzylpalladium(II) system that enables the selective functionalization of benzylic C–H bonds provides a powerful means of rapid conversion to such motifs, and has the potential to achieve various other chemical transformations in water. This multicomponent synthesis provides ample opportunities to construct a quinazolinone library.

Experimental Section

General procedure: A mixture of isatoic anhydrides **1** (1 mmol), palladium(II) acetate (5–10 mol%), TPPMS (10–20 mol%), benzylic alcohols **2** (5 mmol), amines (2.5 mmol) and AcOH (3 mmol) in water (4 mL) was heated at 100–140 °C for 16–20 h in a sealed tube under air. 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, hexane/EtOAc) to give the desired product **3**.

Acknowledgements

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UPDATES

Direct Use of Benzylic Alcohols for Multicomponent Synthesis of 2-Aryl Quinazolinones Utilizing the π-Benzylpalladium(II) System in Water

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