ChemPubSoc Europe

DOI: 10.1002/ejoc.201901606

EurJOC European Journal of Organic Chemistry

Full Paper

Borrowing Hydrogen Strategy

A Borrowing Hydrogen Strategy for Dehydrative Coupling of Aminoisoquinolines with Benzyl Alcohols in Water

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Abstract: We report a borrowing hydrogen strategy for a palladium-catalyzed dehydrative coupling of aminoisoquinolines with benzylic alcohols in water. This cascade reaction using the π-benzylpalladium system can be achieved in an atom-economic process without the need for base or other additives, furnishing the *N*-benzylated aminoisoquinolines in moderate to excellent yields along with water as the sole co-product. The crossover experiment using [D_7]benzyl alcohol and 4-methoxybenzyl alcohol afforded H/D scrambled products. KIE experiments showed that benzylic C–H bond cleavage of benzyl alcohol was involved in the turnover limiting step (KIE = 4.4). The coupling reaction was found to be first order in benzyl alcohol with a kinetic solvent isotope effect (KSIE) of 1.6. These experimental results are consistent with a borrowing hydrogen mechanism in water. Notably, the water-soluble Pd^0/TPPMS system can be applied to the more challenging catalytic benzylic amination with aminoisoquinoline nucleophiles despite the possible deactivation of Pd^{II} species.

Introduction

Isoquinolines are among the most common nitrogen-containing heterocycles found in bioactive natural products and pharmaceutical drug candidates (Figure 1). For example, papaverine hydrochloride is a well-known opium alkaloid used as an antispasmodic drug.[1] Recently, 1-aminoisoquinoline derivatives[2] have been widely used as a PKA inhibitor,[3] JAK2 inhibitor,[4] adenosine A_3 receptor ligand (VUF8504),[5] topoisomerase I inhibitor,[6] and PDE5 inhibitor.[7] Therefore, efficient methods for the direct introduction of diverse functionalities on isoquinolines are gaining increasing interest in modern drug discovery. The use of alkyl halides under basic conditions is one of the conventional protocols for *N*-alkylation.[7,8] However, the multistep and hazardous processes involved in this method must be improved due to their low atom economy and the production of stoichiometric amounts of waste. Reductive amination also has drawbacks such as the use of toxic reagents (oxidizing and reducing agents) and unstable aldehydes.[9]

The borrowing hydrogen (or hydrogen autotransfer) methodology is recognized as an alternative atom-economic synthetic strategy for straightforward and efficient dehydrative coupling of amines with alcohols, since this method can be performed using stable, available, and low-toxic alcohols instead of halides or aldehydes.[10] However, heterocyclic amines nucleophiles pose a challenging in catalytic borrowing hydrogen reactions. In general, these nucleophiles are considered unsuitable to late-transition metal-catalyzed reactions due to the poisoning effects. Indeed, Lindlar's catalyst is a palladium catalyst poisoned with traces of lead and quinoline, which is used for reduction of alkynes to alkenes. Recently, transition metal catalysts such as Mn,[11a] Co[11b] and Fe[11c] were shown to be highly effective for dehydrative coupling of 8-aminoquinoline with benzyl alcohol (Scheme 1A). However, these methods also suffer from disadvantages such as the use of strong base and hazardous organic solvents with high temperatures and long reaction times under exclusion of moisture conditions. Therefore, a greener process under base-free aqueous conditions would satisfy the goal to minimize environmental impacts in chemical production. In 2008, Milstein et al. reported the selective synthesis of primary amines directly from alcohols and aqueous ammonia using pincer-type Ru complexes.[12] Encouraged by this pioneering study, several researchers have reported new greener borrowing hydrogen protocols for sustainable C–N bond formation without a base in water.[13–15] However, to the best of our knowledge, there are no examples of the borrowing hydrogen reactions of aminoisoquinolines with benzyl alcohols.

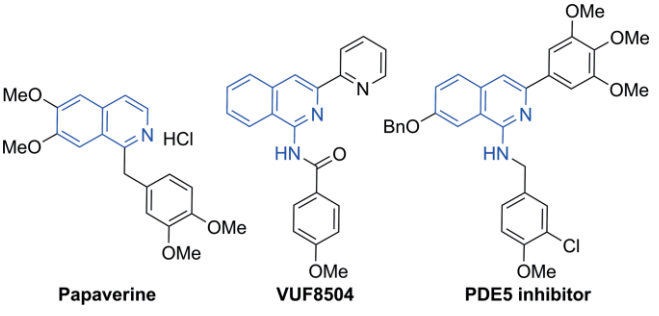

Figure 1. Representative biologically active isoquinolines.

We have been developing a unique strategy for dehydrative benzylation by the π-benzylpalladium(II) species[16] generated

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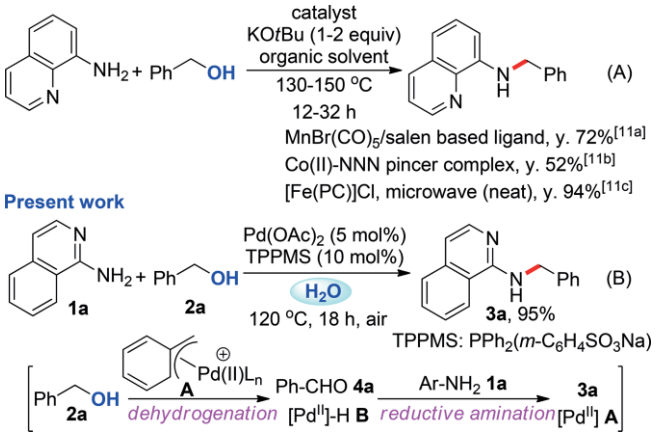
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201901606.



Scheme 1. Borrowing hydrogen methodology.

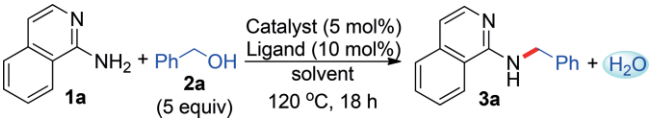
from Pd^0/sodium diphenylphosphinobenzene-3-sulfonate (TPPMS) and benzyl alcohol in water.[17] We recently developed a new environmentally benign borrowing hydrogen methodology for dehydrative coupling of 2-aminopyridines under base-free aqueous conditions.[18] However, we could not provide enough support for the catalytic pathway and the scopes of the pyridine nucleophiles were limited. In this paper, we describe new insights into the chemistry of the palladium-catalyzed *N*-benzylation pathway via π-benzylpalladium(II) complexes in water and the development of a borrowing hydrogen process as a new synthetic route for series of *N*-benzylated aminoisoquinolines (Scheme 1B). Notably, our highly efficient Pd^0/TPPMS system is successfully applied to the more challenging catalytic dehydrative benzylic amination with aminoisoquinoline nucleophiles using water as a reaction medium despite the possible deactivation of Pd^{II} species. Furthermore, water molecules dramatically accelerate dehydrogenation of benzyl alcohol followed by dehydrative C–N bond formation due to their unusual chemical and physical properties such as strongly polar hydrogen bonds.[19] This base-free protocol can achieve the dehydrogenation of benzyl alcohols under mild conditions, whereas strong bases are generally used in hydrogen-transfer reactions using organic solvents.[20]

Results and Discussion

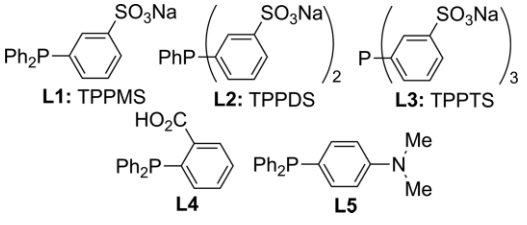
1. Optimization of Reaction Conditions

Initially, 1-aminoisoquinoline (**1a**) and benzyl alcohol (**2a**) were chosen as the model compounds to optimize the dehydrative C–N bond formation. The reaction of amine **1a** with alcohol **2a** (5 equiv.) using $Pd(OAc)_2$ (5 mol-%) and TPPMS **L1** (10 mol-%) in water at 120 °C for 18 h gave the desired *N*-monobenzylated product **3a** selectively in 84 % yield despite the possibility of forming the corresponding *N*,*N*-dibenzylated product (Table 1, entry 1). The reaction proceeded to completion when using 10 mol-% of $Pd(OAc)_2$ and 20 mol-% of **L1** (entry 2). No reaction occurred in the absence of phosphine ligand **L1** (entry 3) or when using a Brønsted acid such as $TsOH{\cdot}H_2O$ (entry 4), excluding an S_N2 type reaction mechanism in the formation of **3a**. With regard to the palladium(II) catalysts, $Pd(OAc)_2$ gave the best result (entry 1 vs. entries 5–7). The use of zero-valent palladium, $Pd_2(dba)_3$, also afforded the product **3a** in good yield (78 %, entry 8). No reaction occurred when using other salts such as Fe^{II}, Cu^{II} and Ir^{III} (entries 9–11). Other water-soluble phosphine ligands **L2–5** resulted in lower yields (entries 12–15). Replacing water with polar organic solvents such as DMSO, 1,4-dioxane and EtOH resulted in no reaction (entries 16–18).

Table 1. Comparison of solvents for the Pd-catalyzed reaction.[a]



Entry	Catalyst	Ligand	Solvent	Yield [%][b]
1	$Pd(OAc)_2$	**L1**	H_2O	84
2[c]	$Pd(OAc)_2$	**L1**	H_2O	95
3	$Pd(OAc)_2$	None	H_2O	0
4	$TsOH{\cdot}H_2O$	None	H_2O	0
5	$PdCl_2$	**L1**	H_2O	56
6	$PdBr_2$	**L1**	H_2O	63
7	$Pd(OCOCF_3)_2$	**L1**	H_2O	13
8	$Pd_2(dba)_3{\cdot}CHCl_3$	**L1**	H_2O	78
9	$FeCl_2$	**L1**	H_2O	0
10	$CuCl_2$	**L1**	H_2O	0
11	$IrCl_3{\cdot}xH_2O$	**L1**	H_2O	0
12	$Pd(OAc)_2$	**L2**	H_2O	29
13	$Pd(OAc)_2$	**L3**	H_2O	29
14	$Pd(OAc)_2$	**L4**	H_2O	20
15	$Pd(OAc)_2$	**L5**	H_2O	48
16	$Pd(OAc)_2$	**L1**	DMSO	0
17	$Pd(OAc)_2$	**L1**	1,4-dioxane	0
18	$Pd(OAc)_2$	**L1**	EtOH	0

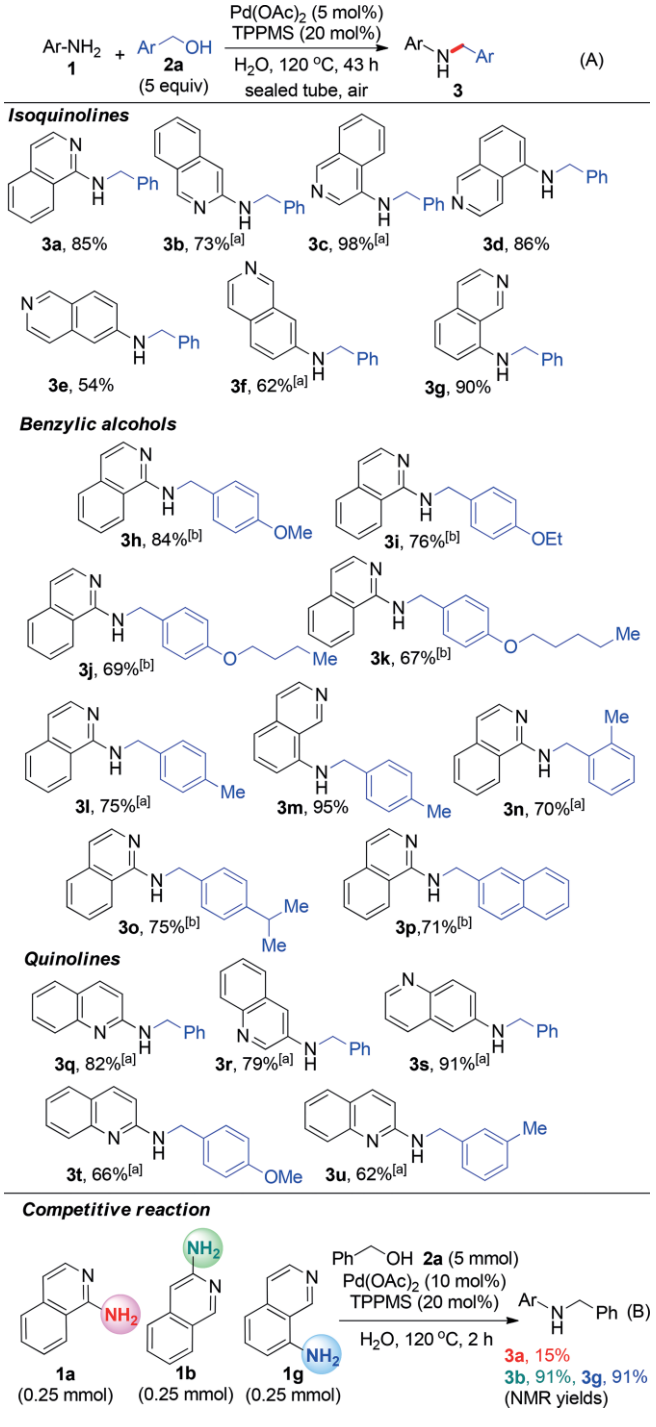


[a] Reaction conditions: 1-aminoisoquinoline **1a** (1 mmol), catalyst (5 mol-%), TPPMS (10 mol-%), benzyl alcohol **2a** (5 equiv.), solvent (4 mL), 120 °C, 18 h in a sealed tube under air. [b] The conversion was determined by ^1H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard. [c] 10 mol-% of $Pd(OAc)_2$ and 20 mol-% of TPPMS **L1** were used.

2. Reaction Scope

With the optimized conditions in hand, we examined the substrate scope of the dehydrative coupling reaction (Scheme 2A). A series of isoquinolines **1** with amino groups at different positions could be employed with benzyl alcohol **2a** to give the corresponding *N*-benzylated products **3a**–**g** in moderate to excellent yields (54–98 %). The use of benzyl alcohols with electron-donating methyl, methoxy and ethoxy groups resulted in good yields (67–95 %). Significantly, hydrophobic butoxy and pentyloxy groups were also tolerated well to produce the corresponding products **3j**–**k** in water. A sterically demanding methyl group at the *ortho* position was tolerated in the direct

substitution (**3n**, 70 %). 2-Naphthalenemethanol led to desired product **3p** in 71 % yield. Legros et al. reported that the loss of resonance energy for the formation of the (η^3-naphthalenemethyl)palladium is less important than for the π-benzylpalladium.[21] In contrast, the *N*-benzylation using 4-nitrobenzyl alcohol did not occur since the electron-deficient π-benzylpalladium(II) cation species was not formed. Additionally, phenethyl alcohol resulted in no reaction. We next evaluated the utility of this method for dehydrative couplings of aminoquinolines. The coupling reaction of several aminoquinolines with benzylic alcohols proceeded smoothly to afford the desired products in moderate to excellent yields (**3q**–**u**).

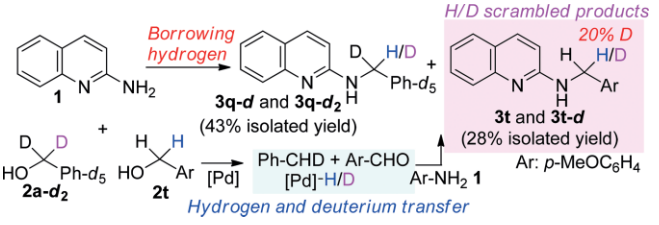


Scheme 2. *N*-Benzylation of various aminoisoquinolines with benzylic alcohols. Yield of isolated product. [a] 10 mol-% of $Pd(OAc)_2$ was used for 18 h. [b] 10 mol-% of $Pd(OAc)_2$ was used at 140 °C for 18 h.

To determine the reactivity of amino groups at different substitution positions of the isoquinoline structure under these conditions, a competitive reaction using **1a**, **1b** and **1g** (0.25 mmol each) was carried out (Scheme 2B). The coupling reactions of amines **1b** and **1g** proceeded completely in just 2 h, while amine **1a** was converted into **3a** in only 15 % yield. This result clearly shows the low reactivity of 1-aminoisoquinoline **1a** due to steric and electronic effects.

3. Crossover Experiment

To rule out the nucleophilic substitution pathway for C–N bond formation in our catalytic system, a crossover experiment was carried out between deuterium-labeled alcohol **2a**-d_2 and *para*-methoxybenzyl alcohol **2t**. As expected, a mixture of **3t** and deuterated **3t**-***d*** as the H/D scrambling products was obtained in 28 % isolated yield (Scheme 3). The deuterium incorporation at the methylene position of **3t**-***d*** was indicated by NMR analysis. In the ^{13}C NMR spectrum, the methylene carbon is a 1:1:1 triplet at 45.0 ppm for **3t**-***d*** but a singlet at 45.3 ppm for **3t** (see SI). In the ^1H NMR spectrum, the ratio of the integration values of the methylene doublet at 4.6 ppm to the doublet at 6.6 ppm is 1.8:1.0, yielding 20 % D incorporation in **3t**-***d*** (see SI).

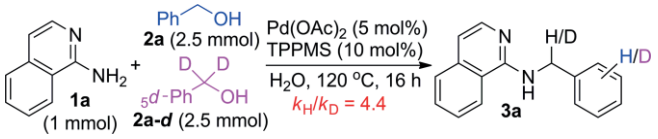


Scheme 3. Crossover experiment. Reaction conditions: 2-aminoquinoline **1** (1 mmol), $Pd(OAc)_2$ (5 mol-%), TPPMS (20 mol-%), [D_7]benzyl alcohol **2a**-d_2 (2.5 mmol) and 4-methoxybenzyl alcohol **2t** (2.5 mmol), H_2O (4 mL), 120 °C, 18 h in a sealed tube under air.

4. Kinetic Isotope Effect (KIE) and Rate Law Measurements

First, to determine whether benzylic C-H bond cleavage is involved in the turnover limiting step of the catalytic cycle, a kinetic isotope effect (KIE) study was performed employing the intermolecular competition between alcohol **2a** and its deuterium-labeled analog **2a**-***d***. The competition reaction yielded a KIE = 4.4 on the basis of ^1H NMR analysis (Scheme 4). Spitzer et al. reported a KIE value of 9.4 in the aqueous sodium dichromate oxidation of benzyl alcohol.[22]

Next, the reaction progress for dehydrative coupling of amine **1a** (1 mmol) with alcohol **2a** (5 mmol) at 110 °C was monitored by ^1H NMR spectroscopy. The time course of the reaction showed the formation of benzaldehyde (**4a**) as a key intermediate along with *N*-benzylated product **3a** (Figure 2A). Subsequently, the experimental rate laws were determined us-



Scheme 4. Kinetic isotope effect.

ing the method of initial rates (up to 20 % conversion), providing insight into the turnover limiting step of the catalytic reaction. The initial rate was independent of the substrate concentration of **1a** in the examined range (Figure 2B). This zero-order behavior with respect to amine **1a** eliminated reductive amination as the turnover limiting step. In contrast, the initial rates followed a linear relationship with the concentration of **2a** over the range between 0.75 and 1.5 M (Figure 2C and D). Therefore, the first-order dependence of **2a** was consistent with the turnover limiting dehydrogenation of alcohol **2a** in the catalytic cycle.

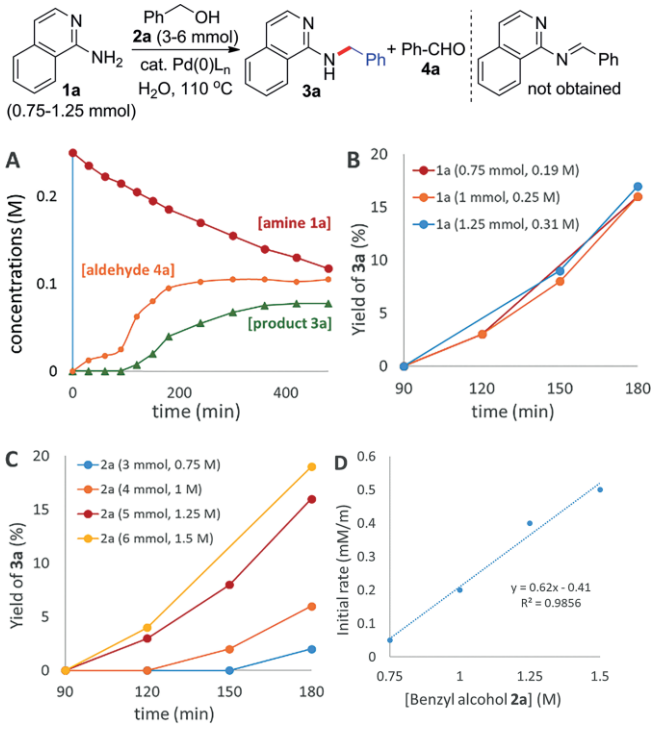


Figure 2. (A) Reaction time course. Reaction conditions: 1-aminoisoquinoline **1a** (1 mmol), $Pd(OAc)_2$ (0.1 mmol), TPPMS (0.2 mmol), benzyl alcohol **2a** (5 mmol), H_2O (4 mL), 110 °C in a sealed tube under air. (B) Initial rates obtained when amine **1a** (0.75–1.25 mmol) was varied. (C) Initial rates obtained when alcohol **2a** (3–6 mmol) was varied. (D) First-order dependence of the initial rate of the formation of **3a** on the concentration of alcohol **2a**.

The coupling of **1a** with **2a** proceeded smoothly in H_2O compared to D_2O (Figure 3A). Furthermore, the reaction rate was significantly slower under neat conditions.[23] The first-order plot clearly shows a faster rate in H_2O than in D_2O with a kinetic solvent isotope effect (KSIE) of 1.6 (Figure 3B),[24] suggesting that hydrogen bonding activation plays an important role in our catalytic system.[25]

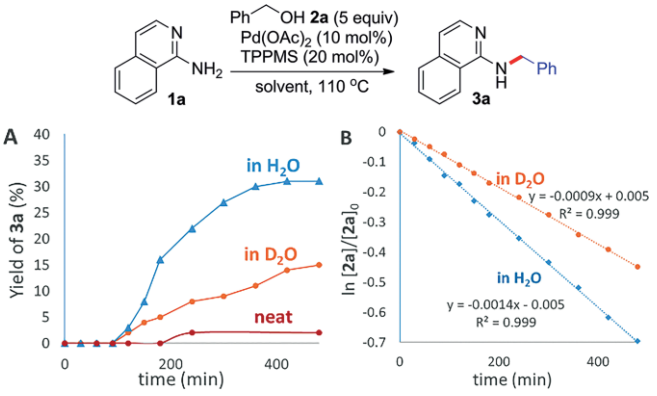


Figure 3. (A) Reaction time course in H_2O, D_2O and neat condition. (B) Comparison of reaction rates in H_2O and D_2O. Reaction conditions: 1-aminoisoquinoline **1a** (1 mmol), $Pd(OAc)_2$ (0.1 mmol), TPPMS (0.2 mmol), benzyl alcohol **2a** (5 mmol), H_2O or D_2O (4 mL), 110 °C in a sealed tube under air.

5. Disproportionation of Benzyl Alcohol

To better understand the dehydrogenation step, disproportionation of alcohol **2a** was examined. If the dehydrogenation of alcohol **2a** to aldehyde **4a** occurs, toluene (**5a**) should be formed through β-hydride elimination of the palladium hydride species. We were delighted to observe the formation of aldehyde **4a** (25 %) and toluene **5a** (21 %) in the reaction mixture (Figure 4). In contrast, in the absence of the water-soluble phosphine ligand or under neat conditions, lower yields resulted. Furthermore, the reaction kinetics were faster in H_2O than in D_2O with a KSIE of 2.3.[26] This is consistent with the results of Figure 4 right, which show that the water molecules significantly affect the reactivity for the dehydrogenation of benzyl alcohol.

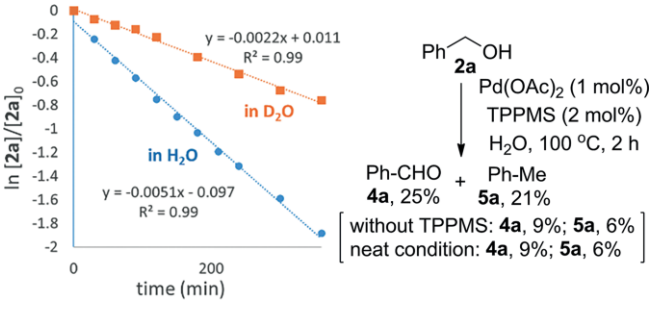
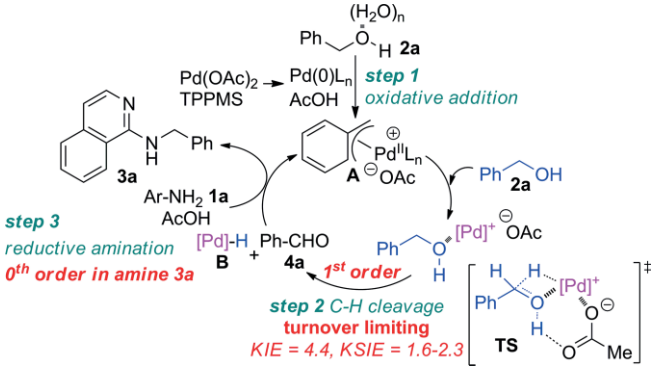


Figure 4. Disproportionation of benzyl alcohol (**2a**). Reaction conditions: benzyl alcohol **2a** (5 mmol), $Pd(OAc)_2$ (0.05 mmol), TPPMS (0.1 mmol), H_2O or D_2O (4 mL), 100 °C, 2 h in a sealed tube under air.

6. Mechanistic Considerations

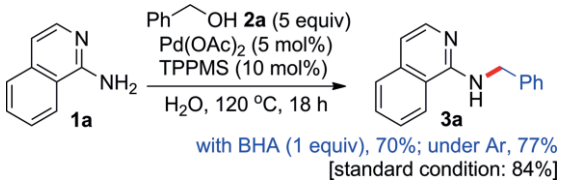
On the basis of these results and our previous report,[18] we propose a catalytic mechanism for the dehydrative coupling of 1-aminoisoquinoline (**1a**) with benzyl alcohol (**2a**) in water as illustrated in Scheme 5. First, oxidative addition of hydrated alcohol **2a** to the water-soluble Pd^0/TPPMS catalyst affords the cationic π-benzylpalladium(II) complex **A** (step 1). This process should be favored by electron-donating groups on intermediate **A**, since these will stabilize the positive charge on Pd^{II}. The re-

sulting cationic charge of complex **A** would also be stabilized by water molecules. Next, the Pd^{II}-catalyzed dehydrogenation of alcohol **2a** generates the benzaldehyde (**4a**) through β-hydride elimination (step 2). After the coordination of alcohol **2a** to **A**, benzylic C-H cleavage and deprotonation of **2a** would proceed synchronously to form the aldehyde **4a** along with palladium(II) hydride **B**. The KIE of 4.4 indicates that the C-H cleavage in **TS** is involved in the turnover-limiting step (see Scheme 4). Furthermore, the KSIEs of 1.6 (Figure 3 right) and 2.3 (Figure 4) suggest that water molecules accelerate the dehydrogenation of alcohol **2a** in water. The acetoxy anion would act as a base to remove the acidic proton of the cationic alcohol–Pd^{II} intermediate, whereas the use of strong bases is essential in traditional protocols. Finally, reductive amination of amine **1a** with aldehyde **4a** catalyzed by palladium(II) hydride **B** affords the *N*-benzylated product **3a** and regenerates the π-benzylpalladium(II) species **A** (step 3).



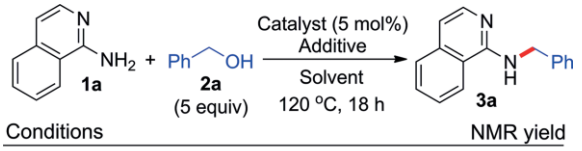
Scheme 5. Proposed mechanism.

Control experiments were performed to exclude the possibility of other reaction pathways and support the proposed mechanism (Scheme 6). In the presence of a radical scavenger (BHA: 3-*tert*-butyl-4-hydroxyanisole, 1 equiv.) or under an Ar atmosphere, the yield of the desired product **3a** remained unchanged, suggesting that a radical pathway based on a single electron transfer (SET) is not included in our catalytic system, nor is oxygen essential to the oxidation (dehydrogenation) step.



Scheme 6. Control experiments.

To compare our π-benzylpalladium system with other efficient catalytic systems for dehydrative C–N bond formation, the reaction of substrate **1a** with alcohol **2a** at 120 °C for 18 h was carried out (Scheme 7). While our catalytic system proceeded smoothly to give desired product **3a** in 84 % yield, the prior borrowing hydrogen methods using $[Cp^*IrCl_2]_2/K_2CO_3$[27a] $RuCl_2(PPh_3)_3/KO\,t\,Bu$[27b] or $Pd(OAc)_2/CsOH$[27c] resulted in lower yields (15–37 %). Furthermore, no reaction occurred when using $FeBr_2$ catalyst with $KHSO_4$ system for the direct nucleophilic substitution of **2a** in toluene,[27d] clearly showing the superiority of the π-benzylpalladium(II) system for the direct dehydrative coupling of **1a**. Notably, our simple protocol could be achieved under neutral aqueous conditions, which should be advantageous for organic synthesis.

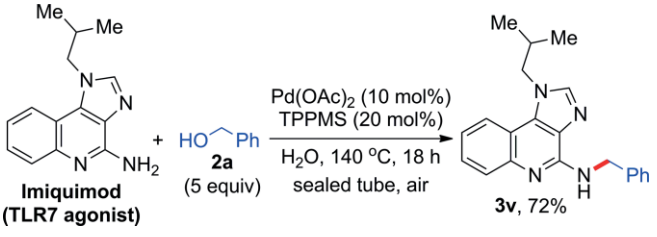


Conditions	NMR yield
$Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), H_2O	84%
$[Cp^*IrCl_2]_2$ (5 mol%), K_2CO_3 (5 mol%), toluene	15%
$RuCl_2(PPh_3)_3$ (5 mol%), KOtBu (1 equiv), toluene	37%
$Pd(OAc)_2$ (5 mol%), $CsOH·H_2O$ (1 equiv), toluene	31%
$FeBr_2$ (5 mol%), $KHSO_4$ (1 equiv), toluene	0%

Scheme 7. Comparison of catalytic dehydrative *N*-benzylation of substrate **1a** with alcohol **2a**.

7. Late-Stage *N*-Benzylation in Bioactive Molecule

To demonstrate the power of the efficient C–N bond formation, we applied the late-stage direct modification of a drug molecule (Scheme 8).[28,29] The dehydrative coupling of Imiquimod with alcohol **2a** proceeded smoothly in water, then crude product could be purified simply by recrystallization from hexane and EtOAc to give the desired product **3v** in 72 % isolated yield. Notably, the developed process avoids using column chromatography.



Scheme 8. Late-stage direct modification of a drug molecule.

Conclusions

In summary, we have developed an environmentally benign borrowing hydrogen strategy for dehydrative coupling of aminoisoquinolines or aminoquinolines with benzylic alcohols using a water-soluble palladium(0)/TPPMS system in water. This catalytic system provides rapid access to valuable *N*-benzylated products as a common structural motif found in pharmaceuticals. To the best of our knowledge, this is the first example of direct modification of aminoisoquinolines with benzylic alcohols in water. Notably, the water-soluble π-benzylpalladium system promotes the reactions without the need for strong bases or other additives, whereas strong bases are generally used in hydrogen transfer strategies using organic solvents. Furthermore, water molecules significantly accelerate the dehydrogenation of alcohols followed by C–N bond formation. A borrowing

hydrogen pathway was proposed based on kinetic studies and crossover experiments.

Experimental Section

General Procedure I: A mixture of amines **1** (1 mmol), palladium(II) acetate (12 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 72 mg, 0.2 mmol) and benzylic alcohols **2** (5 mmol) in H_2O (4 mL) was heated at 120 °C for 43 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 with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to give desired product **3**.

General Procedure II: A mixture of amines **1** (1 mmol), palladium(II) acetate (24 mg, 0.1 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 72 mg, 0.2 mmol) and benzylic alcohols **2** (5 mmol) in H_2O (4 mL) was heated at 120 °C for 18 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 with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to give desired product **3**.

General Procedure III: A mixture of amines **1** (1 mmol), palladium(II) acetate (24 mg, 0.1 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 72 mg, 0.2 mmol) and benzylic alcohols **2** (5 mmol) in H_2O (4 mL) was heated at 140 °C for 18 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 with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to give desired product **3**.

***N*-Benzylisoquinolin-1-amine (3a):**[30] Following the general procedure I, **3a** was obtained as a white solid. Yield 201 mg (85 %); m.p. 91–93 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3441, 1621; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.82 (d, J = 5.3 Hz, 2H), 5.43 (brs, 1H), 6.98 (dd, J = 6.0, 0.7 Hz, 1H), 7.28–7.46 (m, 6H), 7.59 (ddd, J = 8.2, 7.1, 1.1 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 8.03 (d, J = 5.7 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 21.1, 45.9, 111.2, 118.0, 121.4, 125.9, 127.2, 128.1, 129.4, 130.0, 136.3, 137.1; MS (FAB): m/z 235 [M + H]$^+$.

***N*-Benzylisoquinolin-3-amine (3b):**[31] Following the general procedure II, **3b** was obtained as a pale yellow solid. Yield 172 mg (73 %); m.p. 170–172 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3242, 1624; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.52 (d, J = 2.1 Hz, 2H), 5.19 (brs, 1H), 6.49 (s, 1H), 7.20 (ddd, J = 8.0, 6.4, 1.4 Hz, 1H), 7.27–7.63 (m, 7H), 7.74 (dd, J = 8.2, 0.9 Hz, 1H), 8.82 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 47.2, 96.0, 122.6, 124.9, 127.2, 127.3, 127.8, 128.7, 130.4, 138.8, 139.0, 151.8, 155.4; MS (FAB): m/z 235 [M + H]$^+$.

***N*-Benzylisoquinolin-4-amine (3c):**[32] Following the general procedure II, **3c** was obtained as a white solid. Yield 230 mg (98 %); m.p. 127–130 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3264, 1545; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.52 (m, 3H), 7.30–7.47 (m, 5H), 7.54–7.69 (m, 2H), 7.81 (d, J = 8.5, 1H), 7.91–7.93 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 48.5, 119.2, 123.8, 125.9, 127.0, 127.7, 127.9, 128.1, 128.5, 128.9, 129.0, 138.5; MS (FAB): m/z 235 [M + H]$^+$.

***N*-Benzylisoquinolin-5-amine (3d):**[33] Following the general procedure I, **3d** was obtained as a pale yellow solid. Yield 202 mg (86 %); m.p. 115–117 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3337, 1579; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.50 (d, J = 4.4 Hz, 2H), 4.74 (brs, 1H), 6.78 (d, J = 7.1 Hz, 1H), 7.29–7.50 (m, 7H), 7.58 (dt, J = 6.2, 0.7 Hz, 1H), 8.47 (d, J = 6.0 Hz, 1H), 9.17 (d, J = 0.7 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 48.3, 108.0, 113.3, 116.4, 125.9, 127.6, 128.0, 128.8, 129.3, 138.4, 142.1, 142.2, 152.9; MS (FAB): m/z 235 [M + H]$^+$.

***N*-Benzylisoquinolin-6-amine (3e):** Following the general procedure I, **3e** was obtained as a pale yellow solid. Yield 127 mg (54 %); m.p. 128–130 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3284, 1621; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.45 (d, J = 5.3 Hz, 2H), 4.62 (brs, 1H), 6.68 (d, J = 2.3 Hz, 1H), 6.96 (dd, J = 8.8, 2.3 Hz, 1H), 7.29–7.42 (m, 6H), 7.71 (d, J = 8.9, 1H), 8.30 (d, J = 5.7 Hz, 1H), 8.94 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 47.9, 101.7, 118.9, 123.1, 127.5, 127.6, 128.8, 129.0, 138.2, 143.5, 149.1, 151.4; MS (FAB): m/z 235 [M + H]$^+$. HRMS (FAB): m/z [M + H]$^+$ calcd. for $C_{16}H_{14}N_2$ 235.1235, found 235.1236.

***N*-Benzylisoquinolin-7-amine (3f):** Following the general procedure II, **3f** was obtained as a pale yellow solid. Yield 146 mg (62 %); m.p. 142–144 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3263; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.39 (brs, 1H), 4.46 (d, J = 5.0 Hz, 1H), 6.88 (d, J = 2.3 Hz, 1H), 7.11 (dd, J = 8.9, 2.3 Hz, 1H), 7.28–7.34 (m, 1H), 7.34–7.44 (m, 4H), 7.47 (d, J = 5.7 Hz, 1H), 7.62 (d, J = 8.7 Hz, 1H), 8.27 (d, J = 5.7 Hz, 1H), 9.00 (s, 1H); ^{13}C-NMR (100 MHz, [D_6]DMSO) δ = 48.2, 103.1, 120.2, 122.2, 127.5, 127.6, 128.8, 129.8, 130.6, 138.5, 139.7, 146.7, 150.5; MS (FAB): m/z 235 [M + H]$^+$. HRMS (FAB): m/z [M + H]$^+$ calcd. for $C_{16}H_{14}N_2$ 235.1235, found 235.1235.

***N*-Benzylisoquinolin-8-amine (3g):** Following the general procedure I, **3g** was obtained as a pale yellow solid. Yield 212 mg (90 %); m.p. 126–128 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3277, 1572; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.52 (d, J = 5.0 Hz, 2H), 5.21 (brs, 1H), 6.65 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.30–7.68 (m, 7H), 8.47 (d, J = 5.7, 1H), 9.32 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 48.2, 105.9, 115.3, 118.6, 120.9, 127.5, 127.6, 128.8, 131.7, 137.0, 138.3, 143.1, 144.3, 145.3; MS (FAB): m/z 235 [M + H]$^+$. HRMS (FAB): m/z [M + H]$^+$ calcd. for $C_{16}H_{14}N_2$ 235.1235, found 235.1235.

***N*-(4-Methoxybenzyl)isoquinolin-1-amine (3h):**[34] Following the general procedure III, **3h** was obtained as a yellow oil. Yield 222 mg (84 %); IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3445, 1623; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3H), 4.74 (d, J = 4.6 Hz, 2H), 5.36 (brs, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 6.0 Hz, 1H), 7.37 (d, J = 8.7 Hz, 2H), 7.43 (ddd, J = 8.2, 8.0, 0.9 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 8.03 (d, J = 6.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 45.6, 55.4, 111.2, 114.1, 118.3, 121.7, 126.0, 127.2, 129.5, 129.8, 131.6, 137.2, 141.4, 155.1, 159.0; MS (FAB): m/z 265 [M + H]$^+$.

***N*-(4-Ethoxybenzyl)isoquinolin-1-amine (3i):** Following the general procedure III, **3i** was obtained as a yellow oil. Yield 213 mg (76 %); IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3442, 1622; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, J = 6.9 Hz, 3H), 4.04 (q, J = 7.3 Hz, 2H), 4.73 (d, J = 5.0 Hz, 2H), 5.35 (brs, 1H), 6.89 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 6.0 Hz, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.43 (ddd, J = 8.2, 6.9, 1.4 Hz, 1H), 7.55–7.61 (m, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 6.0, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 15.0, 45.6, 63.6, 111.2, 114.7, 118.2, 121.7, 126.0, 127.2, 129.5, 129.8, 131.4, 137.2, 141.5, 155.1, 158.4; MS (FAB): m/z 279 [M + H]$^+$; HRMS (FAB): m/z [M + H]$^+$ calcd. for $C_{18}H_{18}N_2O$ 279.1497, found 279.1497.

***N*-(4-Butoxybenzyl)isoquinolin-1-amine (3j):** Following the general procedure III, **3j** was obtained as a yellow oil. Yield 211 mg (69 %); IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3448, 1622; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.96 (t, J = 7.8 Hz, 3H), 1.47 (sext, J = 7.3 Hz, 2H), 1.47 (quin, J = 7.3 Hz, 2H), 3.91 (t, J = 6.4 Hz, 2H), 4.70 (d, J = 5.0 Hz, 2H), 5.43 (brt, J = 4.8 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 6.0 Hz, 1H), 7.30 (d, J = 8.7 Hz, 2H), 7.36 (ddd, J = 8.2, 6.9, 1.4 Hz, 1H), 7.53 (dt, J = 6.9, 1.4 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 8.01

(d, J = 5.5 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.0, 19.4, 31.4, 45.7, 67.8, 111.2, 114.8, 118.2, 121.6, 126.0, 127.2, 129.5, 129.8, 131.3, 137.2, 141.5, 155.0, 158.7; MS (FAB): m/z 307 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd. for $C_{20}H_{22}N_2O$ 307.1810, found 307.1809.

***N*-[4-(Pentyloxy)benzyl]isoquinolin-1-amine (3k):** Following the general procedure III, **3k** was obtained as a yellow oil. Yield 214 mg (67 %); IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3444, 1624; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.91 (t, J = 7.3 Hz, 3H), 1.25–1.50 (m, 4H), 1.74 (quin, J = 6.9 Hz, 2H), 3.87 (t, J = 6.9 Hz, 2H), 4.68 (d, J = 5.0 Hz, 2H), 5.48 (brt, J = 4.6 Hz, 1H), 6.80 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 6.0 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H), 7.31 (ddd, J = 8.2, 6.9, 0.9 Hz, 1H), 7.49 (ddd, J = 8.2, 6.9, 0.9 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 6.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.2, 22.6, 28.4, 29.1, 45.7, 68.1, 111.2, 114.8, 118.2, 121.6, 126.0, 127.2, 129.5, 129.8, 131.3, 137.2, 141.5, 155.1, 158.7; MS (FAB): m/z 321 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd. for $C_{21}H_{25}N_2O$ 321.1967, found 321.1966.

***N*-(4-Methylbenzyl)isoquinolin-1-amine (3l):** Following the general procedure II, **3l** was obtained as a brown oil. Yield 186 mg (75 %); IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3310, 1623; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 4.76 (d, J = 5.0 Hz, 2H), 5.39 (brs, 1H), 6.96 (dd, J = 6.0, 0.5 Hz, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.43 (ddd, J = 8.5, 7.1, 1.4 Hz, 1H), 7.58 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 8.04 (d, J = 6.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 21.1, 45.9, 111.2, 118.0, 121.4, 125.9, 127.2, 128.1, 129.4, 129.7, 136.3, 137.1, 141.4, 154.9; MS (FAB): m/z 249 $[M + H]^+$. HRMS (FAB): m/z $[M + H]^+$ calcd. for $C_{17}H_{16}N_2$ 249.1392, found 249.1392.

***N*-(4-Methylbenzyl)isoquinolin-8-amine (3m):** Following the general procedure I, **3m** was obtained as a white solid. Yield 236 mg (95 %); m.p. 120–121 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3269, 1568; ^{1}H-NMR (400 MHz, [D_6]DMSO): δ = 2.26 (s, 3H), 4.47 (d, J = 5.5 Hz, 2H), 6.45 (d, J = 7.3 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 7.8 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.38 (t, J = 8.2 Hz, 1H), 7.54 (t, J = 6.0 Hz, 1H), 7.60 (d, J = 5.5 Hz, 1H), 8.39 (d, J = 5.5 Hz, 1H), 9.63 (s, 1H); ^{13}C-NMR (100 MHz, [D_6]DMSO) δ = 21.2, 46.4, 105.6, 113.6, 118.8, 120.8, 127.4, 129.5, 132.2, 136.2, 136.9, 137.0, 143.3, 145.3, 147.4; MS (FAB): m/z 249 $[M + H]^+$. HRMS (FAB): m/z $[M + H]^+$ calcd. for $C_{17}H_{16}N_2$ 249.1392, found 249.1392.

***N*-(2-Methylbenzyl)isoquinolin-1-amine (3n):**[34] Following the general procedure II, **3n** was obtaine as a yellow solid. Yield 174 mg (70 %); m.p. 77–80 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3251, 1623; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 4.78 (d, J = 4.8 Hz, 2H), 5.24 (brs, 1H), 6.98 (d, J = 6.0 Hz, 1H), 7.16–7.25 (m, 3H), 7.38 (d, J = 7.1 Hz, 1H), 7.43 (ddd, J = 8.2, 6.8, 1.1 Hz, 1H), 7.58 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.69 (d, J = 4.4 Hz, 1H), 7.71 (d, J = 5.0 Hz, 1H), 8.05 (d, J = 6.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 19.1, 44.3, 111.1, 118.0, 121.4, 125.9, 126.2, 127.2, 127.7, 129.0, 129.7, 130.6, 137.0, 141.4, 154.8; MS (FAB): m/z 249 $[M + H]^+$.

***N*-(4-Isopropylbenzyl)isoquinolin-1-amine (3o):** Following the general procedure III, **3o** was obtaine as a yellow oil. Yield 206 mg (75 %); IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3447, 1623; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, J = 7.3 Hz, 6H), 2.88 (sep, J = 6.9 Hz, 1H), 4.74 (d, J = 5.0 Hz, 1H), 5.46 (brs, 1H), 6.91 (d, J = 5.5 Hz, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.28–7.36 (m, 3H), 7.50 (dd, J = 7.8, 6.9 Hz, 1H), 7.62 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 6.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 24.2, 34.0, 46.0, 111.3, 118.2, 121.6, 126.0, 126.9, 127.3, 128.4, 129.8, 136.9, 137.2, 141.6, 148.2, 155.1; MS (FAB): m/z 277 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd. for $C_{19}H_{20}N_2$ 277.1705, found 277.1705.

***N*-(Naphthalen-2-ylmethyl)isoquinolin-1-amine (3p):** Following the general procedure III, **3p** was obtained as a white solid. Yield 202 mg (71 %); m.p. 134–136 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3417, 1619; ^{1}H-NMR (400 MHz, [D_6]DMSO): δ = 4.93 (d, J = 6.0 Hz, 2H), 6.91 (d, J = 5.5 Hz, 2H), 7.40–7.50 (m, 2H), 7.53 (ddd, J = 8.2, 6.9, 1.4 Hz, 1H), 7.57 (dd, J = 6.9, 1.8 Hz, 1H), 7.64 (ddd, J = 8.2, 6.9, 1.4 Hz, 1H), 7.72 (d, J = 7.3 Hz, 1H), 7.78–7.92 (m, 5H), 8.12 (d, J = 5.5 Hz, 1H), 8.36 (d, J = 7.8 Hz, 1H); ^{13}C-NMR (100 MHz, [D_6]DMSO) δ = 44.6, 110.3, 118.4, 123.6, 125.5, 125.9, 126.2, 126.5, 126.6, 127.1, 128.0, 128.2, 130.3, 132.6, 133.5, 137.2, 139.1, 142.0, 155.7; MS (FAB): m/z 285 $[M]^+$; HRMS (FAB): m/z $[M]^+$ calcd. for $C_{17}H_{16}N_2$ 284.1313, found 284.1313; Anal. Calcd for $C_{20}H_{16}N_2 \cdot 0.1H_2O$: C, 83.95; H, 5.64; N, 9.79; found C, 83.94; H, 5.57; N, 9.74.

***N*-Benzylquinolin-2-amine (3q):**[35] Following the general procedure II, **3q** was obtained as a white solid. Yield 192 mg (82 %); m.p. 100–102 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3265, 1622; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.73 (d, J = 5.7 Hz, 2H), 5.03 (brs, 1H), 6.62 (d, J = 8.9 Hz, 1H), 7.22 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.27–7.42 (m, 5H), 7.54 (ddd, J = 8.5, 7.1, 1.6 Hz, 1H), 7.59 (dd, J = 1.4, 8.0 Hz, 1H), 7.71 (dd, J = 8.4, 0.7 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 45.9, 111.4, 122.2, 123.6, 126.3, 127.4, 127.5, 127.8, 128.7, 130.0, 137.5, 139.4, 148.0, 156.7; MS (FAB): m/z 235 $[M + H]^+$.

***N*-Benzylquinolin-3-amine (3r):**[36] Following the general procedure II, **3r** was obtained as a yellow solid. Yield 187 mg (79 %); m.p. 96–100 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3344, 1615; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.43 (m, 3H), 7.02 (d, J = 2.8 Hz, 1H), 7.29–7.47 (m, 7H), 7.58 (dd, J = 6.0, 3.7 Hz, 1H), 7.94 (dd, J = 6.2, 3.4 Hz, 1H), 8.49 (d, J = 2.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 48.0, 110.5, 125.0, 126.0, 127.0, 127.5, 127.6, 128.9, 129.1, 129.4, 138.2, 141.4, 142.2, 143.3; MS (FAB): m/z 235 $[M + H]^+$.

***N*-Benzylquinolin-6-amine (3s):**[37] Following the general procedure II, **3s** was obtained as a yellow solid. Yield 214 mg (91 %); m.p. 124–125 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3316, 1622; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.44 (m, 3H), 6.72 (d, J = 2.8 Hz, 1H), 7.13 (dd, J = 9.2, 2.5 Hz, 1H), 7.25 (dd, J = 8.4, 4.4 Hz, 1H), 7.28–7.52 (m, 5H), 7.89 (d, J = 8.7 Hz, 2H), 8.61 (dd, J = 4.1, 1.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 48.3, 103.3, 121.3, 121.4, 127.4, 127.5, 128.7, 130.1, 130.3, 133.9, 138.6, 143.3, 145.9, 146.3; MS (FAB): m/z 235 $[M + H]^+$.

***N*-(4-Methoxybenzyl)quinolin-2-amine (3t):**[38] Following the general procedure II, **3t** was obtained. Yield 176 mg (66 %) as a yellow oil; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3285, 1608; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3H), 4.65 (d, J = 3.9 Hz, 2H), 5.05 (brs, 1H), 6.62 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.22 (ddd, J = 8.0, 7.1, 1.4 Hz, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.54 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H), 7.59 (dd, J = 7.7, 1.4 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 45.5, 55.4, 111.4, 114.1, 122.2, 123.6, 126.2, 127.5, 129.2, 129.7, 131.4, 137.5, 156.8, 159.0; MS (FAB): m/z 265 $[M + H]^+$.

***N*-(3-Methylbenzyl)quinolin-2-amine (3u):** Following the general procedure II, **3u** was obtained as a colorless oil. Yield 152 mg (62 %); IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3277, 1619; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3H), 4.67 (d, J = 5.0 Hz, 2H), 5.07 (brs, 1H), 6.61 (d, J = 9.2, 1.4 Hz, 1H), 7.09 (d, J = 7.3 Hz, 1H), 7.15–7.30 (m, 4H), 7.53 (dd, J = 8.2, 6.9 Hz, 2H), 7.58 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 21.5, 46.0, 111.4, 122.2, 123.6, 124.9, 126.3, 127.5, 128.2, 128.6, 128.7, 129.7, 137.5, 138.4, 139.3, 148.1, 156.9; MS (FAB): m/z 249 $[M + H]^+$; HRMS (FAB): m/z $[M + H]^+$ calcd. for $C_{17}H_{16}N_2$ 249.1392, found 249.1391.

***N*-Benzyl-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (3v):**[39] A mixture of Imiquimod (240 mg, 1 mmol), palladium(II) acetate (24 mg, 0.1 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 72 mg, 0.2 mmol) and benzyl alcohol (**2**) (515 µL, 5 mmol) in H_2O (4 mL) was heated at 140 °C for 18 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 with $MgSO_4$ and concentrated in vacuo. The residue was purified by recrystallization from hexane and EtOAc to give the desired product **3v** as a white solid. Yield 228 mg (72 %); m.p. 162–164 °C; IR (KBr) /cm^{-1}: $\tilde{\nu}$ = 3295, 1597; ^{1}H-NMR (400 MHz, [D$_6$]DMSO): δ = 0.92 (d, J = 6.9 Hz, 6H), 2.17 (sept, J = 6.9 Hz, 6H), 4.40 (d, J = 7.3 Hz, 2H), 4.79 (d, J = 6.0 Hz, 2H), 2.17 (sept, J = 6.9 Hz, 6H), 7.19 (tt, J = 7.3, 1.4 Hz, 1H), 7.24–7.32 (m, 3H), 7.40–7.46 (m, 3H), 7.60 (t, J = 6.4 Hz, 1H), 2.17 (sept, J = 6.9 Hz, 6H), 7.64 (dd, J = 8.2, 0.9 Hz, 1H), 7.99 (dd, J = 6.9 Hz, 1H), 8.19 (s, 1H); ^{13}C-NMR (100 MHz, [D$_6$]DMSO) δ = 19.8, 29.0, 43.6, 54.0, 115.4, 120.9, 121.8, 126.9, 127.3, 127.4, 128.0, 128.6, 128.9, 131.8, 141.5, 143.8, 145.4, 151.0; MS (FAB): m/z 331 [M + H]$^+$.

((PM: Der Autor hat einige Abbildungen in mehreren Teilen geliefert: Bitte o201901606_figure2_TOP, o201901606_figure2A, o201901606_figure2B, o201901606_figure2C und o201901606_figure2D nach der Grafik im Original.PDF kombinieren. Auch o201901606_figure3_TOP, o201901606_figure3A und o201901606_figure3B genauso kombinieren, und noch o201901606_figure4LEFT und o201901606_figure4RIGHT bitte auch.))

Acknowledgments

This work was supported by JSPS KAKENHI Grant Number 19K07003.

Keywords: Isoquinoline · Borrowing hydrogen · Palladium · Reaction mechanisms · Benzyl alcohol

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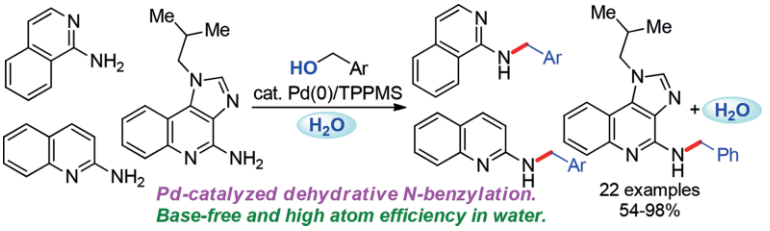
Received: November 1, 2019



A borrowing hydrogen strategy for the palladium-catalyzed dehydrative coupling of aminoisoquinolines or aminoquinolines with benzylic alcohols by a water-soluble π-benzylpalladium(II) system has been developed.

DOI: 10.1002/ejoc.201901606

