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Water-promoted dehydrative coupling of 2-aminopyridines in heptane *via* a borrowing hydrogen strategy†

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A synthetic method for dehydrative *N*-benzylation promoted by water molecules in heptane using a π-benzylpalladium system has been developed. The presence of water significantly accelerates carbon–nitrogen bond formation, which is accomplished in an atom-economical process to afford the corresponding *N*-monobenzylated products. A crossover experiment afforded H/D scrambled products, which is consistent with a borrowing hydrogen mechanism. Kinetic isotope effect measurements revealed that benzylic carbon–hydrogen bond cleavage was the rate-determining step.

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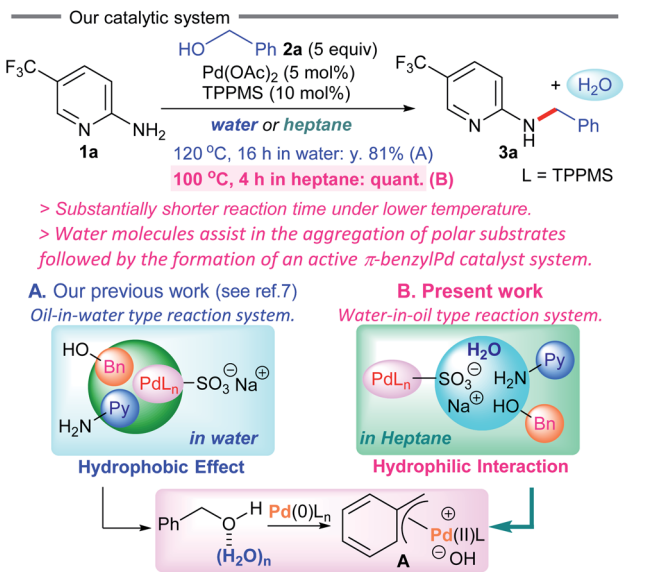
Introduction

The borrowing hydrogen methodology has emerged as a promising greener synthetic strategy for straightforward carbon–nitrogen bond formation utilizing readily available and low-toxicity benzyl alcohols instead of benzyl halides as coupling partners.[1] Various catalyst systems using iridium(III),[2] ruthenium(II),[3] or other metals[4] have been developed. Although this strategy affords an attractive atom-economical pathway and is an appealing synthetic shortcut for constructing valuable products, the reactions generally require high temperatures, organic solvents and strong bases. Thus, an efficient system possessing greater catalytic activity that can be performed at lower temperatures in greener solvents without any additives is highly desirable for sustainable carbon–nitrogen bond forming reactions.[5] Recently, our group has been exploring a greener borrowing hydrogen methodology involving π-benzylpalladium(II) complexes[6] in water.[7]

Recent studies disclosed that hydrophilic interactions play an important role in controlling self-assembly in biological processes.[8] In 2008, McLain *et al.* showed that charge-based interactions play an important role in dipeptide association in aqueous solution.[8b] In non-polar organic solvents, reverse micelles (RMs), with the polar groups concentrated in the interior of the aggregate, are formed *via* the self-assembly of surfactant molecules.[9] Notably, the presence of water molecules is the driving force for reverse micelle formation in nanosized water pools.[9b] In 2014, Zhao *et al.* prepared gold cluster catalysts within interfacially cross-linked reverse micelles *via* extraction of $HAuCl_4$ in the hydrophilic core for intramolecular alkyne carboxylation.[9c]

Inspired by these reports, we became interested in designing a new catalytic system *via* water-assisted self-assembly of polar substrates with a palladium catalyst in non-polar solvents (Scheme 1). We herein present the dehydrative coupling of 2-aminopyridines with benzylic alcohols in heptane using a π-benzylpalladium system, furnishing the corresponding *N*-benzyl-2-aminopyridines.[10] As the reaction begins, *in situ* generated water accelerates the aggregation of polar substrates with a Pd(0)/TPPMS catalyst in heptane, forming an active π-benzylpalladium catalyst system. The oxidative addition of



Scheme 1 Pd-catalyzed dehydrative coupling between aminopyridine **1a** and alcohol **2a**.

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† Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra for all compounds. See DOI: 10.1039/d1ra04118e

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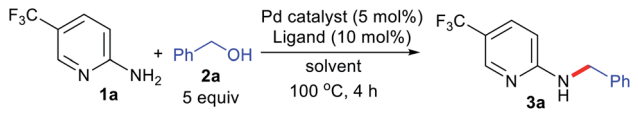
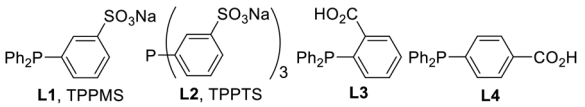
Table 1 Reaction optimization[a]



Entry	Catalyst	Ligand	Solvent	NMR yield (%)
1	$Pd(OAc)_2$	**L1**	Heptane	Quant
2	$Pd(OAc)_2$	**L1**	Heptane	0[b] (quant)[c]
3	$Pd(TFA)_2$	**L1**	Heptane	97
4	$PdCl_2$	**L1**	Heptane	0
5[d]	$Pd_2(dba)_3 \cdot CHCl_3$[e]	**L1**	Heptane	77
6	$Pd(OAc)_2$	**L1**	Octane	Quant
7	$Pd(OAc)_2$	**L1**	Hexane	2
8	$Pd(OAc)_2$	**L1**	MCH[f]	38
9	$Pd(OAc)_2$	**L1**	Toluene	4
10	$Pd(OAc)_2$	**L1**	$(CHCl_2)_2$	0
11	$Pd(OAc)_2$	**L1**	1,4-Dioxane	20
12	$Pd(OAc)_2$	**L1**	None	8
13	$Pd(OAc)_2$	**L2**	Heptane	5
14	$Pd(OAc)_2$	**L3**	Heptane	0
15	$Pd(OAc)_2$	**L4**	Heptane	6
16	$Pd(OAc)_2$	None	Heptane	30
17[g]	$Pd(OAc)_2$	**L1**	Heptane	99



[a] Optimizations were performed with 1 mmol of **1a** and 5 mmol of **2a** in the presence of 5 mol% Pd catalyst and 10 mol% TPPMS (10 mol%) in solvent (4 mL) at 100 °C for 4 h under air. [b] 3 equiv. of alcohol **2a**. [c] For 16 h. [d] Conducted at 120 °C for 16 h. [e] 2.5 mol%. [f] Methylcyclohexane. [g] Under Ar.

alcohols to palladium(0) complexes is generally difficult due to the poor performance of the hydroxyl moiety as a leaving group. In the present work, the first example of direct conversion of non-activated benzyl alcohols to the π-benzylPd(II) system has been developed in organic solvents, and applied to the dehydrative cross-coupling reaction. This water-in-oil reaction system is substantially different from our previous method (an oil-in-water type reaction system) concerning the self-assembly between palladium catalysts and polar substrates (Scheme 1A *vs.* B), and shows a significant advancement over our previous synthetic protocol for more sustainable chemistry.

Achieving the direct introduction of various functionalities to aminopyridines, which are found in a wide variety of pharmaceuticals, is of enormous interest.[11] Notably, our π-benzylPd(II) system can be applied to a variety of 2-aminopyridine substrates and benzylic alcohols under mild conditions.

Results and discussion

1. Optimization of *N*-benzylation

We initially examined the Pd-catalyzed reaction between 5-(trifluoromethyl)pyridin-2-amine (**1a**) and benzyl alcohol (**2a**) in heptane (Table 1). The reaction was completed in 4 h at 100 °C under air, furnishing the desired product **3a** (entry 1). When using 3 equiv. of alcohol **2**, the reaction did not proceed after 4 h, but was completed in 16 h (entry 2). Screening of other palladium catalysts found that palladium(II) trifluoroacetate resulted in an almost quantitative yield, whereas palladium(II) dichloride was not applicable (entries 3 and 4). The reaction using tris(dibenzylideneacetone)dipalladium(0) at 120 °C for 16 h gave **3a** in 77% yield (entry 5). Although the reaction proceeded to completion using octane instead of heptane (entry 6), the use of other low-polarity organic solvents resulted in lower yields (entries 7–11). Furthermore, little reaction occurred under neat conditions (entry 12). Other water-soluble phosphine ligands such as $P(C_6H_4SO_3Na)_3$ **L2** (TPPTS) and (diphenylphosphino)benzoic acids **L3–4** were less effective than TPPMS (entries 13–15), and a lower yield was also obtained without a phosphine ligand (entry 16). Since the reaction was completed in 4 h under an Ar atmosphere, oxygen was not essential to the borrowing hydrogen reaction (entry 17).

2. Reaction scope

Next, we explored the scope of 2-aminopyridines **1** and benzylic alcohols **2** capable of undergoing a borrowing hydrogen reaction (Scheme 2). A variety of 2-aminopyridines **1** were well tolerated, giving the desired products **3b–e** in 75–96% yields (Scheme 2A). The reaction of simple 2-aminopyridine, bearing no substituent at the 5-position, also proceeded smoothly (**3f**, 90%). Advantageously, a substrate containing a sensitive reducible nitro group could be utilized, furnishing the corresponding desired product **3g**, albeit in low yield. The reaction of 6-aminonicotinic acid gave an extremely poor result (only 7% isolated yield of *N*-benzylated product **3h**). To our delight, the utilization of benzyl alcohol (**2a**) directly as a coupling partner could be applied to 3-aminopyridine, 2-aminoquinoline and nicotinamide (niacinamide) as amine substrates, furnishing the corresponding pharmaceutically active *N*-benzylated motifs in moderate to excellent yields (**3i** 88%; **3j**, 82%; **3k**, 66%).[12] Unfortunately, no reactions occurred when using 4-aminopyridine, 2-aminopyrimidine and 2-(methylamino)pyridine since the amino groups had poor nucleophilicity. Benzylic alcohols with electron-donating groups were effective coupling partners (**3j–s**, 65–93%) (Scheme 2B). A sterically hindered 2-methoxybenzyl alcohol (**2s**) was well tolerated to obtain the *N*-benzylated product **3s** in 84% yield. Furthermore, the reactions of electron-deficient fluorobenzyl alcohols afforded the desired products **3t–v** in 56–88% yields, although in octane, higher temperatures were required to achieve better yields. In contrast, no reaction proceeded when using 4-nitrobenzyl alcohol and 2-phenylethyl alcohol, likely because the corresponding π-benzyl Pd(II) cation species was not generated.

3. Effect of water

To measure the full reaction profile, dehydrative coupling between 2-aminopyridine **1a** and alcohol **2a** at 100 °C in heptane was monitored by ^1H NMR spectroscopy. The formation of *N*-benzylated product **3a** along with benzaldehyde (**4a**) was observed (Fig. 1A). No imine intermediate was detected, suggesting its rapid hydrogenation to the corresponding

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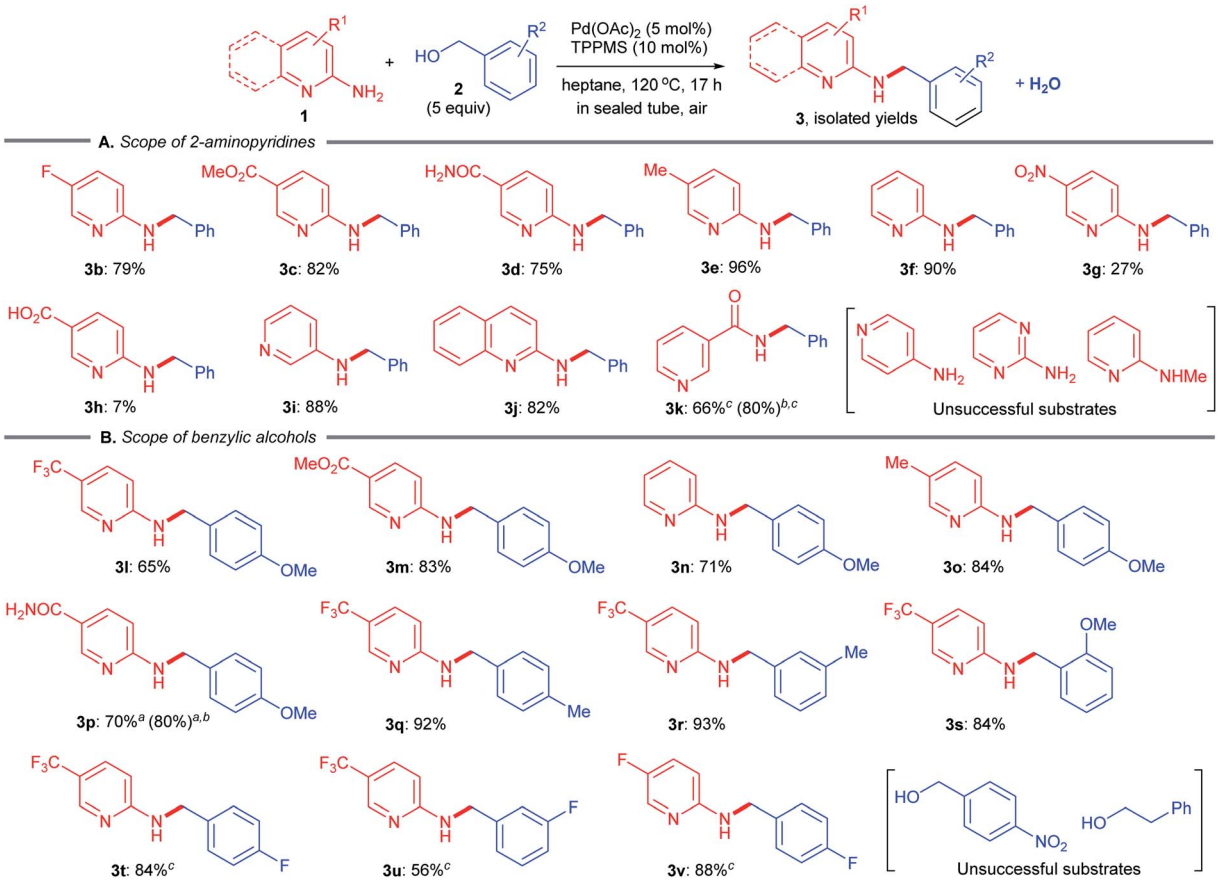


Scheme 2 Substrate scope of *N*-benzylation. Yield of isolated products. [a]3 equiv. of alcohol. [b]NMR yield. [c]10 mol% $Pd(OAc)_2$, 20 mol% TPPMS, 150 °C, 24 h in octane.

desired product **3a**. The consumption of alcohol **2a** followed pseudo-first-order kinetics including the presence of two mechanistic periods (0–2 h: $k_1 = 0.01\ h^{-1}$; 2–4 h: $k_2 = 0.35\ h^{-1}$) (Fig. 1B). Based on these results, we hypothesized that *in situ* generated water molecules might promote the dehydrogenation of **2a**. Therefore, we investigated the detailed reaction mechanism, especially the role of water molecules in heptane.

Thus, we conducted the reaction while adding different amounts of water (0.5, 1 and 2 mmol) (Scheme 3). As expected, the initial reaction rate in heptane dramatically increased upon addition of 0.5 mmol water compared to no water. The addition of 1 mmol water resulted in almost the same outcome (60%). In contrast, no benzylation was observed in the presence of excess water (2 mmol). When changing the additional water ratio, the reaction was accelerated in the following order: 0.5 mmol ≈ 1 mmol > no addition of water (*in situ* generated 0.35 mmol of water molecules after 3 h) ≫ 2 mmol, suggesting that traces of water present *in situ* (≤1 mmol) promoted aggregation between the polar substrates and the Pd catalyst in heptane, forming the active π-benzylpalladium(II) catalyst system. Since the formation of reverse micelles *via* aggregation of polar substrates did not occur by adding excess water, the water-in-oil type reaction employing the π-benzylpalladium species did not take place. Indeed, the addition of water (1 mmol) was not effective without stirring or addition of *n*-Bu_4NBr.

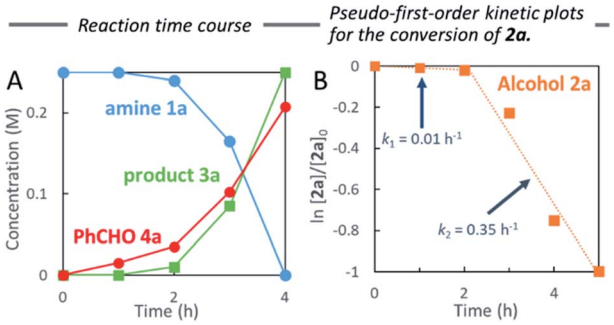
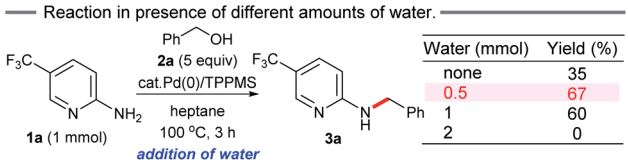


Fig. 1 Monitoring the reaction.



Scheme 3 *N*-Benzylation in the presence of different amounts of water.

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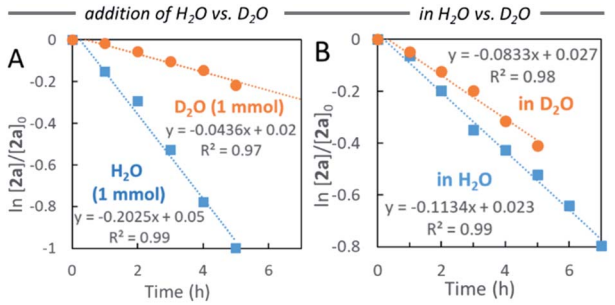
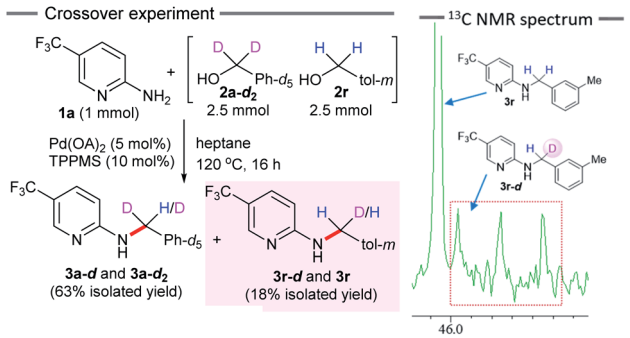


Fig. 2 Comparison of pseudo-first-order kinetic plots for reaction of **2a** in heptane (A) with addition of H_2O *vs.* D_2O, and (B) in H_2O *vs.* D_2O.



Scheme 4 Deuterium labeling experiment.

Water-promoted dehydrogenation of **2a** in heptane exhibited pseudo-first-order plots with a higher primary kinetic solvent isotope effect (KSIE = 4.6). This value was much larger than the KSIE value of 1.4 measured in water reactions (Fig. 2A and B),[7b] suggesting that hydrogen bonds play a significant role in the dehydrative coupling reaction in heptane.

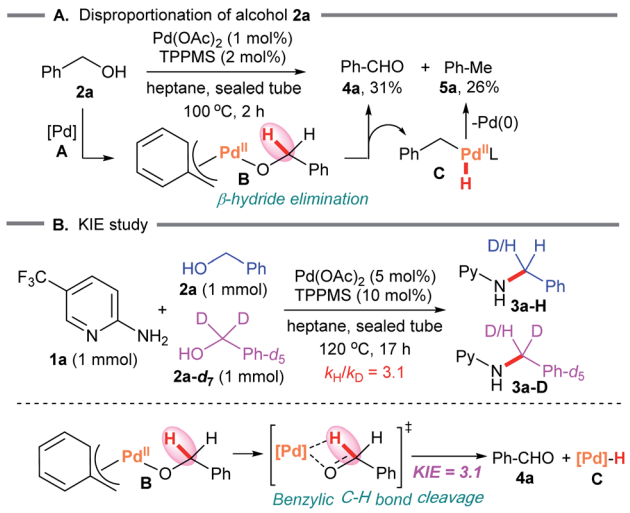
4. Deuterium labeling experiment

We performed a crossover experiment by subjecting an equimolar amount of deuterated benzyl alcohol **2a-d_2** (5 mmol) and 3-methylbenzyl alcohol **2r** (5 mmol) to the standard reaction conditions (Scheme 4). If the nucleophilic substitution of alcohol **2r** (dehydrative Tsuji–Trost type reaction) proceeds, deuterium labeled product **3r-*d*** would not be obtained. In contrast, a borrowing hydrogen reaction would afford the H/D scrambled *N*-benzylated product **3r-*d***. As expected, a mixture of crossover product **3r-*d*** and non-crossover product **3r** was obtained in 18% yield. The results obtained from a ^{13}C NMR analysis showed that the carbon of the methylene group exhibited a 1 : 1 : 1 triplet for **3r-*d***. Furthermore, the ratio of the integrated values in the ^1H NMR spectrum showed 18% incorporation of deuterium at the benzylic position of **3r-*d*** (see ESI†). This experimental evidence clearly indicates a borrowing hydrogen reaction and rules out an alternative Pd-catalyzed S_N2-type substitution reaction.

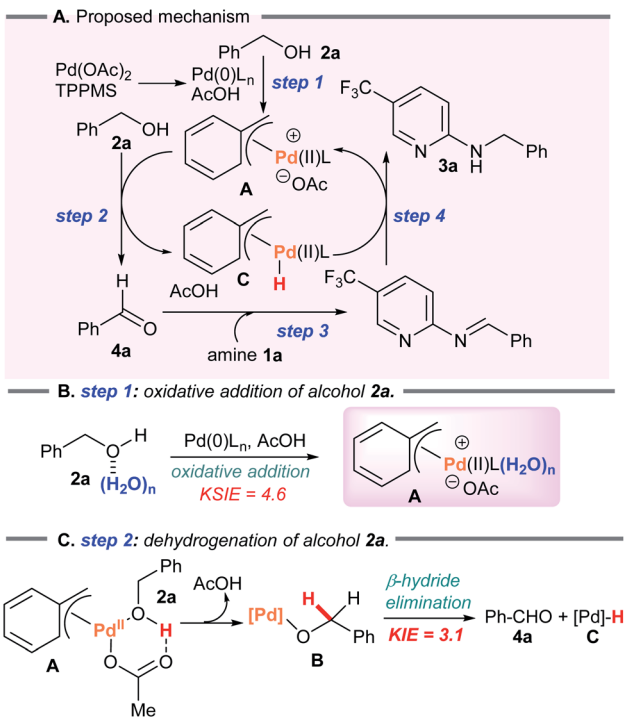
5. Mechanistic studies

First, we examined the Pd-catalyzed disproportionation of alcohol **2a** (Scheme 5A). When the alcohol **2a** was converted to aldehyde **4a**, the generation of toluene (**5a**) was clearly observed by ^1H NMR spectroscopy. This result suggested that β-hydride elimination of benzylPd(II)-alkoxide complex **B** led to the aldehyde **4a**, which then reacted with benzylPd(II) hydride species **C** *via* reductive elimination to form toluene **5a** with regenerated $Pd(0)L_n$.

We next studied the kinetic isotope effect in an intermolecular competition experiment using benzyl alcohol and its deuterium-labeled analog. As expected, a kinetic isotope effect (KIE) of 3.1 was observed for the reaction with substrate **1a** (Scheme 5B). A KIE of this magnitude is in agreement with the benzylic C–H bond cleavage featured in the turnover limiting step.



Scheme 5 Mechanistic studies.



Scheme 6 Proposed catalytic cycle.

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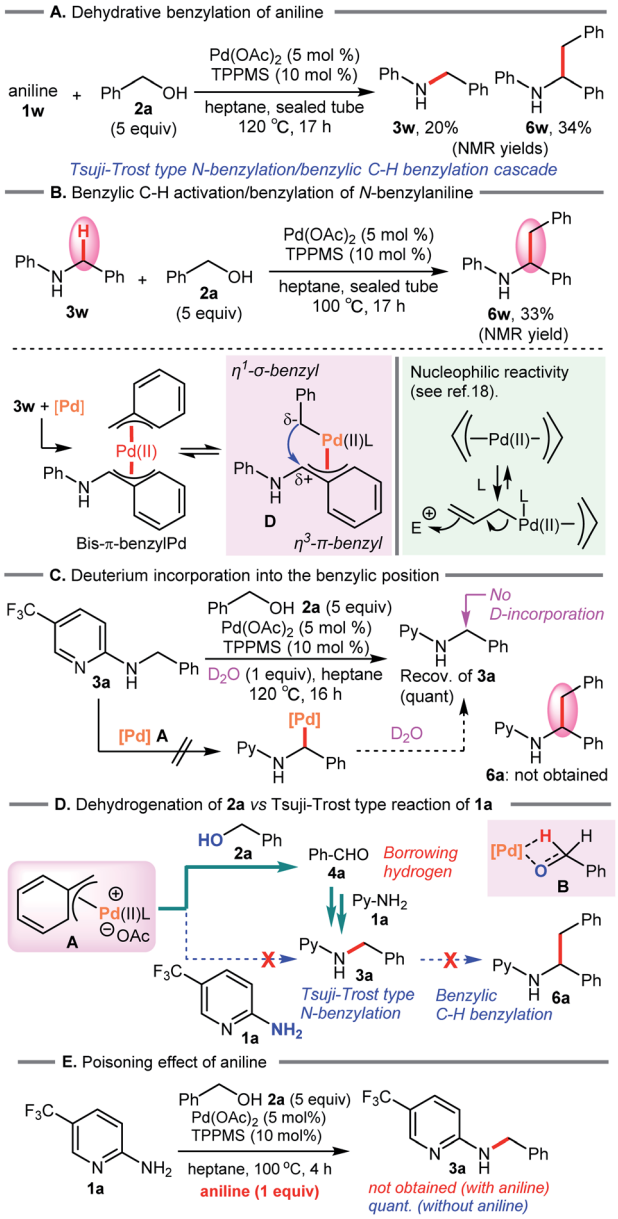
6. Mechanistic considerations

Considering the results above, a proposed catalytic cycle for the borrowing hydrogen reaction in heptane is illustrated in Scheme 6.

Step 1. Initially, oxidative addition of alcohol **2a** to the Pd(0) species[13] generates the π-benzylPd(II) intermediate **A**.[14] In this step, polar substrates with water molecules activate the hydroxy group of **2a** through a hydrogen bonding network to generate complex **A**.[15,16] This mechanism is consistent with the observed KSIE ($kH_2O/kD_2O = 4.6$).

Step 2. Next, β-hydride elimination affords the key intermediate aldehyde **4a**.[17] Since the alcohol–Pd(II) complex is deprotonated by the acetoxy anion,[17b,18] strong bases are not required.



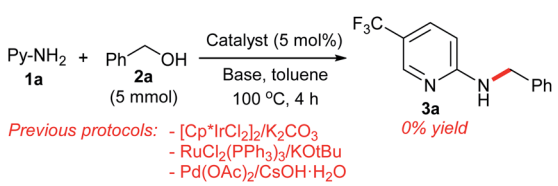
Scheme 7 (A) and (B) Pd-catalyzed benzylation of aniline. (C) Deuterium labeling study. (D) Proposed reaction pathway. (E) *N*-Benzylation of 2-aminopyridine **1a** in the presence of aniline.

The C–H bond cleavage of alcohol **2a** *via* β-hydride elimination is the rate-determining step (KIE value of 3.1 in Scheme 5B). Notably, water molecules promote the aggregation of polar substrates with palladium catalysts in heptane, furnishing the active π-benzylpalladium system smoothly in the rate-determining step. Furthermore, benzyl alcohol (**2a**) disproportionates to benzaldehyde with toluene (Scheme 5A), which provides support for the proposed π-benzylpalladium catalyst mechanism.

Steps 3 and 4. Finally, reductive amination between aldehyde **4a** and the amine substrate catalyzed by Pd(II) hydride **C** proceeds to generate the desired product **3a** and regenerates the benzylPd(II) **A**.

To verify the formation of the π-benzylpalladium catalyst system, we examined the Tsuji–Trost type reaction of aniline (**1w**) in heptane (Scheme 7A). An electron-sufficient amine substrate should react with the π-benzylPd(II) species by nucleophilic substitution. As expected, the reactivity of **1w** was significantly different from that of 2-aminopyridine **1a**, furnishing not only *N*-benzylaniline (**3w**) but also dibenzylated product **6w** (**3w**, 20%; **6w**, 34%). Furthermore, when using **3w** as a starting material, the corresponding dibenzylated product **6w** was formed *via* the condensation of an alcohol with a benzylic C–H bond (Scheme 7B). These results provide convincing evidence supporting the formation of the π-benzylPd(II) species. This catalyst system enables the dehydrative *N*-benzylation C–H bond activation cascade reaction of electron-rich analog **3w**. The η^1-σ-benzyl nucleophile attacks an electrophilic η^3-π-benzyl moiety in the bis-benzylPd(II) complex **D**, generating a new benzylic C–C bond. This proposed mechanism is consistent with the nucleophilic reactivity of bis-π-allylpalladium complexes reported by Yamamoto *et al.*[19] Indeed, Pd-catalyzed benzylic C–H benzylation of electron-sufficient *N*-benzylpyridine substrate **3a** did not occur (Scheme 7C). Furthermore, the treatment of **3a** with D_2O (1 equiv.) as the D-atom source in heptane showed no deuterium incorporation at the benzylic position of **3a** (The reaction in D_2O as a solvent also gave the same result, see ESI†). These results clearly demonstrated that Pd-catalyzed benzylic C–H bond cleavage of **3a** did not occur, and therefore rule out D/H exchange between *N*-benzylated product **3a**-d_2 and **3r** in our crossover experiment (see Scheme 4).

On the basis of these results, dehydrogenation of benzyl alcohol (**2a**) by π-benzylPd(II) complex **A** proceeds faster than nucleophilic substitution of species **A**, and leaves the weak 2-aminopyridine nucleophile **1a** intact (Scheme 7D). Subsequently, reductive amination of **1a** with the resulting aldehyde **4a** leads to **3a** *via* the borrowing hydrogen pathway. This is consistent with the result of the crossover experiment (see Scheme 4). When adding aniline (**1w**), *N*-benzylated product **3a** was not obtained due to the poisoning effect of aniline (Scheme 7E).



Scheme 8 Comparison of the catalytic activity.

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Having established a successful dehydrative *N*-benzylation strategy, we compared the catalytic activity of our π-benzylpalladium catalyst system with other efficient systems (Scheme 8). While the Pd(0)/TPPMS-catalyzed reaction in heptane proceeded to completion within 4 h (see Table 1), the previous borrowing hydrogen protocols[10c,20] resulted in no reaction. Furthermore, the Pd-catalyzed reaction in water (our previous work)[7b] was not effective (only 40% yield), clearly demonstrating the superiority of the present catalytic strategy using heptane.

To highlight the synthetic utility, we performed the *N*-benzylation on a gram scale (see ESI†). *N*-Benzylated product **3a** (1.56 g) was facilely isolated in 88% yield from pyridine substrate **1a** with alcohol **2a**. The developed simple operations also avoided the use of column chromatography for a gram scale reaction.

Conclusions

In summary, we report an efficient palladium-catalyzed dehydrative *N*-benzylation in heptane *via* the borrowing hydrogen methodology. The strategy provides an efficient method for the facile synthesis of benzylaminopyridines, which are found in a wide variety of pharmaceuticals. Notably, the use of a Pd(0)/TPPMS catalyst in a non-polar heptane solvent with a trace amount of water is critical for our catalytic system. Water molecules assist in the aggregation of polar substrates followed by the formation of an active π-benzylpalladium catalyst system in heptane, which significantly boosts the borrowing hydrogen reaction. We expect that this study will aid in the design of new catalytic systems using non-polar solvents, and will serve as an entry point for reaction discovery.

Experimental

General procedure

To a sealed tube were added 2-aminopyridines **1** (1 mmol), Pd catalyst (0.05 mmol), phosphine ligand (0.1 mmol), alcohols **2** (5 mmol) and heptane (4 mL). The resulting reaction mixture was heated at 120 °C for 17 h under air. After completion of the reaction, the mixture was cooled to room temperature. The reaction mixture was diluted with water, and then extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, and filtered and concentrated to dryness under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc) to obtain desired products **3**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

AcknowledgementsThis work was supported by JSPS KAKENHI grant number 19K07003.

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