Green Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: H. Hikawa, R. Ichinose, S. Kikkawa and I. Azumaya, *Green Chem.*, 2018, DOI: 10.1039/C7GC03780E.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/green-chem

View Article Online
DOI: 10.1039/C7GC03780E

Journal Name

ARTICLE

Palladium-catalyzed dehydrative *N*-benzylation/C-H benzylation cascade of 2-morpholinoanilines on water

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Hidemasa Hikawa,* Risa Ichinose, Shoko Kikkawa, and Isao Azumaya*

A strategy for the palladium-catalyzed dehydrative tandem benzylation of 2-morpholinoanilines with benzyl alcohols has been developed. This cascade reaction is devised as a straightforward and efficient synthetic route for *N*-(1,2-diphenylethyl)-2-morpholinoanilines in moderate to good yields (50-81%). The dehydrative sp^3 C-H bond benzylation proceeds chemoselectively at the benzylic position of *N*-benzyl-2-morpholinoaniline to form a new C(sp^3)-C (sp^3) bond. KIE experiments show that C-H bond activation is involved in the rate-determining step (KIE = 2.7). A Hammett study of the 2-morpholinoanilines gives a negative ρ value, suggesting that there is a build-up of positive charge in the transition state. The "on water" protocol, which affords the corresponding desired products with water as the sole co-product, can be achieved under mild reaction conditions without the need for base or other additives on the atom-economic process.

Introduction

2-Morpholinoaniline moieties are found in drug candidates for treatment of cancer,[1] Alzheimer's disease,[2] wet age-related macular degeneration (wet AMD)[3] and infectious disease[4] (Figure 1). However, these compounds are limited to structures containing an amide moiety. Therefore, efficient methods for the direct introduction of diverse functionalities on 2-morpholinoanilines are gaining increasing interest in medicinal chemistry. For example, the palladium-catalyzed (hetero)arylation (Buchwald-Hartwig amination) of 2-morpholinoanilines has recently been reported. [5]

Palladium-catalyzed Tsuji-Trost type benzylation has become one of the most powerful strategies for the formation of carbon-carbon and carbon-nitrogen bonds.[6] Early studies on the generation of π-benzylpalladium(II) complexes used benzyl halides. [7] Furthermore, the use of benzyl carbonates, acetates and phosphonates as activated alcohols has been reported to be effective under neutral conditions.[8] In contrast, the direct use of benzyl alcohols for benzylation is especially challenging because of their low reactivity towards Pd(0) compared with benzyl halides. Therefore, the development of a direct catalytic substitution of benzyl alcohols as electrophilic partners, which affords the desired products along with water as the sole co-product, is highly attractive in synthetic organic chemistry.[9] In this regard, early studies on the Pd-catalyzed carbonylation of benzyl alcohols have been reported by Sheldon *et al.* [10] In 2014, Tunge *et al.* developed the Tsuji-Trost type benzylation *via* retro-Claisen activation of carbon nucleophiles utilizing benzyl alcohols.[11] In 2016, Zhang *et al.* reported *in situ* C-O bond activation by dimethylcarbonate.[12]

Recently, the scope of π-allylpalladium chemistry has been extended to electrophilic umpolung allylic substitutions via bis-π-allylpalladium intermediates. This work was pioneered by Yamamoto *et al.* in 1996 (Scheme 1A).[13] In 2017, Bao and Yamamoto demonstrated the palladium-catalyzed allylation of benzyl chlorides with allyl pinacolborates through coupling of the η^1-allyl ligand with the η^3-benzyl ligand of η^3-allyl-η^3-benzylpalladium intermediates (Scheme 1B).[14] Pincer complexes have also been employed in the catalytic allylation of electrophiles, since the allyl moiety is constrained to an η^1-coordination state required for the nucleophilic reactivity. [15]

We have been developing a unique strategy for benzylation by the π-benzylpalladium(II) species **A** from Pd(0)/TPPMS (TPPMS: sodium diphenylphosphinobenzene-3-sulfonate) and non-activated benzyl alcohol (Scheme 2A).[16] Water activates the sp^3 C-O bond by hydrogen bonds between water and the hydroxyl group of the alcohol to form complex **A**. We recently reported a new type of palladium-catalyzed tandem benzylation of anilines with benzyl alcohols for direct construction of *N*-(1,2-diphenylethyl)anilines.[17] These processes involve the formation of bis-π-benzylpalladium intermediates followed by the coupling of the η^1-benzyl ligand (nucleophiles) with the η^3-benzyl ligand (electrophiles). Although elegant protocols for the synthesis of *N*-(1,2-diphenylethyl)anilines have been establish to date (e.g., the benzylation of imines,[18] hydroamination of alkynes/reduction,[19] and reductive amination of ketones),[20] these methods require the use of toxic reagents and organic solvents under anhydrous conditions.

Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan. E-mail: hidemasa.hikawa@phar.toho-u.ac.jp and isao.azumaya@phar.toho-u.ac.jp

Electronic Supplementary Information (ESI) available: [Copies of ^{1}H and ^{13}C NMR spectra for new compounds.]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C7GC03780E

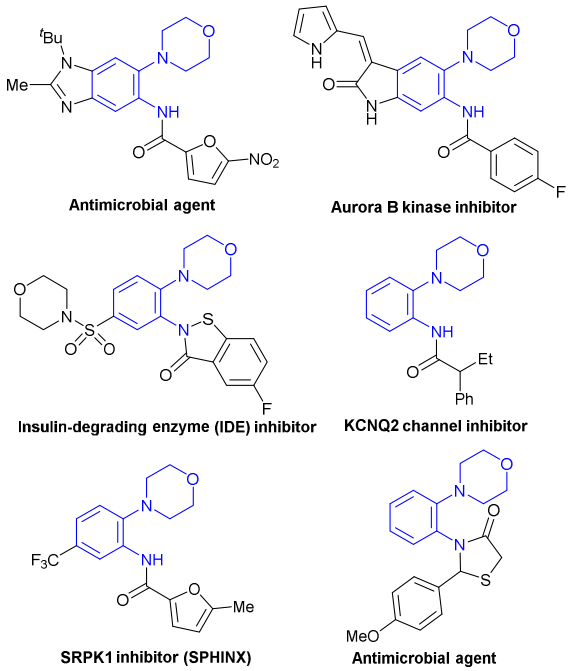
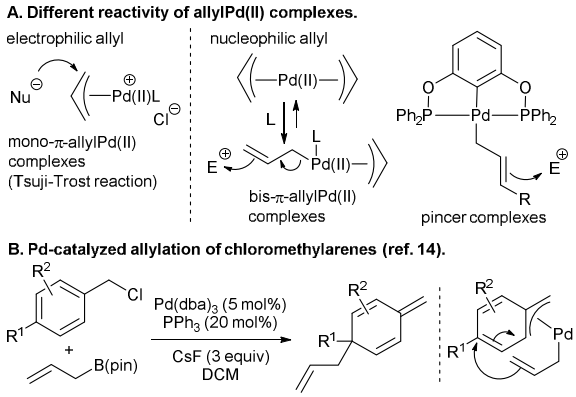
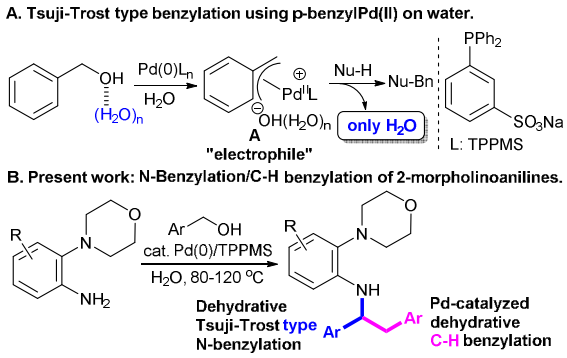


Figure 1. Representative biologically active 2-morpholinoanilines.

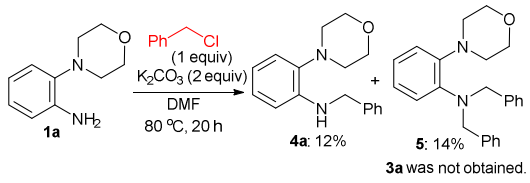


Scheme 1. Reactions of bis-π-allylPd(II) complexes.

As an extension of our investigation of the π-benzylpalladium system, we herein present the palladium-catalyzed dehydrative *N*-benzylation/benzylic C-H benzylation cascade of 2-morpholinoanilines on water (Scheme 2B). The tandem reaction proceeds smoothly to produce *N*-(1,2-diphenylethyl)-2-morpholinoanilines in moderate to good yields, which can potentially be used for the construction of a diverse chemical library in drug discovery. The dehydrative sp^3 C-H bond benzylation reaction chemoselectively occurs on the benzylic position of the *N*-monobenzylated intermediate to form a new $C(sp^3)$-$C(sp^3)$ bond, a reaction that cannot proceed by traditional benzylation protocols such as the use of benzyl chloride with base (Scheme 3). Therefore, direct catalytic functionalization of the sp^3 C-H bond has emerged as an attractive alternative to traditional synthetic methods. Notably, the "on water" protocol is essential for achieving this efficient strategy in our catalytic system.[21] This green method has reduced waste generation, uses safer solvents and reaction conditions, and increases energy efficiency, all of which contribute to the efficiency of a chemical transformation.



Scheme 2. Strategy for the tandem benzylation by π-benzylPd(II) **A** on water.



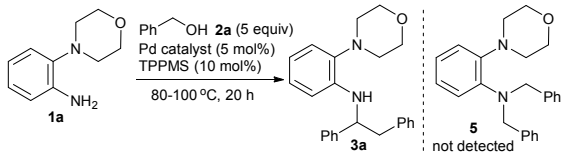
Scheme 3. Reaction of **1a** with benzyl chloride.

Results and discussion

1. Effects of catalysts and solvents. Initially, 2-morpholinoaniline (**1a**) and benzyl alcohol (**2a**) were chosen as the model compounds to optimize the reaction conditions. When using $Pd(OAc)_2$ (5 mol%) and sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 10 mol%) as the catalyst, the desired *N*-(1,2-diphenylethyl)-2-morpholinoaniline (**3a**) was obtained selectively in 75% yield (Table 1, entry 1). In contrast, no reaction occurred in the absence of TPPMS (entry 2). With regard to the palladium(II) catalysts, $Pd(OAc)_2$ gave the best result (entry 1 vs entries 3-7). When the reaction was performed at 100 °C, the yield of **3a** was increased to 95% (entry 8). Replacing water with organic solvents such as toluene, heptane, EtOH, 1,4-dioxane or DMF resulted in no reaction (entries 9-14). Furthermore, low yield or no reaction occurred with the use of D_2O or under the neat condition, respectively (entries 15-16). These results suggested that the "on water" accelerated reaction would proceed since the organic-water interface effect of dangling OH groups could enhance the reaction rates. The use of zero-valent palladium, $Pd_2(dba)_3{\cdot}CHCl_3$, afforded the product **3a** in 81% yield (entry 17).

View Article Online
DOI: 10.1039/C7GC03780E

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

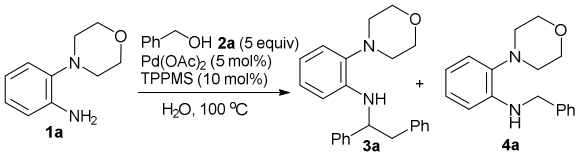


Entry	Pd catalyst	T (°C)	Solvent	Conv. (%) [b]
1	$Pd(OAc)_2$	80	H_2O	75
2 [c]	$Pd(OAc)_2$	80	H_2O	0
3	$PdBr_2$	80	H_2O	0
4	$PdCl_2$	80	H_2O	36
5	$PdCl_2(CH_3CN)_2$	80	H_2O	62
6	$Pd(OCOCF_3)_2$	80	H_2O	47
7	$[PdCl(allyl)]_2$	80	H_2O	0
8 [d]	$Pd(OAc)_2$	100	H_2O	95
9	$Pd(OAc)_2$	80	toluene	0
10	$Pd(OAc)_2$	80	heptane	0
11	$Pd(OAc)_2$	80	EtOH	0
12	$Pd(OAc)_2$	80	dioxane	0
13	$Pd(OAc)_2$	80	DMF	0
14	$PdCl_2(PPh_3)_2$	80	DMF	0
15	$Pd(OAc)_2$	80	D_2O	44
16	$Pd(OAc)_2$	80	neat	0
17 [e]	$Pd_2(dba)_3{\cdot}CHCl_3$	120	H_2O	81

[a] Reaction conditions: aniline **1a** (1 mmol), Pd catalysts (5 mol%), TPPMS (10 mol%), benzyl alcohol **2a** (5 equiv), solvent (4 mL), 80 °C, 20 h under air. [b] The conversion was determined by ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard. [c] without TPPMS. [d] under Ar. [e] Using **2a** (10 equiv).

2. Reaction progress. To gain further understanding of the reaction progress, the reaction of 2-morpholinoaniline (**1a**) with benzyl alcohol (**2a**) was monitored by ^{1}H NMR spectroscopy. After 6 h, the reaction of **1a** afforded *N*-benzyl-2-morpholinoaniline (**4a**) in 73% yield smoothly. In contrast, *N*-(1,2-diphenylethyl)-2-morpholinoaniline (**3a**) was formed slowly while **4a** was reduced (Figure 2). Furthermore, the *N*-monobenzylated **4a** as a starting material afforded dibenzylated product **3a** smoothly (Figure 3). These results indicated that *N*-benzylation of **1a** with **2a** occurred quickly to form mono-*N*-benzylated product **4a**, which then slowly converted to desired **3a** through benzylic C-H benzylation.

3. Kinetic isotope effect. KIE studies were performed to gain further mechanistic details of the benzylic C-H activation. The intermolecular competition between mono-*N*-benzylated **4a** and its deuterium-labeled substrate **4a-*d*** gave KIE = 2.7 on the basis of ^{1}H NMR analysis, suggesting that C-H bond cleavage was involved in the rate-determining step (Scheme 4A). Next, the rates for Pd-catalyzed benzylic C-H benzylation "on H_2O" and "on D_2O" were compared. The reaction rates were faster "on H_2O" than "on D_2O" with a primary H/D effect of 1.6 (Scheme 4B). In general, the KIE for protonation shows values of 5-7.[22] Therefore, these low deuterium isotope values suggested that hydrogen bonding activation occurred for the benzylic C-H benzylation on water.



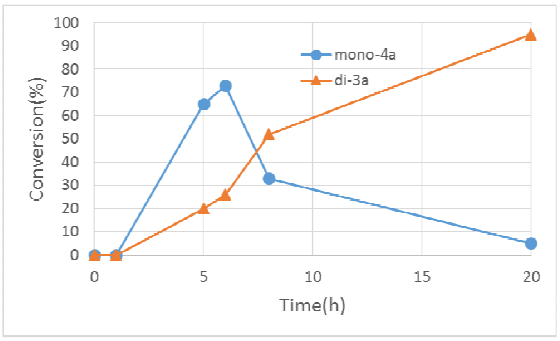
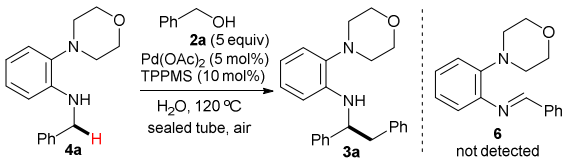


Figure 2. Reaction time course for the conversion of 2-morpholinoaniline (**1a**, 0.5 mmol) with benzyl alcohol (**2a**, 5 equiv) into desired **3a** and *N*-benzyl-2-morpholinoaniline (**4a**).



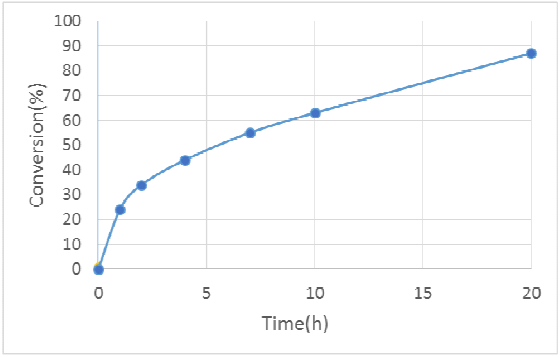
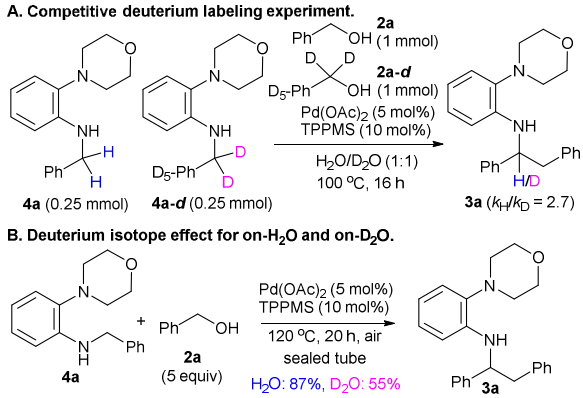


Figure 3. Conversion of *N*-benzyl-2-morpholinoaniline (**4a**, 0.5 mmol) with benzyl alcohol (**2a**, 5 equiv) into desired **3a** at different time intervals in the "on water" reaction.

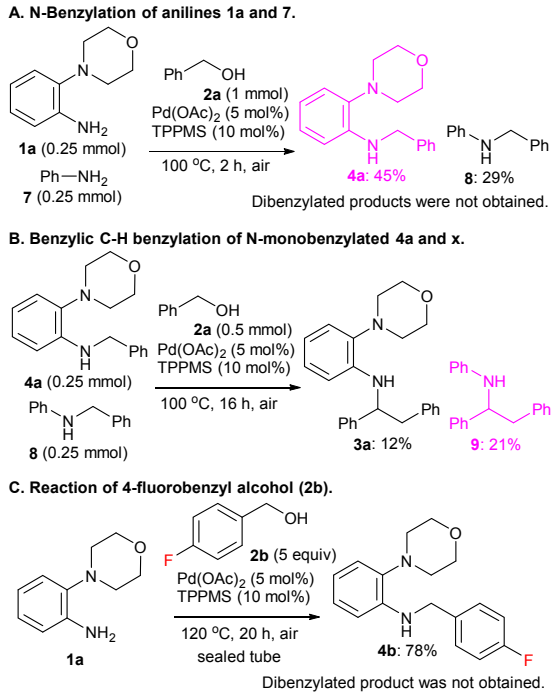
4. Control experiments. We conducted competition experiments to investigate the role of the 2-morpholino group on the palladium-catalyzed *N*-benzylation and benzylic C-H benzylation steps. The *N*-benzylation of 2-morpholinoaniline (**1a**) proceeded smoothly to give **4a** in 45% yield, while aniline (**7**) was produced in only 29% yield (Scheme 5A). This result suggested that this process was favored by the electron-donating 2-morpholino group on aniline. In contrast, the C-H benzylation of electron-sufficient **4a** is slower than that of **8**, suggesting that *N*-benzylated **4a** would act as an electrophile (Scheme 5B). Next, the reaction of **1a** with an electron-

View Article Online
DOI: 10.1039/C7GC03780E

deficient benzylic alcohol, 4-fluorobenzyl alcohol (**2b**), did not afford the dibenzylated product but gave *N*-monobenzylated **4b** in 78% yield (Scheme 5C). No reaction occurred when using **4b** as a starting material in the palladium-catalyzed reaction, indicating the electron-deficient benzyl moiety generated from the 4-fluorobenzyl alcohol (**2b**) could not act as a nucleophile in the C-H benzylation step.

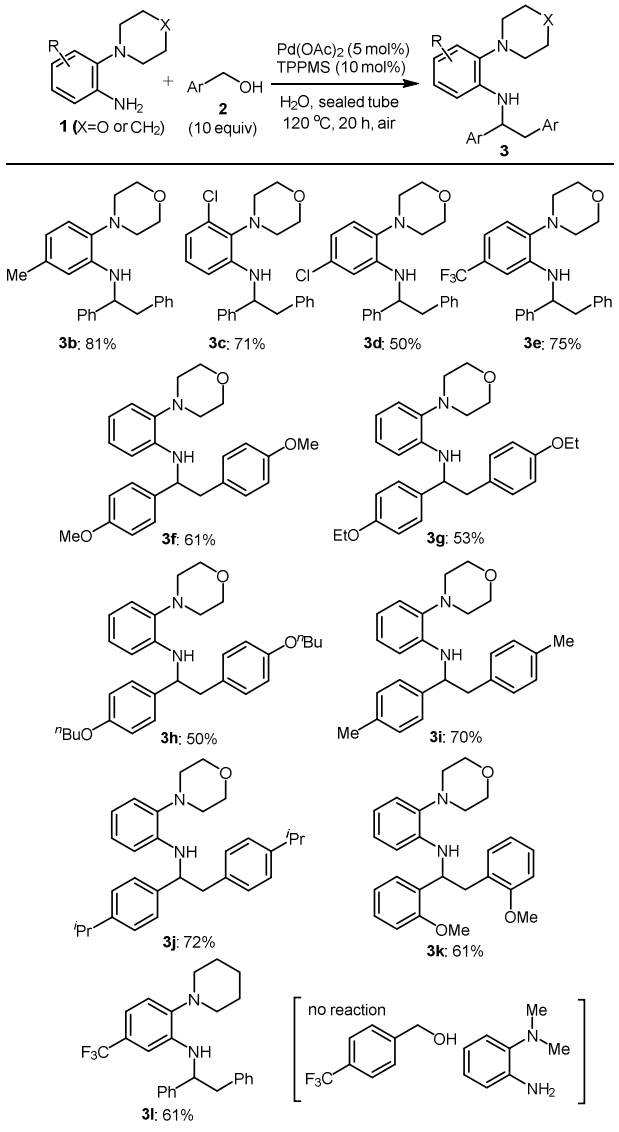


Scheme 4. Kinetic isotope effects.



Scheme 5. Control experiments.

5. Reaction scope. Results for the reactions of several 2-morpholinoanilines **1** with benzyl alcohols **2** using $Pd(OAc)_2$ and TPPMS are summarized in Scheme 6. Both electron-donating methyl and electron-withdrawing chloro and trifluoromethyl groups on the benzene ring of substituted 2-morpholinoanilines **1** were tolerated well to produce the corresponding products **3b-e** in moderate to good yields. The scope of benzyl alcohols **2** was examined next with 2-morpholinoaniline (**1a**) as the coupling partner. The use of benzyl alcohols with electron-donating alkoxy and alkyl groups resulted in moderate to good yields (**3f-j**). A sterically demanding methoxy group at the *ortho* position was tolerated in the benzylic C-H benzylation (**3k**, 61%). In contrast, the benzyl alcohol with an electron-withdrawing trifluoromethyl group resulted in no reaction. Furthermore, replacement of the morpholino group with a piperazino group on the benzene ring was tolerated in our catalytic system (**3l**, 61%).[23] In contrast, 2-dimethylaminoaniline did not react due to the poisoning of the Pd(II) cation species (morpholine: *p*Ka value of 8.5 *vs* dimethylamine: *p*Ka value of 10.6).[24]



Scheme 6. Scope of anilines **1** and benzyl alcohols **2**. Reaction conditions: anilines **1** (1 mmol), $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), benzyl alcohols **2** (5 equiv), H_2O (4 mL), 120 °C, 20 h in a sealed tube. Yield of isolated products.

6. Hammett study. To demonstrate the electronic effect of the tandem benzylation, the relative rates of coupling of 3- and 5-substituted 2-morpholinoanilines **1** (X = Me, Cl and CF_3 groups)

View Article Online
DOI: 10.1039/C7GC03780E

with benzyl alcohol (**2a**) were examined. Figure 4 shows good correlation between the $\log(k_X/k_H)$ and the σ values of the respective substituents. The resulting negative ρ value of 2.2 suggests that there is a build-up of positive charge in the transition state.

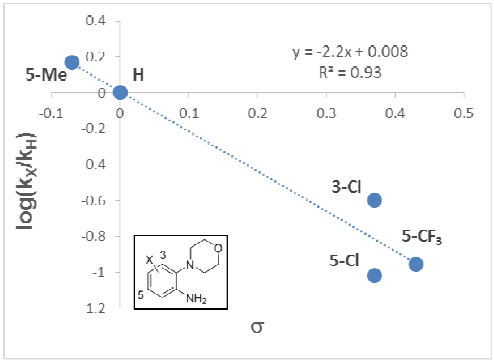
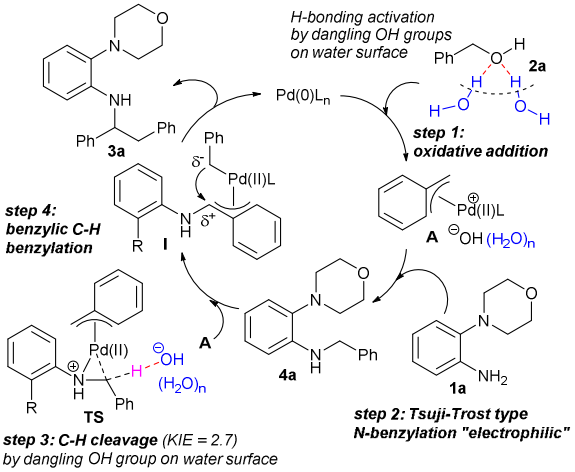
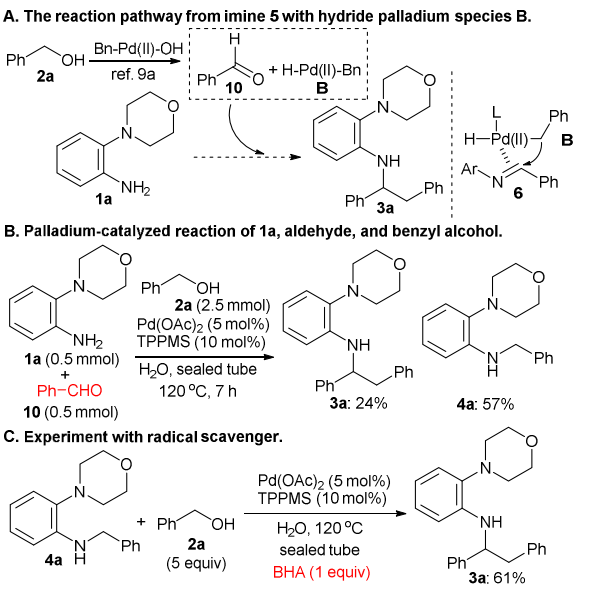


Figure 4. Hammett plot for the rate constants of benzylation by various substituted 2-morpholinoanilines **1**.

7. Mechanistic considerations. On the basis of these results and our previous report,[16,17] we propose a catalytic system for the benzylation of 2-morpholinoaniline (**1a**) with benzyl alcohol (**2a**) on water as illustrated in Scheme 7. First, oxidative addition of benzyl alcohol **2a** to the water-soluble Pd(0)/TPPMS species affords the cationic mono-π-benzylpalladium(II) complex **A** (step 1). The dangling OH groups on the water surface activate the sp^3 C-O bond of the alcohol **2a** by forming hydrogen bonds, and the resulting cationic charge of complex **A** is also stabilized by water (see Table 1). This process should be favored by electron-donating groups on intermediate **A**, since these will stabilize the positive charge on Pd(II). Therefore, the benzylation using 4-trifluoromethylbenzyl alcohol did not proceed since the alcohol could not form cationic intermediate **A** (see Scheme 6). In contrast, the *N*-benzylation of 4-fluorobenzyl alcohol (**2b**) proceeded due to the weaker electron-withdrawing ability of a fluoro group than a CF_3 group (fluoro group: Hammett σ_p value of 0.06 *vs* CF_3: Hammett σ_p value of 0.54). Next, the nucleophilic substrate **1a** attacks intermediate **A** smoothly to afford the *N*-monobenzylated product **4a** and regenerate Pd(0) (the dehydrative Tsuji-Trost type benzylation). Indeed, the reaction rate of electron-sufficient substrate **1a** is faster than that of aniline (**7**) (see Scheme 5A). Next, the *N*-monobenzylated **4a** coordinates with π-benzylpalladium(II) **A** to form a cationic *N*-palladated intermediate, with its positive charge stabilized by the electron-donating 2-morpholino group. Hammett studies show that there is a build-up of positive charge in the transition state. The dehydrative C-H cleavage at the benzylic position proceeds since the positive charge of *N*-palladated complex **TS** increases the acidity of the benzylic proton. This is followed by formation of the bis-π-benzyl palladium(II) intermediate (step 3). The KIE of 2.7 suggests that the C-H cleavage process is involved in the turnover-limiting step. White and co-workers reported the electrophilic allylic C-H cleavage of α-olefins using a palladium(II)/sulfoxide catalyst to afford π-allylpalladium(II) intermediates.[25] The bis-π-benzyl palladium(II) intermediate is converted to the η^3-π-benzyl/η^1-σ-benzyl palladium complex **I** by coordination of a ligand such as TPPMS, which would involve the nucleophilic η^1-σ-benzyl ligand and electrophilic η^3-π-benzyl ligand. Therefore, the η^1-σ-benzyl ligand attacks the η^3-π-benzyl ligand of intermediate **I** to form a new C(sp^3)-C(sp^3) bond at the benzylic position in the reductive elimination step (step 4). The reaction of 4-fluorobenzyl alcohol did not afford the desired product **3**, since the electron-deficient η^1-σ-benzyl ligand is disadvantageous for nucleophilic benzylation (see Scheme 5C). Additionally, the electron-donating groups on the benzene ring of intermediate **I** stabilize the δ^+ charge in the π-benzyl Pd(II) species, which makes it the more electrophilic position for direct intramolecular nucleophilic attack from the σ-benzyl anion ligand. This δ^+ charge is also stabilized by the nitrogen lone pair.



Scheme 7. Proposed mechanism.

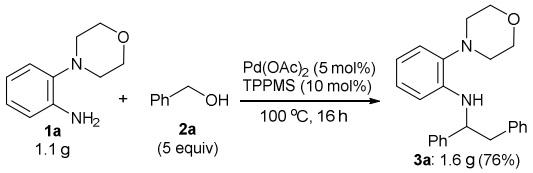


View Article Online
DOI: 10.1039/C7GC03780E

Scheme 8. Possible reaction pathways from the imine and the hydride palladium species.

To exclude the possibility of the reaction pathway from imine **5** and the hydride palladium species, the palladium-catalyzed reaction of 2-morpholinoaniline (**1a**),[18] benzaldehyde (**10**), and benzyl alcohol (**2a**) was investigated (Scheme 8A). After 1 h, the imine **6** was detected by ^{1}H NMR analysis of reaction mixture. After 7 h, desired product **3a** and *N*-monobenzylated **4a** were formed in 24% and 57% yields, respectively (Scheme 8B). In contrast, the desired **3a** was obtained in 55% yield when using **4a** as the starting material (see Figure 2). These results suggested that *N*-monobenzylated **4a** not imine **6** would be the intermediate in the benzylic C-H benzylation process. Furthermore, the reaction of **4a** was not inhibited by the addition of a radical scavenger (BHA: 3-*tert*-butyl-4-hydroxyanisole, 1 equiv) (Scheme 8C). Therefore, the possibility of a reaction pathway through the carbon radical addition to the imine via a single electron transfer process was also excluded.

8. Scale-up experiment. Finally, we examined the scalability of our catalytic system (Scheme 9). To demonstrate the utility of our environmentally benign, efficient and simple protocol, a gram scale reaction of **1a** with **2a** in the presence of $Pd(OAc)_2$ (5 mol%) and TPPMS (10 mol%) on water was carried out. The gram-scale synthesis of desired **3a** was achieved successfully in 76% isolated yield.



Scheme 9. Scale-up experiment.

Conclusions

In summary, we have demonstrated a straightforward and efficient synthetic route to *N*-(1,2-diphenylethyl)-2-morpholinoanilines using the π-benzylpalladium system on water. This simple protocol, which affords the corresponding desired products with water as the sole co-product, can be achieved under mild conditions without the need for bases or other additives on the atom-economic process. The dehydrative C-H benzylation on the benzylic position of *N*-benzyl-2-morpholinoanilines is involved in the new C-C bond formation. Notably, the "on water" protocol is essential for the success of our catalytic system.

Experimental

General procedure: A mixture of anilines **1** (1 mmol), palladium(II) acetate (12 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 36 mg, 0.1 mmol) and benzyl alcohol **2** (5-10 mmol) in H_2O (4 mL) was heated for 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 washed with hexanes, then purified by flash column chromatography (silica gel, hexanes/EtOAc) to give desired product **3**.

N-(1,2-Diphenylethyl)-2-morpholinoaniline **3a**
Following the scale-up experiment (see SI), **3a** was obtained as a pale yellow solid. 1.63 g (76%); mp 95-97 °C; IR (KBr) (cm^{-1}) 3320, 2961, 2844, 1601, 1508; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.64 (brs, 2H), 2.89 (brs, 2H), 2.96 (dd, *J*=14.0, 9.6 Hz, 1H), 3.24 (dd, *J*=14.0, 4.8 Hz, 1H), 3.77 (brs, 4H), 4.55 (brs, 1H), 5.30 (brs, 1H), 6.27 (dd, *J*=7.6, 1.2 Hz, 1H), 6.60 (td, *J*=7.2, 1.2 Hz, 1H), 6.81 (td, *J*=7.6, 1.2 Hz, 1H), 6.94 (dd, *J*=7.6, 1.2 Hz, 1H), 7.18-7.40 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 45.7, 51.7, 59.2, 67.8, 111.6, 116.8, 119.6, 126.2, 126.8, 128.5, 128.6, 129.3, 137.9, 138.5, 142.4, 143.9; MS (FAB): *m/z* 359 $[M+H]^+$; Anal. Calcd for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.37; H, 7.17; N, 7.78.

N-(1,2-Diphenylethyl)-5-methyl-2-morpholinoaniline **3b**
Following the general procedure, **3b** was obtained as a white solid. 302 mg (81%); mp 135-137 °C; IR (KBr) (cm^{-1}) 3400, 3332, 3060, 3030, 2961, 2856, 2813, 1607, 1582, 1521; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.85 (brs, 4H), 2.96 (dd, *J*=14.4, 9.2 Hz, 1H), 3.22 (dd, *J*=14.4, 4.8 Hz, 1H), 3.76 (brs, 4H), 4.55 (ddd, *J*=9.2, 4.4, 4.4 Hz, 1H), 5.31 (d, *J*=4.0 Hz, 1H), 6.10 (d, *J*=1.6 Hz, 1H), 6.40 (dd, *J*=7.6, 1.2 Hz, 1H), 6.84 (d, *J*=8.0 Hz, 1H), 7.15-7.39 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.4, 45.6, 52.0, 59.1, 67.8, 112.3, 117.2, 119.6, 126.2, 126.7, 126.9, 128.5, 128.6, 129.3, 134.8, 136.2, 138.0, 142.3, 144.0; MS (FAB): *m/z* 373 $[M+H]^+$; Anal. Calcd for $C_{25}H_{28}N_2O \cdot 0.1H_2O$: C, 80.22; H, 7.59; N, 7.48. Found: C, 79.81; H, 7.58; N, 7.41.

3-Chloro-*N*-(1,2-diphenylethyl)-2-morpholinoaniline **3c**
Following the general procedure, **3c** was obtained as a white solid. 279 mg (71%); mp 120-122 °C; IR (KBr) (cm^{-1}) 3376, 3054, 3023, 2850, 1595, 1584, 1569; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (d, *J*=11.2 Hz 1H), 2.57 (d, *J*=11.2 Hz 1H), 3.00 (dd, *J*=14.0, 9.2 Hz 1H), 3.26 (dd, *J*=14.0, 4.4 Hz 1H), 3.32 (dd, *J*=11.2, 2.8 Hz 1H), 3.57 (dd, *J*=10.8, 2.0 Hz 1H), 3.63-3.79 (m, 3H), 3.90 (d, *J*=9.2 Hz 1H), 4.61 (dt, *J*=9.6, 5.2 Hz 1H), 6.00 (d, *J*=4.4 Hz 1H), 6.16 (d, *J*=8.0 Hz 1H), 6.49 (dd, *J*=8.4, 1.6 Hz 1H), 6.76 (t, *J*=8.4 Hz 1H), 7.17 (d, *J*=7.2 Hz 2H), 7.19-7.35 (m, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 45.2, 48.7, 58.5, 68.1, 68.4, 109.7, 118.0, 126.2, 126.9, 127.1, 127.6, 128.6, 128.7, 129.2, 132.2, 133.5, 137.6, 143.4, 146.8; MS (FAB): *m/z* 393 $[M+H]^+$, 395 $[M+H+2]^+$; Anal. Calcd for $C_{24}H_{25}ClN_2O$: C, 73.36; H, 6.41; N, 7.13. Found: C, 73.64; H, 6.43; N, 7.14.

5-Chloro-*N*-(1,2-diphenylethyl)-2-morpholinoaniline **3d**
Following the general procedure, **3d** was obtained as a white solid. 196 mg (50%); mp 128-130 °C; IR (KBr) (cm^{-1}) 3326, 2844, 1588, 1501; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.59 (brs, 2H), 2.82 (brs, 2H), 2.95 (dd, *J*=14.4, 9.2 Hz, 1H), 3.24 (dd, *J*=14.4, 5.2 Hz, 1H), 3.75 (brs, 4H), 4.53 (dt, *J*=9.2, 4.8 Hz, 1H), 5.35 (d, *J*=4.4 Hz, 1H), 6.23 (d, *J*=2.4 Hz, 1H), 6.54 (dd, *J*=8.4, 2.4 Hz, 1H), 6.82 (d, *J*=8.4 Hz, 1H), 7.17 (dd, *J*=6.4, 2.0 Hz, 2H), 7.19-7.38 (m, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 45.4, 51.8, 58.9, 67.7, 111.3, 116.3, 120.7, 126.1, 126.9, 127.3, 128.6, 128.8, 129.3, 130.7, 137.1, 137.6, 143.1, 143.5; MS (FAB): *m/z* 393 $[M+H]^+$, 395 $[M+H+2]^+$; Anal. Calcd for $C_{24}H_{25}ClN_2O$: C, 73.36; H, 6.41; N, 7.13. Found: C, 73.50; H, 6.41; N, 7.13.

View Article Online
DOI: 10.1039/C7GC03780E

N-(1,2-Diphenylethyl)-2-morpholino-5-(trifluoromethyl)aniline **3e**
Following the general procedure, **3e** was obtained as a white solid. 320 mg (75%); mp 120-122 °C; IR (KBr) (cm^{-1}) 3330, 2845, 1604, 1587, 1517; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.66 (brs, 2H), 2.90 (brs, 2H), 2.99 (dd, *J*=14.4, 9.2 Hz, 1H), 3.27 (d, *J*=14.4, 5.2 Hz, 1H), 3.77 (brs, 4H), 4.58 (dt, *J*=9.2, 4.4 Hz, 1H), 5.30 (d, *J*=4.0 Hz, 1H), 6.48 (d, *J*=2.0 Hz, 1H), 6.85 (dd, *J*=8.0, 1.6 Hz, 1H), 6.95 (dd, *J*=7.6 Hz, 1H), 7.18 (d, *J*=6.8, 1.6 Hz, 2H), 7.21-7.37 (m, 8H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 44.7, 51.3, 58.8, 67.1, 107.1 (q, J_{CF}=3.8 Hz), 113.6 (q, J_{CF}=3.8 Hz), 119.9, 125.0 (q, J_{CF}=270.8 Hz), 125.3 (q, J_{CF}=31.5 Hz), 126.8, 127.1, 127.6, 128.9, 129.0, 129.8, 138.8, 142.2, 143.9; MS (FAB): *m/z* 427 $[M+H]^+$; Anal. Calcd for $C_{25}H_{25}F_3N_2O$: C, 70.41; H, 5.91; N, 6.57. Found: C, 70.71; H, 5.84; N, 6.59.

N-(1,2-Bis(4-methoxyphenyl)ethyl)-2-morpholinoaniline **3f**
Following the general procedure, **3f** was obtained as a white solid. 255 mg (61%); mp 125-127 °C; IR (KBr) (cm^{-1}) 3394, 2818, 1609, 1598, 1585, 1511; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.55 (brs, 2H), 2.75 (brs, 2H), 2.87 (dd, *J*=14.0, 10.0 Hz, 1H), 3.03 (dd, *J*=14.0, 4.8 Hz, 1H), 3.69 (s, 3H), 3.71 (s, 3H), 3.71 (brs, 4H), 4.45 (dt, *J*=9.6, 4.8 Hz, 1H), 5.20 (d, *J*=5.6 Hz, 1H), 6.19 (dd, *J*=8.4, 1.6 Hz, 1H), 6.47 (td, *J*=7.6, 1.6 Hz, 1H), 6.70 (d, *J*=8.0, 1.6 Hz, 1H), 6.81-6.90 (m, 5H), 7.18 (d, *J*=8.4 Hz, 2H), 7.29 (d, *J*=8.4 Hz, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 44.3, 51.8, 55.5, 58.4, 67.4, 111.4, 114.2, 116.7, 119.8, 125.1, 127.8, 130.8, 136.5, 138.8, 142.3, 158.4, 158.5; MS (FAB): *m/z* 419 $[M+H]^+$; Anal. Calcd for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.23; N, 6.69. Found: C, 74.77; H, 7.31; N, 6.65.

N-(1,2-Bis(4-ethoxyphenyl)ethyl)-2-morpholinoaniline **3g**
Following the general procedure, **3g** was obtained as a white solid. 237 mg (53%); mp 111-113 °C; IR (KBr) (cm^{-1}) 3400, 3326, 2818, 1607, 1598, 1584, 1509; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J*=7.2 Hz, 3H), 1.41 (t, *J*=7.2 Hz, 3H), 2.68 (brs, 2H), 2.89 (dd, *J*=14.4, 8.8 Hz, 1H), 2.92 (brs, 2H), 3.12 (dd, *J*=14.4, 5.2 Hz, 1H), 3.99 (q, *J*=6.8 Hz, 2H), 4.01 (qd, *J*=7.2, 1.2 Hz, 2H), 4.44 (dt, *J*=8.4, 4.0 Hz, 1H), 5.25 (d, *J*=3.6 Hz, 1H), 6.30 (dd, *J*=8.4, 0.8 Hz, 1H), 6.59 (td, *J*=7.2, 1.6 Hz, 1H), 6.76-6.88 (m, 5H), 6.93 (dd, *J*=7.6, 1.2 Hz, 1H), 7.05 (d, *J*=8.8 Hz, 2H), 7.22 (d, *J*=8.8 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.8, 14.9, 44.9, 51.7, 58.7, 63.4, 67.8, 111.6, 114.4, 114.5, 116.6, 119.5, 125.1, 127.3, 129.8, 130.3, 135.8, 138.5, 142.5, 157.8, 157.9; MS (FAB): *m/z* 447 $[M+H]^+$; Anal. Calcd for $C_{28}H_{34}N_2O_3$: C, 75.31; H, 7.67; N, 6.27. Found: C, 75.48; H, 7.58; N, 6.25.

N-(1,2-Bis(4-butoxyphenyl)ethyl)-2-morpholinoaniline **3h**
Following the general procedure, **3h** was obtained as a white solid. 252 mg (50%); mp 86-88 °C; IR (KBr) (cm^{-1}) 3407, 3320, 2949, 2869, 1597, 1585, 1509; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.96 (t, *J*=7.6 Hz, 3H), 0.97 (t, *J*=7.6 Hz, 3H), 1.48 (sext, *J*=7.2 Hz, 2H), 1.49 (sext, *J*=7.2 Hz, 2H), 1.75 (sext, *J*=7.2 Hz, 4H), 2.66 (brs, 2H), 2.88 (dd, *J*=14.0, 9.2 Hz, 1H), 2.90 (brs, 2H), 3.12 (dd, *J*=13.6, 4.4 Hz, 1H), 3.78 (brs, 2H), 3.92 (t, *J*=7.2 Hz, 2H), 3.94 (t, *J*=7.2 Hz, 2H), 4.44 (dt, *J*=8.8, 4.0 Hz, 1H), 5.24 (d, *J*=3.6 Hz, 1H), 6.29 (dd, *J*=8.4, 1.6 Hz, 1H), 6.59 (td, *J*=8.0, 1.6 Hz, 1H), 6.77-6.88 (m, 5H), 6.93 (dd, *J*=8.0, 1.6 Hz, 1H), 7.06 (d, *J*=8.8 Hz 2H), 7.21 (d, *J*=8.8 Hz 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.9, 19.2, 19.3, 31.3, 31.4, 44.9, 51.7, 58.8, 67.7, 67.8, 111.6, 114.5, 116.6, 119.5, 127.2, 129.8, 130.3, 135.8, 138.5, 142.5, 158.0, 158.1; MS (FAB): *m/z* 503 $[M+H]^+$; Anal. Calcd for $C_{32}H_{42}N_2O_3$: C, 76.46; H, 8.42; N, 5.57. Found: C, 76.49; H, 8.43; N, 5.62.

N-(1,2-Di-*p*-tolylethyl)-2-morpholinoaniline **3i**
Following the general procedure, **3i** was obtained as a white solid. 269 mg (70%); mp 118-120 °C; IR (KBr) (cm^{-1}) 3400, 3326, 2818, 1597, 1510; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.25 (s, 3H), 2.27 (s, 3H), 2.54 (brs, 2H), 2.73 (brs, 2H), 2.90 (dd, *J*=13.2, 9.2 Hz, 1H), 3.07 (dd, *J*=13.6, 4.4 Hz, 1H), 3.71 (brs, 4H), 4.49 (dt, *J*=9.6, 4.8 Hz, 1H), 5.23 (d, *J*=4.8 Hz, 1H), 6.19 (d, *J*=8.4 Hz, 1H), 6.47 (td, *J*=7.2, 1.2 Hz, 1H), 6.70 (dd, *J*=7.6, 1.2 Hz, 1H), 6.88 (d, *J*=7.6, 1.2 Hz, 1H), 7.10 (d, *J*=7.6 Hz, 2H), 7.12 (d, *J*=7.6 Hz, 2H), 7.17 (d, *J*=8.4 Hz, 2H), 7.28 (dd, *J*=8.4 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.2, 44.7, 51.9, 58.7, 67.3, 111.4, 116.7, 119.8, 125.1, 126.7, 129.4, 129.5, 129.7, 135.8, 136.0, 136.2, 138.8, 141.7, 142.3; MS (FAB): *m/z* 387 $[M+H]^+$; Anal. Calcd for $C_{26}H_{30}N_2O$: C, 80.79; H, 7.82; N, 7.25. Found: C, 80.87; H, 7.90; N, 7.20.

N-(1,2-Bis(4-isopropylphenyl)ethyl)-2-morpholinoaniline **3j**
Following the general procedure, **3j** was obtained as a white solid. 319 mg (72%); mp 104-106 °C; IR (KBr) (cm^{-1}) 3387, 3326, 2964, 2850, 1595, 1507; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.22 (d, *J*=6.8 Hz, 6H), 1.22 (dd, *J*=6.8, 1.2 Hz, 6H), 2.59 (brs, 2H), 2.80-2.95 (m, 5H), 3.21 (dd, *J*=14.4, 4.8 Hz, 1H), 3.75 (brs, 4H), 4.49 (dt, *J*=10.0, 4.0 Hz, 1H), 5.25 (d, *J*=3.6 Hz, 1H), 6.28 (dd, *J*=7.6, 0.8 Hz, 1H), 6.58 (td, *J*=7.6, 1.2 Hz, 1H), 6.81 (td, *J*=7.2, 1.6 Hz, 1H), 6.92 (dd, *J*=8.0, 1.6 Hz, 1H), 7.15 (s, 4H), 7.19 (d, *J*=8.0 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.0, 24.1, 33.7, 45.5, 51.7, 59.0, 67.8, 111.5, 116.5, 119.5, 125.1, 126.0, 126.6, 126.7, 129.2, 135.5, 138.5, 141.6, 142.7, 147.3, 147.4; MS (FAB): *m/z* 443 $[M+H]^+$; Anal. Calcd for $C_{30}H_{38}N_2O$: C, 81.40; H, 8.65; N, 6.33. Found: C, 81.67; H, 8.77; N, 6.29.

N-(1,2-Bis(2-methoxyphenyl)ethyl)-2-morpholinoaniline **3k**
Following the general procedure, **3k** was obtained as a white solid. 254 mg (61%); mp 132-134 °C; IR (KBr) (cm^{-1}) 3357, 2964, 2835, 1598, 1511; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.73 (brs, 2H), 2.91 (brs, 2H), 3.05 (dd, *J*=13.6, 8.8 Hz, 1H), 3.18 (dd, *J*=13.6, 4.8 Hz), 3.81 (s, 3H), 3.82 (brs, 4H), 3.91 (s, 3H), 5.03 (brs, 1H), 5.38 (brs, 1H), 6.32 (dd, *J*=8.4, 1.2 Hz, 1H), 6.40 (td, *J*=7.6, 1.2 Hz, 1H), 6.79-6.87 (m, 4H), 6.89-6.93 (m, 2H), 7.09-7.26 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 36.7, 51.7, 52.6, 55.4, 55.6, 67.8, 110.4, 110.6, 111.2, 116.0, 119.2, 120.3, 120.7, 125.1, 126.9, 127.5, 127.6, 130.8, 132.0, 138.3, 142.4, 156.9, 157.9; MS (EI): *m/z* (%) 418 (M^+, 8.9), 297 (100); HRMS-EI: *m/z* (M^+) calcd for $C_{26}H_{30}N_2O_3$418.2256, found 418.2253.

N-(1,2-Diphenylethyl)-2-(piperidin-1-yl)-5-(trifluoromethyl)aniline **3l**
Following the general procedure, **3l** was obtained as a white solid. 260 mg (61%); mp 139-141 °C; IR (KBr) (cm^{-1}) 3350, 3326, 2936, 1602, 1584; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.67 (brs, 4H), 2.64 (brs, 2H), 2.86 (brs, 2H), 3.01 (dd, *J*=13.6, 8.8 Hz 1H), 3.22 (dd, *J*=14.0, 5.2 Hz 1H), 4.54 (dt, *J*=9.2, 5.2 Hz 1H), 5.38 (d, *J*=4.4 Hz 1H), 6.47 (s, 2H), 6.82 (d, *J*=8.0 Hz, 1H), 6.93 (d, *J*=8.0 Hz, 1H), 7.17 (d, *J*=6.8 Hz, 2H), 7.20-7.35 (m, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.3, 26.8, 45.4, 52.6, 59.4, 107.3 (q, J_{CF}=3.8 Hz), 113.5 (q, J_{CF}=3.8 Hz), 119.1, 124.4 (q, J_{CF}=269.9 Hz), 126.1 (q, J_{CF}=31.5 Hz), 126.2, 126.7, 127.2, 128.5, 128.7, 129.3, 137.7, 142.3, 143.2; MS (FAB): *m/z* 425 $[M+H]^+$; Anal. Calcd for $C_{26}H_{27}F_3N_2$: C, 73.56; H, 6.41; N, 6.60. Found: C, 73.31; H, 6.13; N, 6.58.

N-(4-Fluorobenzyl)-2-morpholinoaniline **4b**
Following the general procedure, **4b** was obtained as a white solid. 223 mg (78%); mp 94-96 °C; IR (KBr) (cm^{-1}) 3345, 2967, 1595, 1508; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.92 (t, *J*=4.6 Hz, 4H), 3.83 (brs, 4H), 4.33 (brs, 2H), 5.14 (brs, 1H), 6.56 (dd, *J*=9.2, 1.4 Hz, 1H), 6.72 (td,

View Article Online
DOI: 10.1039/C7GC03780E

J=7.8, 1.4 Hz, 1H), 6.96-7.02 (m, 2H), 7.04 (dd, *J*=8.7, 2.8 Hz, 2H), 7.31 (dd, *J*=8.7, 5.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 47.4, 51.8, 67.7, 110.5, 115.4 (d, J_{CF}=21.1 Hz), 117.2, 119.6, 125.3, 128.5 (d, J_{CF}=7.7 Hz), 135.5 (d, J_{CF}=3.8 Hz), 138.5, 142.9, 161.9 (d, J_{CF}=244.4 Hz); MS (FAB): *m/z* 287 $[M+H]^+$; Anal. Calcd for $C_{17}H_{19}FN_2O$: C, 71.31; H, 6.69; N, 9.78. Found: C, 71.41; H, 6.73; N, 9.70.

A mixture of 2-morpholinoailine (**1a**) (1.78 g, 10 mmol), K_2CO_3 (2.76 g, 20 mmol), and benzylchloride (1.15 mL, 10 mmol) in DMF (20 mL) was stirred at 80 °C for 20 h under Ar. 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 the *N*-monobenzylated product **4a** (385 mg, 1.43 mmol, 14%) and *N,N*-dibenzylated product **5** (412 mg, 1.15 mmol, 12%).

N-Benzyl-2-morpholinoaniline **4a** [26]
Amorphous; IR (KBr) (cm^{-1}) 3338, 2852, 1601, 1508; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.93 (d, *J*=4.8 Hz, 4H), 2.83 (brs, 4H), 4.37 (d, *J*=5.6 Hz, 2H), 5.16 (brs, 1H), 6.60 (dd, *J*=7.6, 1.2 Hz, 1H), 6.71 (td, *J*=7.6, 1.2 Hz, 1H), 7.00 (td, *J*=8.0, 1.6 Hz, 1H), 7.04 (dd, *J*=7.6, 1.2 Hz, 1H), 7.26-7.30 (m, 1H), 7.34 (d, *J*=1.6 Hz, 2H), 7.36 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 48.2, 51.9, 67.8, 110.6, 117.1, 119.6, 125.4, 127.1, 128.7, 138.6, 139.9, 143.2; MS (EI): *m/z* (%) 268 (M^+, 65.5), 72 (100).

N,N-Dibenzyl-2-morpholinoaniline **5**
White solid; mp 149-151 °C; IR (KBr) (cm^{-1}) 3066, 3030, 2955, 1588; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.27 (brt, *J*=4.4 Hz, 4H), 3.86 (t, *J*=4.4 Hz, 4H), 4.35 (s, 4H), 6.76 (d, *J*=8.0 Hz, 1H), 6.87-6.94 (m, 1H), 6.99 (d, *J*=5.2, 0.8 Hz, 2H), 7.08 (dd, *J*=8.0, 1.6 Hz, 4H), 7.20-7.30 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 50.6, 53.6, 67.7, 118.8, 121.9, 122.7, 123.1, 127.0, 128.3, 129.0, 138.4, 143.7, 144.4; MS (EI): *m/z* (%) 358 (M^+, 3.4), 267 (100); Anal. Calcd for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.17; H, 7.42; N, 7.96.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Number 16K08179.

Notes and references

1 Z, Leilei, Y. Tianming, X. Xilei, L. Gang, *Bioorg. Med. Chem. Lett.* 2015, **25**, 2937-2942.
2 (*a*) S. O. Abdul-Hay, T. D. Bannister, H. Wang, M. D. Cameron, T. R. Caulfield, A. Masson, J. Bertrand, E. A. Howard, M. P. McGuire, U. Crisafulli, T. R. Rosenberry, C. L. Topper, C. R. Thompson, S. C. Schurer, F. Madoux, P. Hodder, M. A. Leissring, *ACS Chem. Biol.* 2015, **10**, 2716-2724; (*b*) Y.-Y. Cheung, H. Yu, K. Xu, B. Zou, M. Wu, O. B. McManus, M. Li, C. W. Lindsley, C. R. Hopkins, *J. Med. Chem.* 2012, **55**, 6975-6979.
3 V. G. Melissa, F. Oleg, I. David, D. Chunyun, C. Tamsyn, H. Claire, H. Masatoshi, D. D. Andrew, C. Russell, J. H. Steven, C. H. Jules, K. Stefan, O. B. David, *Invest. Ophthalmol. Vis. Sci*. 2013, **54**, 6052-6062.
4 (*a*) Y. Gong, K. S. Somersan X. Guo, P. Zheng, B. Gold, Y. Ma, D. Little, J. Roberts, T. Warrier, X. Jiang, M. Pingle, C. F. Nathan, G. Liu, *Eur. J. Med. Chem.* 2014, **75**, 336-353; (*b*) A. Nagaraj, G. Ravi, S. S. Kumar, S. Raghaveer, N. Rana, *Research & Reviews: Journal of Chemistry,* 2014, **3**, 17-21.
5 (*a*) M. Su, N. Hoshiya, S. L. Buchwald, *Org. Lett.* 2014, **16**, 832-835; (*b*) Y. Hirai, Y. Uozumi, *Chem. Asian J.* 2010, **5**, 1788-1795.
6 Reviews see: (*a*) B. M. Trost, L. C. Czabaniuk, *Angew. Chem., Int. Ed.* 2014, **53**, 2826–2851; (*b*) R. Kuwano, *Synthesis* 2009, 1049- 1061.
7 (*a*) S. Sahnoun, S. Messaoudi, J.-D. Brion, M. Alami, *ChemCatChem* 2011, **3**, 893–897; (*b*) L. Ackermann, S. Barfsser, C. Kornhaass, A. R. Kapdi, *Org. Lett*. 2011, **13**, 3082–3085; (*c*) S. L. Marquard, D. C. Rosenfeld, J. F. Hartwig, *Angew. Chem., Int. Ed.* 2010, **49**, 793 –796; (*d*) S. Fan, C.-Y. He, X. Zhang, *Chem. Commun.* 2010, 4926–4928; (e) A. M. Kearney, A. Landry-Bayle, L. Gomez, *Tetrahedron Lett.* 2010, **51**, 2281–2283; (*f*) T. Mukai, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* 2010, **12**, 1360–1363.
8 M. Yokogi, R. Kuwano, *Tetrahedron Lett*. 2007, **48**, 6109–6112.
9 (*a*) H. Narahashi, I. Shimizu, A. Yamamoto, *J. Organometallic Chem.* 2008, **693**, 283–296; (*b*) H. Narahashi, A. Yamamoto, I. Shimizu, *Chem. Lett.* 2004, **33**, 348–349; (*c*) G. Verspui, G. Papadogianakis, R. A. Sheldon, *Catal. Today*, 1998, **42**, 449–458; (*d*) G. Papadogianakis, L. Maat, R. A. Sheldon, *J. Chem. Tech. Biotechnol.* 1997, **70**, 83–91.
10 (*a*) G. Verspui, G. Papadogianakis, R. A. Sheldon, *Catal. Today*, 1998, **42**, 449‑458; (*b*) G. Papadogianakis, L. Maat, R. A. Sheldon, *J. Chem. Tech. Biotechnol.* 1997, **70**, 83-91.
11 T. Maji, K. Ramakumar, J. A. Tunge, *Chem. Commun.* 2014, 14045-14048.
12 X. Cao, Y. Zhang, *Green. Chem*. 2016, **18**, 2638-2641.
13 (*a*) H. Nakamura, H. Iwama, Y. Yamamoto, *J. Chem. Soc., Chem. Commun.* 1996, 1459–1460; (*b*) H. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* 1996, **118**, 6641–6647.
14 S. Zhang, A. Ullah, Y. Yamamoto, M. Bao, *Adv. Synth. Catal.* 2017, **359**, 2723-2728.
15 N. Solin, J. Kjellgren, K. J. Szabó, *J. Am. Chem. Soc.* 2004, **126**, 7026-7033.
16 (*a*) H. Hikawa, T. Koike, K. Izumi, S. Kikkawa, I. Azumaya, *Adv. Synth. Catal.* 2016, **358**, 784–791; (*b*) H. Hikawa, M. Toyomoto, S. Kikkawa, I. Azumaya, *Org. Biomol. Chem.* 2015, **13**, 11459-11465; (*c*) H. Hikawa, I. Azumaya, *Org. Biomol. Chem.* 2014, **12**, 5964–5972; (*d*) H. Hikawa, N. Matsuda, H. Suzuki, Y. Yokoyama, I. Azumaya, *Adv. Synth. Catal.* 2013, **355**, 2308.
17 (*a*) H. Hikawa, K. Izumi, Y. Ino, S. Kikkawa, Y. Yokoyama, I. Azumaya, *Adv. Synth. Catal*. 2015, **357**, 1037–1048; (*b*) H. Hikawa, Y. Yokoyama, *Org. Lett.* 2011, **13**, 6512–6515.
18 (*a*) H.-H. Zhang, S. Yu, *J. Org. Chem.* 2017, **82**, 9995-10006; (*b*) N. Chen, X.-J. Dai, H. Wang, C.-J. Li, *Angew. Chemie, Int. Ed*. 2017, **56**, 6260-6263; (*c*) H. Mei, X. Ji, J. Han, Y. Pan, *Eur. J. Org. Chem*. 2011, 5783-5786; (*d*) Y. Zhang, T. Yan, W. Cheng, J. Zuo, W. Zhao, *Tetrahedron Lett.* 2009, **50**, 2925–2928; (*e*) E. L. Gall, C. Haurena, S. Sengmany, T. Martens, M. Troupel, *J. Org. Chem*. 2009, **74**, 7970–7973.
19 (*a*) Q. Sun, Y. Wang, D. Yuan, Y. Yao, Q. Shen, *Dalton Trans.,* 2015, **44**, 20352-20360; (*b*) J. C.-H. Yim, J. A. Bexrud, R. O. Ayinla, D. C. Leitch, L. L. Schafer, *J. Org. Chem.* 2014, **79**, 2015−2028; (*c*) C. Brahms, P. Tholen, W. Saak, S. Doye, *Eur. J. Org. Chem.* 2013, 7583–7592; (*d*) K. Born, S. Doye, *Eur. J. Org. Chem.* 2012, 764-771; (*e*) H. Duan, S. Sengupta, J. L. Petersen, N. G. Akhmedov, X. Shi, *J. Am. Chem. Soc*. 2009, **131**, 12100–12102.
20 B. M. Trost, B. M. O'Boyle, D. Hund, *Chem. Eur. J*. 2010, **16**, 9772–9776.
21 (*a*) S. Hajra, S. Singha Roy, S. M. Aziz, D. Das, *Org. Lett*. 2017, **19**, 4082-4085; (*b*) R. S. Tukhvatshin, A. S. Kucherenko, Y. V. Nelyubina, S. G. Zlotin, *ACS Catal.* 2017, **7**, 2981–2989; (*c*) M.

View Article Online
DOI: 10.1039/C7GC03780E

A. Ali, X. Yao, G. Li, H. Lu, *Org. Lett.* 2016, **18**, 1386–1389; (*d*) V. Satheesh, M. Sengoden, T. Punniyamurthy, *J. Org. Chem.* 2016, **81**, 9792–9801; (*e*) G. B. Vamisetti, R. Chowdhury, M. Kumar, S. K. Ghosh, *Org. Lett.* 2016, **18**, 1964–1967; (*f*) M. A. Ali, X. Yao, H. Sun, H. Lu, *Org. Lett.* 2015, **17**, 1513-1516; (*g*) Y. Zhang, B.-W. Wei, H. Lin, L. Zhang, J.-X. Liu, H.-Q. Luo, X.-L. Fan, *Green Chem.* 2015, **17**, 3266-3270; (*h*) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem., Int. Ed.* 2005, **44**, 3275-3279.

22 (*a*) R. N. Butler, A. G. Coyne, *Org. Biomol. Chem.* 2016, **14**, 9945-9960; (*b*) Y. Jung, R. A. Marcus, *J. Am. Chem. Soc.* 2007, **129**, 5492-5502.

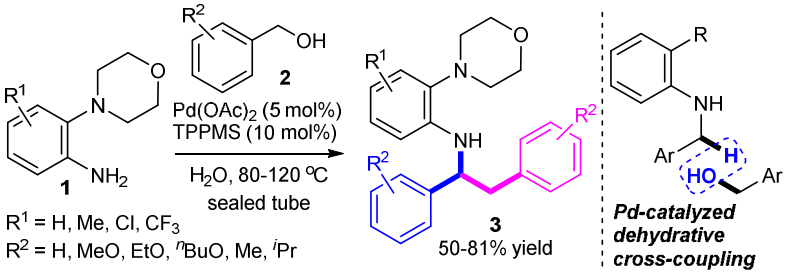
23 SRPIN340, N-[2-(1-piperidinyl)-5-(trifluoromethyl)phenyl]isonicotinamide, inhibits SRPK1 and SRPK2 kinase activities potently. see) Y. Karakama, N. Sakamoto, Y. Itsui, M. Nakagawa, M. Tasaka-Fujita, Y. Nishimura-Sakurai, S. Kakinuma, M. Oooka, S. Azuma, K. Tsuchiya, H. Onogi, M. Hagiwara, M. Watanabe, *Antimicrob. Agents Chemother.* 2010, **54**, 3179-3186.

24 A. Galano, A. Perez-Gonzalez, R. Castaneda-Arriaga, L. Munoz-Rugeles, G. Mendoza-Sarmiento, A. Romero-Silva, A. Ibarra-Escutia, A. M. Rebollar-Zepeda, J. R. Leon-Carmona, M. A. Hernández-Olivares, J. R. Alvarez-Idaboy, *J. Chem. Inf. Model.* 2016, **56**, 1714−1724.

25 (*a*) I. I. Strambeanu, M. C. White, *J. Am. Chem. Soc.* 2013, **135**, 12032–12037; (*b*) A. J. Young, M. C. White, *Angew. Chem. Int. Ed.* 2011, **50**, 6824- 6827; (*c*) E. M. Stang, M. C. White, *Nature Chemistry* 2009, **1**, 547-551; (*d*) S. A. Reed, A. R. Mazzotti, M. C. White, *J. Am. Chem. Soc.* 2009, **131**, 11701−11706; (*e*) M. S. Chen, N. Prabagaran, N. A. Labenz, M. C. White, *J. Am. Chem. Soc.* 2005, **127**, 6970-6971.

26 C. E. Hendrick, S. L. McDonald, Q. Wang, *Org. Lett.* 2013, **15**, 3444-3447.

View Article Online
DOI: 10.1039/C7GC03780E



A strategy for the palladium-catalyzed dehydrative tandem benzylation of 2-morpholinoanilines with benzyl alcohols has been developed. This cascade reaction is devised as a straightforward and efficient synthetic route for *N*-(1,2-diphenylethyl)-2-morpholinoanilines in moderate to good yields. The "on water" protocol, which affords the corresponding desired products with water as the sole co-product, can be achieved under mild reaction conditions without the need for base or other additives on the atom-economic process.