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## Au(III)/TPPMS-catalyzed Friedel—Crafts benzylation of deactivated N-alkylanilines in water†

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The Friedel–Crafts reaction of electronically deactivated anilines including those with strong electron-withdrawing  $NO_2$ , CN or  $CO_2H$  groups is challenging due to the reduced electron density of the aromatic ring. Here, we demonstrate the Au(m)/TPPMS-catalyzed Friedel–Crafts benzylation of deactivated anilines in water. This reaction exhibits operational simplicity and a broad substrate scope with high regio-selectivity, enabling rapid access to 2-benzylanilines.

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## Introduction

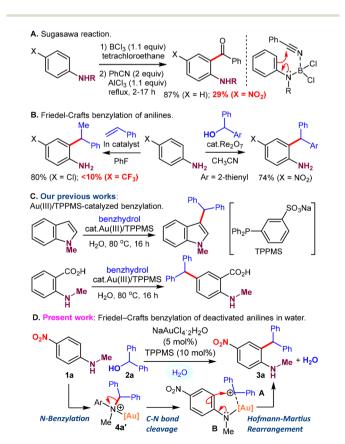
The Friedel-Crafts reaction is one of the oldest and most powerful approaches for creating a C-C bond from an unactivated aromatic C-H bond of an electron-rich arene, which is a fundamental synthetic protocol for the construction of organic molecules. However, this transformation using unprotected anilines is notoriously difficult, leading to the formation of N-substituted anilines instead. 1,2 Furthermore, anilines tend to capture the Lewis acid catalyst and prevent its turnover. In 1978, Sugasawa et al. first developed an ortho-acylation of unprotected anilines with nitriles as the acylating agents by employing a Lewis acid (Scheme 1A).<sup>3,4</sup> Recently, the Gandon and Bour group demonstrated In(1)-catalyzed C-alkylations of para-substituted anilines via a tandem hydroamination/ Hofmann-Martius rearrangement (Scheme 1B, left).<sup>5</sup> Despite these tremendous advancements for the direct transformation of anilines, highly electron-poor arenes such as 4-nitroanilines are more challenging substrates due to the electron density of the aromatic ring which is reduced by the strong electron-withdrawing group.5-7 Therefore, only a few studies with these substrates have been reported to date.<sup>8,9</sup> For example, the Ghorai group demonstrated a dehydrative ortho C-H benzylation of 4-nitroaniline with benzhydrols employing a Re<sub>2</sub>O<sub>7</sub> catalyst (Scheme 1B, right).<sup>8a</sup>

Our group previously reported a new dehydrative C3-benzylation of indoles utilizing the combination of Lewis acidic Au

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† Electronic supplementary information (ESI) available: Copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for all compounds. CCDC 2358605. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4ob01234h

(III)<sup>10</sup> with a water-soluble phosphine ligand,  $Ph_2P(m-C_6H_4SO_3Na)$  (TPPMS), in water.<sup>11</sup> In contrast, no reaction occurred when using  $NaAuCl_4 \cdot 2H_2O$  in organic solvents such as  $CH_2Cl_2$ , 1,4-dioxane, and toluene, suggesting that strong  $\pi$  nucleophilic indole substrates suppress the Lewis acidity of



Scheme 1 Friedel-Crafts reactions of deactivated anilines.

gold(III) catalysts in organic solvents.<sup>12</sup> Notably, our Lewis acidic Au(III)/TPPMS system in water provided a unique strategy to enable catalytic reactions in systems that would otherwise be inert. Based on this encouraging result, we aimed to develop a novel synthetic strategy for the catalytic dehydrative Friedel–Crafts benzylation in water.

We herein present an efficient, green, and convenient protocol for the dehydrative *ortho* C–H selective benzylation of deactivated anilines utilizing the Au(III)/TPPMS catalytic system in water. Our design approach involves a tandem reaction *via* an initial dehydrative *N*-benzylation followed by Hofmann–Martius rearrangement, <sup>13</sup> resulting in the synthesis of a series of novel 2-benzylaniline derivatives with good functional group tolerance. In general, the conventional Friedel–Crafts reaction relies heavily on anhydrous organic solvents. <sup>14,15</sup> Therefore, our catalytic reaction in water should attract a great deal of research interest from synthetic organic chemists. This environmentally friendly approach reduces the use of harmful organic solvents, promoting sustainability in chemical processes. <sup>16</sup>

## Results and discussion

We first examined the reaction between nitroaniline **1a** and alcohol **2a** as model substrates (Table 1). Recent literature reports have shown that the rhenium(vII) catalyst can be efficient in the dehydrative Friedel-Crafts benzylation.<sup>8</sup>

**Table 1** Optimization of the catalytic dehydrative Friedel-Crafts benzylation<sup>a</sup>

Entry	Catalyst	Ligand	Solvent	$Yield^{b}$ (%)	
				3a	4a
1	Re <sub>2</sub> O <sub>7</sub>	TPPMS	H <sub>2</sub> O	8	45
2	$FeCl_2$	TPPMS	$H_2O$	2	60
3	$CuCl_2$	TPPMS	$H_2O$	3	55
4	HCl	None	$H_2O$	7	54
5	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	TPPMS	$H_2O$	87	5
6	AuBr <sub>3</sub>	TPPMS	$H_2O$	79	11
7	HAuCl <sub>4</sub> ·4H <sub>2</sub> O	TPPMS	$H_2O$	79	18
8	$AuCl_3$	TPPMS	$H_2O$	23	26
9	AuCl	TPPMS	$H_2O$	31	30
10	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	None	$H_2O$	0	34
11	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	$TPPMS^b$	$H_2O$	17	13
12	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	$TPPTS^c$	$H_2O$	0	54
13	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	TPPMS	Toluene	20	43
14	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	TPPMS	DMF	0	11
15	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	$PPh_3$	DMF	10	14
$16^d$	NaAuCl <sub>4</sub> ·2H <sub>2</sub> O	TPPMS	$H_2O$	96	4

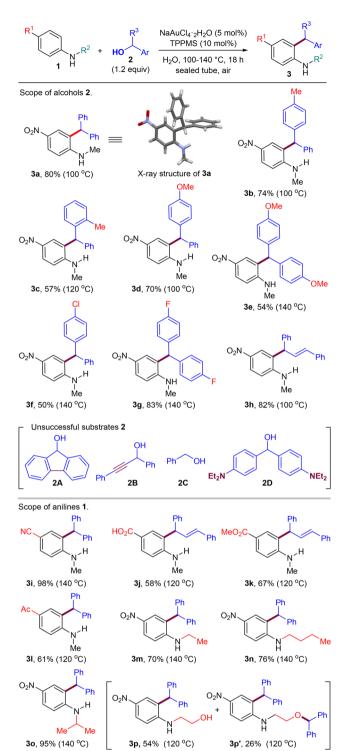
<sup>&</sup>lt;sup>a</sup> 1a (1 mmol), catalysts (5 mol%), ligand (10 mol%), 2a (1.2 mmol), and solvent (4 mL) were used at 90 °C for 18 h. All the reactions were performed in a sealed tube under air. <sup>b</sup> 5 mol% was used. <sup>c</sup>  $P(C_6H_4$ -m- $SO_3Na)_3$ , <sup>d</sup> At 100 °C.

However, the reaction between 1a and 2a using the  $Re_2O_7$  catalyst in water afforded the N-benzylated product 4a in 45% yield along with only 8% of the desired 2-benzylaniline 3a (entry 1). Similar results were obtained when using  $FeCl_2$ ,  $CuCl_2$  or HCl (entries 2–4). Other Lewis acids such as  $ZnCl_2$ ,  $CoCl_2$ , and  $MnCl_2$  exhibited no catalytic activities.

To our delight, the dehydrative coupling utilizing a NaAuCl<sub>4</sub>·2H<sub>2</sub>O catalyst with the TPPMS ligand gave the desired 2-benzylaniline 3a as the major product in contrast to the predominance of the N-benzylated product 4a in similar catalytic scenarios (entry 5 vs. entries 1-4). Replacing NaAuCl<sub>4</sub>·2H<sub>2</sub>O with other gold(III) salts such as AuBr<sub>3</sub> or HAuCl<sub>4</sub>·4H<sub>2</sub>O led to similar yields of 3a (entries 6 and 7). However, AuCl<sub>3</sub> and AuCl were less efficient (entries 8 and 9). Notably, the use of the TPPMS ligand was essential for achieving the Friedel-Crafts reaction (entry 10). Decreasing the amount of TPPMS to 5 mol% also significantly reduced the yield of 3a (entry 11). When replacing TPPMS with another water-soluble phosphine ligand, P(C<sub>6</sub>H<sub>4</sub>-m-SO<sub>3</sub>Na)<sub>3</sub> (TPPTS),<sup>17</sup> product 3a was not obtained (entry 12). When using organic solvents such as toluene or DMF instead of water, either a low yield of 3a or no reaction occurred (entries 13 and 14). The reaction did not proceed in DMF when using PPh3 (entry 15). The dehydrative Friedel-Crafts benzylation proceeded to near completion upon increasing the temperature to 100 °C (entry 16).

With the optimized reaction conditions in hand, we explored the scope of alcohols 2 in the coupling of 4-nitroaniline 1a (Scheme 2). Both electron-withdrawing and electron-donating groups on the benzene ring were well tolerated, furnishing the C-benzylated products 3a–g in moderate to excellent yields (50–83%). The structure of the desired product 3a was unambiguously confirmed by X-ray single-crystal diffraction analysis. Allylic alcohol 2, *trans*-1,3-diphenyl-2-propen-1-ol, was also a viable coupling partner to afford the desired product 3h in 82% yield. In contrast, the desired C-benzylated products were not obtained when using 9-fluorenol 2A, propargylic alcohol 2B and benzyl alcohol 2C. Furthermore, bis(4-diethylaminophenyl)methanol 2D was also not applicable to the Friedel–Crafts benzylation due to its basicity.

Next, we explored the reaction scope of anilines 1 capable of yielding the C-benzylated product 3. Aniline bearing an electron-withdrawing cyano group was a suitable substrate, leading to the formation of C-benzylated aniline 3i in excellent yield (98%). Advantageously, using allylic alcohol 2, the aniline substrate containing an unprotected carboxylic acid functional group could be converted to the desired product 3j in moderate yield (58%) while keeping the acid moiety intact. The ester and acetyl moieties were also well tolerated under the standard conditions (3k, 67%; 3l, 61%). In contrast, when N-methyl-mtoluidine was used instead of deactivated N-alkylanilines 1, the reaction did not proceed efficiently, and the unreacted starting material was recovered. Sterically hindered N-alkylanilines with alkyl side chains including ethyl, n-butyl and isopropyl exhibited good reactivities (3m-o, 70-95%). Interestingly, substitution with the bulky isopropyl group led to the formation of the desired product 30 in excellent yield. This is likely due



Scheme 2 Substrate scope for the dehydrative benzylation.

to increased steric hindrance around the nitrogen atom, which promotes the cleavage of the C-N bond and enhances the rearrangement reaction. The reaction of N-alkylaniline 1p with an alcohol moiety afforded C-benzylated product 3p and C,Odibenzylated product 3p' in 54% and 26% yields, respectively.

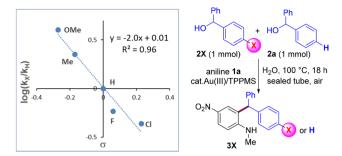


Fig. 1 Hammett plot for the gold-catalyzed C-benzylation of 1a using para-substituted benzhydrols 2X.

A Hammett study was performed to investigate the substituent effects of benzhydrols 2X (X = OMe, Me, F, Cl) (Fig. 1).<sup>18</sup> Hammett plots were obtained against  $log(k_X/k_H)$  and the substitution constant  $\sigma_{\rm p}$  and showed a linear slope ( $R^2 = 0.96$ ) with a  $\rho$  value of -2.0. The negative slope indicates the involvement of a charged transition state in which the positive charge is stabilized inductively.<sup>19</sup> Therefore, the presence of electrondonating groups on the benzhydrols 2X accelerates the reaction compared to electron-withdrawing substituents. These results are consistent with the Hofmann-Martius rearrangement process with the in situ generated benzyl cation species from N-benzylated intermediate 4a involved in the rate-determining step.

The time course reaction profile for the Friedel-Crafts benzylation between 4-nitroaniline 1a and alcohol 2a (1.2 equiv.) in water is shown in Fig. 2. The formation of N-benzylaniline 4a was observed in the initial phase of the reaction along with the slow formation of C-benzylated product 3a. After 60 min, further consumption of 4a was observed, ultimately forming 2-benzylaniline 3a. These observations are in excellent agreement with a cascade reaction involving N-benzylation of 1a, followed by the Hofmann-Martius rearrangement of N-benzylaniline 4a in the rate-determining step. When the conversion of alcohol 2a was monitored, its rapid depletion and the formation of a small amount of ether 5a were observed in the early stages of the reaction (Fig. S2B in the ESI†).<sup>20</sup> This result suggests that upon activation of alcohol 2a, ether 5a was formed via homocoupling of 2a due to the nucleophilicity of

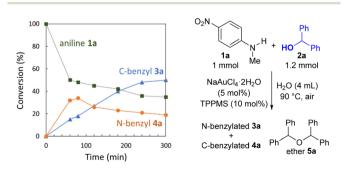


Fig. 2 Reaction profiles for the dehydrative coupling of aniline 1a with alcohol 2a

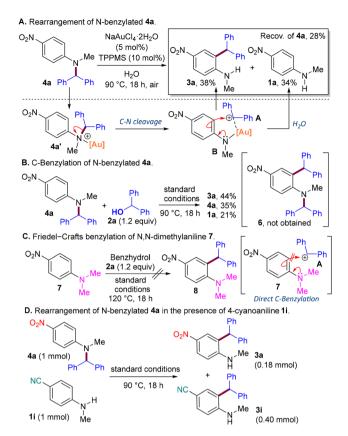
Scheme 3 Comparison of N-benzylation of 4-nitroaniline C-benzylation of N-benzylaniline.

the oxygen atom. However, ether 5a did not decay, suggesting that it did not serve as a coupling partner. We recently reported the Au(III)/TPPMS-catalyzed dehydrative N-benzylation of 2-aminopyridines with benzhydrols in water.<sup>21</sup> Indeed, no reaction occurred when using ether 5a instead of benzhydrol 2a as a coupling partner in a control experiment.

Next, we conducted solvent isotope effect studies for the catalytic Friedel-Crafts benzylation using H<sub>2</sub>O and D<sub>2</sub>O as solvents. In our previous work, the dehydrative N-benzylation of 4-nitroaniline with benzhydrol employing the Au(III)/TPPMS system showed an inverse kinetic solvent isotope effect (KSIE,  $k_{\rm H_2O}/k_{\rm D_2O}$ ) of 0.6,<sup>19</sup> which is consistent with the specific acid catalysis mechanism (Scheme 3A). In contrast, the time course reaction profiles in the Friedel-Crafts benzylation showed almost the same results in H<sub>2</sub>O and D<sub>2</sub>O (Fig. S3 in the ESI†). Although the Lewis acidity of gold catalysts is significantly suppressed by water hydration, the basic nitrogen of N-benzylaniline 4a can coordinate with the Au(III)/TPPMS catalyst without the influence of water molecules (Scheme 3B). Therefore, the resulting active gold complex 4a' is converted to the 2-benzylated product 3a via the rate-determining Hofmann-Martius rearrangement step.

The use of water as a reaction medium is essential for achieving the catalytic Friedel-Crafts benzylation (see Table 1). The transition state TS of the Hofmann-Martius rearrangement step involves benzyl cation A and aniline moiety B linked by the gold catalyst, which is stabilized by hydrophobic interactions between the phenyl rings in water to promote C-C bond formation.<sup>22</sup>

We ran several control experiments to elucidate the reaction mechanism for the dehydrative Friedel-Crafts benzylation in water. As expected, the rearrangement of N-benzylated substrate 4a proceeded successfully to form the desired C-benzylated aniline 3a (Scheme 4A). Additionally, debenzylation of intermediate 4a occurred, leading to the regeneration of 4-nitroaniline 1a in 34% yield. This result suggests that the Lewis acidic Au(III)/TPPMS cation enables the cleavage of the sp<sup>3</sup> C-N bond of intermediate 4a' to generate the benzyl cation A with gold(III)-amide complex B. Cation A is simultaneously trapped by the gold-amide complex B to give the desired 3a as



Scheme 4 Control experiments.

the thermodynamically controlled product. Furthermore, the gold(III) complex B reacts with water as a solvent to regenerate aniline 1a. No dibenzylated product 6 was obtained from N-benzylaniline 4a and alcohol 2a (Scheme 4B), nor did direct C-benzylation of N,N-dimethylaniline 7 occur (Scheme 4C).<sup>23</sup> These results exclude the reaction pathway via direct coupling of the N,N-disubstituted aniline substrates 4a or 7 with the in situ generated benzyl cation species A. A crossover experiment between intermediate 4a and 4-cyanoaniline 1i led to the formation of crossover product 3i along with the rearrangement product 3a in 40% and 18% yields, respectively (Scheme 4D). This indicates that the Hofmann-Martius rearrangement proceeds through an intermolecular pathway via the formation of a carbocation intermediate.

Based on the results from several mechanistic studies, a plausible mechanism for the ortho-C-H benzylation of deactivated aniline 1a with alcohol 2a employing the Au(III)/ TPPMS catalyst is outlined in Scheme 5. Initially, the Lewis acidic gold catalyst promotes the cleavage of the sp<sup>3</sup> C-O bond of alcohol 2a to form the benzyl cation A (step 1). Subsequently, aniline 1a attacks the electrophilically active cation A, generating N-benzylaniline 4a as the kinetically controlled product (step 2). This then undergoes an unprecedented sp<sup>3</sup> C-N bond cleavage of the gold(III) cation complex 4a' to regenerate the benzylcation species A along with the gold-amide complex B. The benzyl group is then introduced into the benzene ring of complex B to give 2-benzylaniline 3a

Scheme 5 Proposed mechanism.

as the thermodynamically controlled product. The cation species B is quenched by water, regenerating the aniline substrate 1a (see Scheme 4A). A Hammett  $\rho$  value of -2.0 in the Friedel-Crafts benzylation is consistent with the Hofmann-Martius rearrangement pathway that generates a cationic charge at the benzylic position of the TS.

#### Conclusions

In summary, we have established a dehydrative Friedel-Crafts benzylation of poorly nucleophilic aromatic amines such as 4-nitroanilines with benzhydrols under environmentally friendly reaction conditions in water. This protocol offers an efficient route for the selective synthesis of a new family of 2-benzylanilines from easily available deactivated anilines and benzhydrols, featuring high regioselectivity and a broad substrate scope. Notably, the Lewis acidic Au(III)/TPPMS catalyst was revealed to be highly efficient for the N-benzylation of deactivated anilines with benzhydrols, followed Hofmann-Martius rearrangement the resulting of N-benzylated intermediates.

## **Experimental**

#### General procedure

A mixture of anilines 1 (1 mmol), alcohols 2 (1.2 mmol), NaAuCl<sub>4</sub>·2H<sub>2</sub>O (5 mol%) and TPPMS (10 mol%) in water (4 mL) was stirred at 90-140 °C for 18 h in a sealed tube under air. After cooling, the reaction mixture was extracted with EtOAc. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, n-hexane/EtOAc) to give the desired product 3.

## Author contributions

H. H. designed the studies and prepared the original draft of the manuscript. A. F., K. K., T. N., and T. E. performed the synthesis and characterization of the compounds. S. K. contributed to reviewing and editing the manuscript. I. A. supervised the project, conceptualized the idea, and contributed to reviewing and editing the manuscript. The manuscript was written through the contributions of all authors.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Conflicts of interest

There are no conflicts to declare.

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