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

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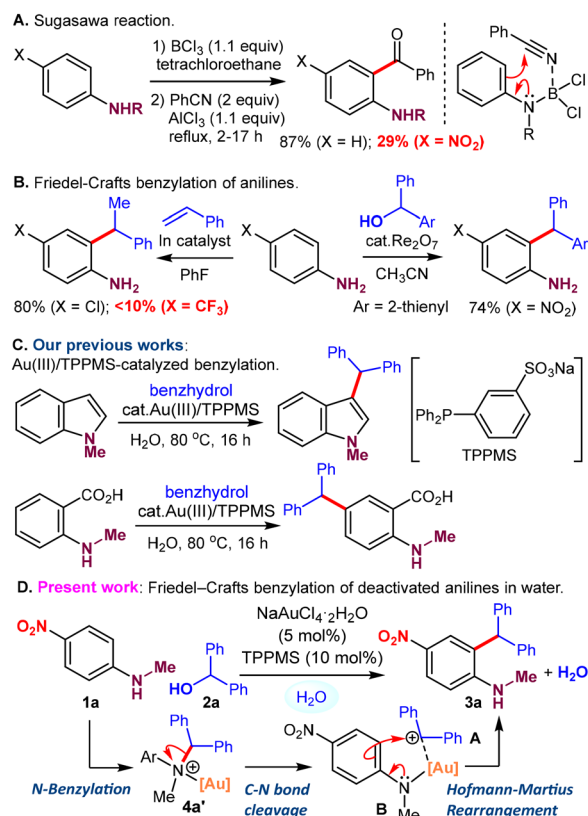Tomokatsu Enda, Shoko Kikkawa ID and Isao Azumaya ID *

The Friedel–Crafts reaction of electronically deactivated anilines including those with strong electron-withdrawing NO$_2$, CN or CO$_2$H groups is challenging due to the reduced electron density of the aromatic ring. Here, we demonstrate the Au(III)/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.

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).[3,4] Recently, the Gandon and Bour group demonstrated In(I)-catalyzed C-alkylations of *para*-substituted anilines *via* a tandem hydroamination/Hofmann–Martius rearrangement (Scheme 1B, left).[5] Despite these tremendous advancements for the direct transformation of anilines,[6] 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.[8,9] For example, the Ghorai group demonstrated a dehydrative *ortho* C–H benzylation of 4-nitroaniline with benzhydrols employing a Re$_2$O$_7$ catalyst (Scheme 1B, right).[8a]

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

(III)[10] with a water-soluble phosphine ligand, Ph$_2$P(*m*-C$_6$H$_4$SO$_3$Na) (TPPMS), in water.[11] In contrast, no reaction occurred when using NaAuCl$_4$·2H$_2$O in organic solvents such as CH$_2$Cl$_2$, 1,4-dioxane, and toluene, suggesting that strong π nucleophilic indole substrates suppress the Lewis acidity of

Scheme 1 Friedel–Crafts reactions of deactivated anilines.

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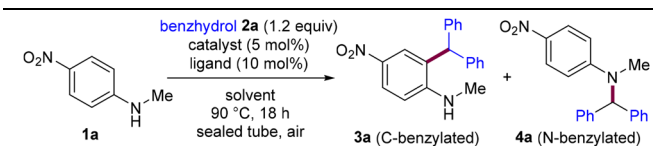This journal is © The Royal Society of Chemistry 2024

gold(III) catalysts in organic solvents.[12] 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,[13] 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.[14,15] 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.[16]

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.[8]

Table 1 Optimization of the catalytic dehydrative Friedel–Crafts benzylation[a]

Entry	Catalyst	Ligand	Solvent	3a	4a
				Yield[b] (%)	
1	Re$_2$O$_7$	TPPMS	H$_2$O	8	45
2	FeCl$_2$	TPPMS	H$_2$O	2	60
3	CuCl$_2$	TPPMS	H$_2$O	3	55
4	HCl	None	H$_2$O	7	54
5	**NaAuCl$_4$·2H$_2$O**	**TPPMS**	**H$_2$O**	**87**	**5**
6	AuBr$_3$	TPPMS	H$_2$O	79	11
7	HAuCl$_4$·4H$_2$O	TPPMS	H$_2$O	79	18
8	AuCl$_3$	TPPMS	H$_2$O	23	26
9	AuCl	TPPMS	H$_2$O	31	30
10	NaAuCl$_4$·2H$_2$O	None	H$_2$O	0	34
11	NaAuCl$_4$·2H$_2$O	TPPMS[b]	H$_2$O	17	13
12	NaAuCl$_4$·2H$_2$O	TPPTS[c]	H$_2$O	0	54
13	NaAuCl$_4$·2H$_2$O	TPPMS	Toluene	20	43
14	NaAuCl$_4$·2H$_2$O	TPPMS	DMF	0	11
15	NaAuCl$_4$·2H$_2$O	PPh$_3$	DMF	10	14
16[d]	**NaAuCl$_4$·2H$_2$O**	**TPPMS**	**H$_2$O**	**96**	**4**

[a] **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. [b] 5 mol% was used. [c] P(C$_6$H$_4$-*m*-SO$_3$Na)$_3$. [d] At 100 °C.
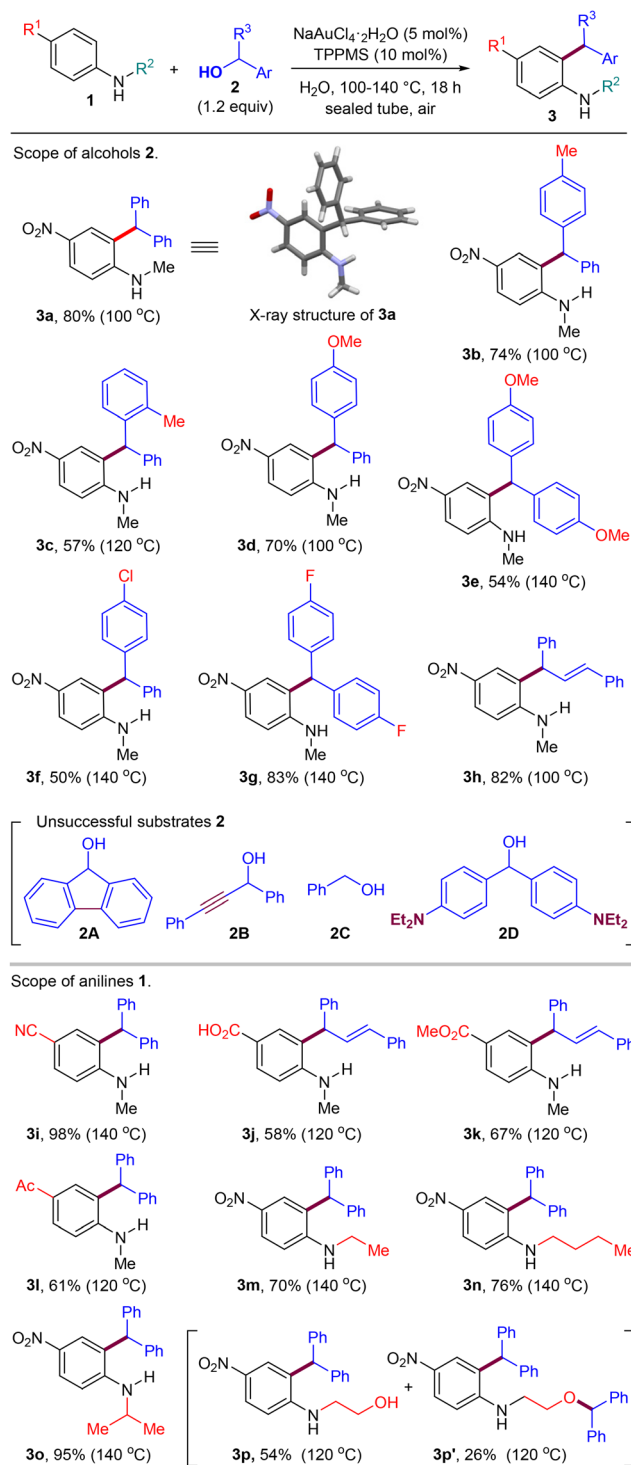
However, the reaction between **1a** and **2a** using the Re$_2$O$_7$ catalyst in water afforded the N-benzylated product **4a** in 45% yield along with only 8% of the desired 2-benzylaniline **3a** (entry 1). Similar results were obtained when using FeCl$_2$, CuCl$_2$ or HCl (entries 2–4). Other Lewis acids such as ZnCl$_2$, CoCl$_2$, and MnCl$_2$ exhibited no catalytic activities.

To our delight, the dehydrative coupling utilizing a NaAuCl$_4$·2H$_2$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$_4$·2H$_2$O with other gold(III) salts such as AuBr$_3$ or HAuCl$_4$·4H$_2$O led to similar yields of **3a** (entries 6 and 7). However, AuCl$_3$ 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$_6$H$_4$-*m*-SO$_3$Na)$_3$ (TPPTS),[17] 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 PPh$_3$ (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.
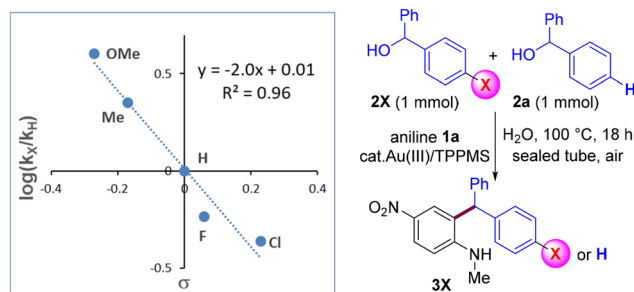
Next, we explored the reaction scope of anilines **1** capable of yielding the C-benzylated product **3**. Aniline bearing an electron-withdrawing cyano group was a suitable substrate, leading to the formation of C-benzylated aniline **3i** in excellent yield (98%). Advantageously, using allylic alcohol **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-*m*-toluidine 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 **3o** in excellent yield. This is likely due

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Scheme 2 Substrate scope for the dehydrative Friedel–Crafts benzylation.

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).[18] Hammett plots were obtained against $\log(k_X/k_H)$ and the substitution constant σ_p and showed a linear slope ($R^2 = 0.96$) with a ρ value of −2.0. The negative slope indicates the involvement of a charged transition state in which the positive charge is stabilized inductively.[19] Therefore, the presence of electron-donating 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†).[20] 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**.
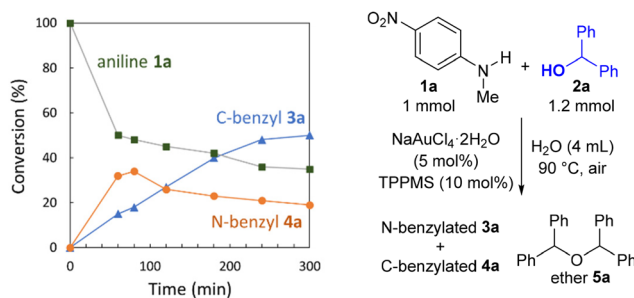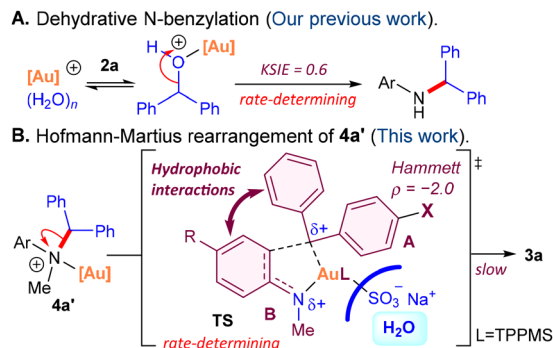
to increased steric hindrance around the nitrogen atom, which promotes the cleavage of the C–N bond and enhances the rearrangement reaction. The reaction of N-alkylaniline **1p** with an alcohol moiety afforded C-benzylated product **3p** and C,O-dibenzylated product **3p'** in 54% and 26% yields, respectively.

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

Scheme 4 Control experiments.

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.[21] 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_2O and D_2O 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_{H_2O}/k_{D_2O}) of 0.6,[19] 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_2O and D_2O (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.[22]

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 sp³ 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
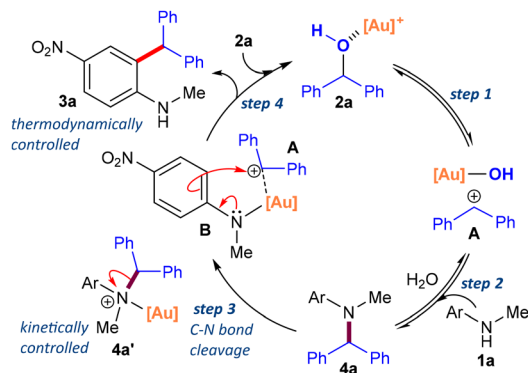
the thermodynamically controlled product. Furthermore, the gold(III) complex **B** reacts with water as a solvent to regenerate aniline **1a**. No dibenzylated product **6** was obtained from *N*-benzylaniline **4a** and alcohol **2a** (Scheme 4B), nor did direct *C*-benzylation of *N*,*N*-dimethylaniline **7** occur (Scheme 4C).[23] 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 sp³ 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 sp³ 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 ρ 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 by the Hofmann–Martius rearrangement of the resulting N-benzylated intermediates.

Experimental

General procedure

A mixture of anilines **1** (1 mmol), alcohols **2** (1.2 mmol), NaAuCl$_4$·2H$_2$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$_2$SO$_4$ 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 syn-

thesis 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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