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Short communication

Solid-supported Pt-catalyzed remote C-H etherification of arylamines: A simple and practical approach for the synthesis of aromatic ethers

Junfen Han, Guodong Wang, Jian Sun, Hongshuang Li, Guiyun Duan, Furong Li, Chengcai Xia*

Pharmacy College, Shandong First Medical University, Shandong Academy of Medical Sciences, Taian 271000, China

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ABSTRACT

A simple and practical approach for a direct remote C-H etherification of arylamines with alcohol is developed herein by using a solid-supported Pt catalyst, hence providing a valuable method for the synthesis of aromatic ethers. The catalyst can easily be recovered from the reaction mixture and reused for six times without apparent loss of activity. Control experiments suggest that a radical pathway is involved in this transformation.

1. Introduction

Aromatic ethers are an important class of compounds that widely exist in pharmaceuticals, natural products and novel materials (Scheme 1a) [1–3]. Therefore, there has been an increasingly urgent need for the development of simple and practical approaches for the synthesis of aromatic ethers. The traditional access to these compounds needs the utilization of pre-functionalized starting materials, such as aromatic boric acid or halides, which leads to the generation of stoichiometric wastes [4,5]. To meet the requirements of step- and atom-economy, a transition-metal-catalyzed C-H functionalization strategy has recently been one of the most efficient and straightforward alternatives. In this strategy, the *N*-containing directing groups including pyridine, triazole, nitroso, oxime, cyano, *N*-methoxy amide, (pyridin-2-yl)isopropyl amine and 8-aminoquinoline are commonly used to make the formation of the C—O bond more feasible [6–9].

Since the pioneering investigation of Daugulis et al. [10], picolinamide (PA) has become one of the commonly used *N*-containing directing groups for the modification of arylamines through C—H functionalization [11–20]. By using this strategy, C—C, C—N, and C—S bond formation has already been into use thus far and has had a major impact in the area of organic synthesis. By contrast, the use of the C—O bond formation reaction remains scarce. In 2018, Punniyamurthy et al. achieved Cu-catalyzed *peri* C—H etherification of naphthylamine through the oxidative addition-reductive elimination mechanism (Scheme 1b, 1) [21]. Very recently, Zhang et al. reported a homogeneous Pt-catalyzed C—H methoxylation of arylamines through a radical mechanism (Scheme 1b, 2) [22]. Despite these considerable advances, the metal catalysts used in these reactions are unrecoverable, which led researchers to develop more valuable catalytic systems for remote C—H etherification.

In recent years, the development of heterogeneous catalysts for C—H functionalization is highly desirable because of the potential advantages such as the easy removal of catalyst from the reaction mixture and the possibility to reuse the catalysts [23–27]. In particular, the generation of C—O bond by heterogeneously catalyzed C—H functionalization is increasingly significant. In 2015, the Cohen et al. reported a C—H bond etherification of benzo[*h*]quinoline using a metal-organic framework-supported Pd catalyst [25]. Subsequently, Ellis et al. demonstrated a C—H bond etherification of benzo[*h*]quinoline with a multiwall carbon nanotube-supported Pd catalyst [26]. These works prove the feasibility of developing heterogeneous catalytic systems for the synthesis of aromatic ethers.

Recently, our research interests focus on the development of novel strategies for the modification of arylamines assisted by PA [13,17]. In addition, we have achieved selective C—H monomethoxylation and trimethoxylation of 8-aminoquinoline [28]. Depending on this background, we reported solid-supported platinum-catalyzed remote C—H etherification of arylamines, providing a simple and practical approach for the synthesis of aromatic ether (Scheme 1c). To the best of our knowledge, this methodology has not yet been achieved.

2. Results and discussion

We started the experiment with reaction of amide (**1a**), with PhI$(OAc)_2$ as the oxidant in methanol (MeOH) at room temperature by using Pd/SiO_2 as a catalyst; the target product **2a** was generated in 29% yield (Table 1, entry 1). Subsequently, other catalysts such as Pt/SiO_2,

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* Corresponding author.
E-mail address: xiachc@163.com (C. Xia).

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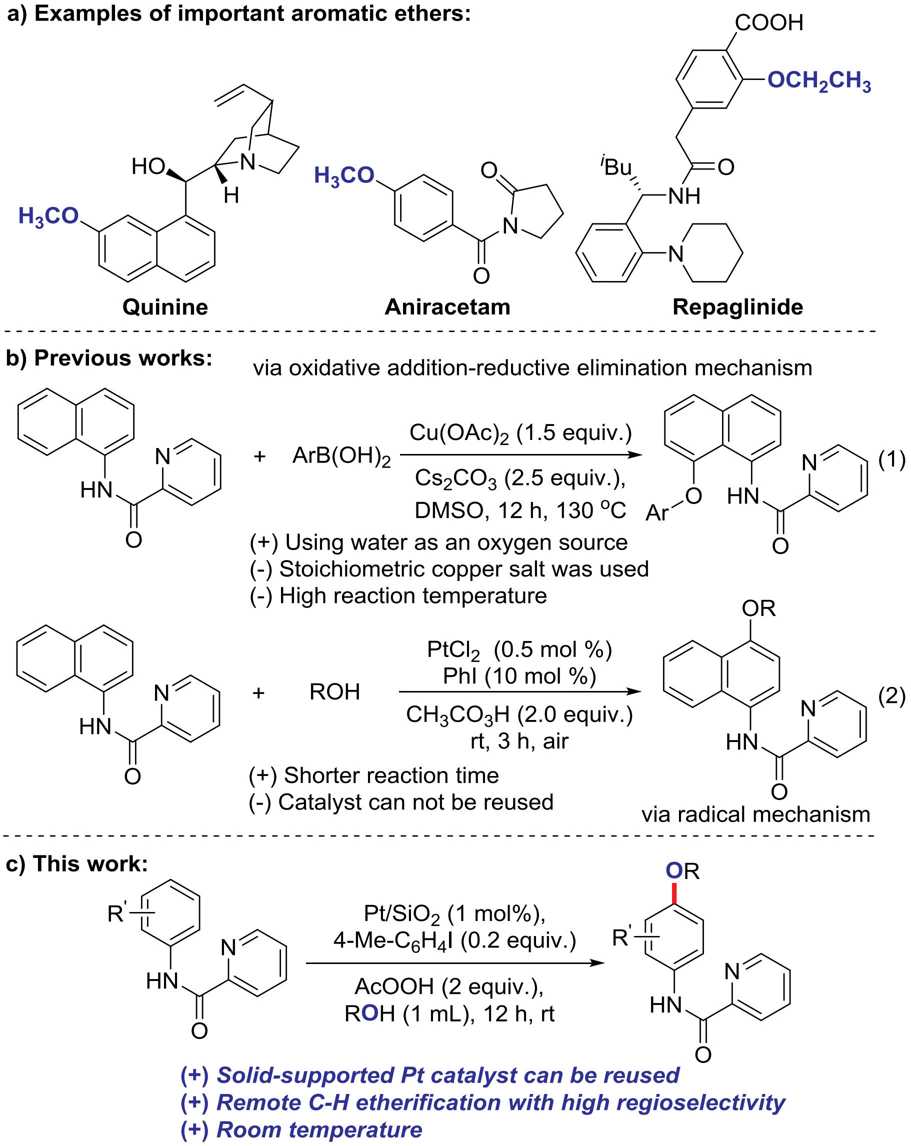


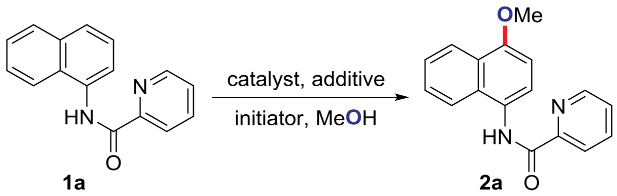
Scheme 1. Examples of important aromatic ethers (a); previous works (b); our strategy (c)

Ru/SiO_2, and Cu/SiO_2 were studied (Table 1, entries 2–4). We found that, the yield of product **2a** was improved to 69% when Pt/SiO_2 was used as the catalyst (Table 1, entry 2). No desirable product was observed by adding only SiO_2 powder into the reaction mixture, which indicated that the transition metals played an important role in this transformation (Table 1, entry 5). Presently, the synthesis of hypervalent iodine reagent has been well studied; it could be generated *in situ* from aryl iodide in the presence of an oxidant [29]. Therefore, some aryl iodides and oxidants were investigated. First, when iodobenzene was used as the additive, some oxidants such as $K_2S_2O_8$, *meta*-chloroperbenzoic acid (*m*-CPBA), *t*-butylhydroperoxide (TBHP), H_2O_2, and AcOOH were studied, and only *m*-CPBA and AcOOH could promote the reaction, resulting in target product **2a** in 31% and 59% yield, respectively (Table 1, entries 6–11). After determining the optimal oxidant, we further studied the additives (Table 1, entries 12–16) and found that higher yield of product **2a** was obtained when 1-iodo-4-methylbenzene was employed as the additive (Table 1, entry 13). Further studies in reaction temperature and atmosphere did not enhance the product yield (Table 1, entries 17 and 18). It is worth noting that the reaction also proceeds well when $PtCl_2$ was used as the catalyst. This result proved that Pt was the catalytic species (Table 1, entry 19).

After determining the optimal reaction conditions, we subsequently tried to determine a better directing group for the synthesis of aromatic ethers (Table 2). Therefore, some aromatic amides, which were synthesized by the amidation of 1-naphthylamine with various aromatic carboxylic acids, were used as reactants. We found that the substrate with a PA group could be converted to product **2a** in 81% yield, and substrates with other *N*-containing directing groups were transformed into corresponding products (**2b–f**) in lower yields. In addition, substrates without *N*-containing directing group (**2g** and **2h**) showed no reactivity under standard conditions. These results suggested that the N atom of pyridine moiety played a significant role in this transformation. Finally, we chose PA as the directing group for this reaction.

Subsequently, a variety of aromatic amides with different substituent groups were studied (Table 3). Amide derivatives bearing different functional groups could undergo the methoxylation reaction smoothly, providing corresponding products in moderate to good yields. The electronic effect has little effect on this reaction; for example, compared with halo- and phenyl-substituted amide derivatives (**2k**, **2l**, **2o**, **2p**), methyl, methoxyl, and nonsubstituted amide derivatives (**2i**, **2j**, **2m**, **2n**, **2q**) could afford the target products in higher yields. In addition, the reactivity of phenylamine derivatives (**2m–q**) was relatively lower than that of naphthylamine derivatives (**2i–l**). Similarly, ethoxylation reaction could also be performed efficiently when

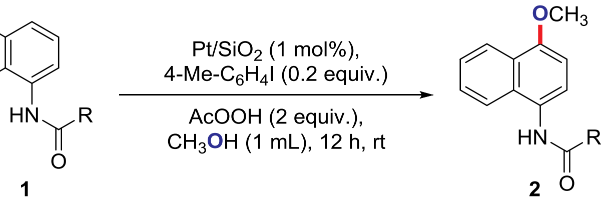
Table 1
Screening of reaction conditions[a].

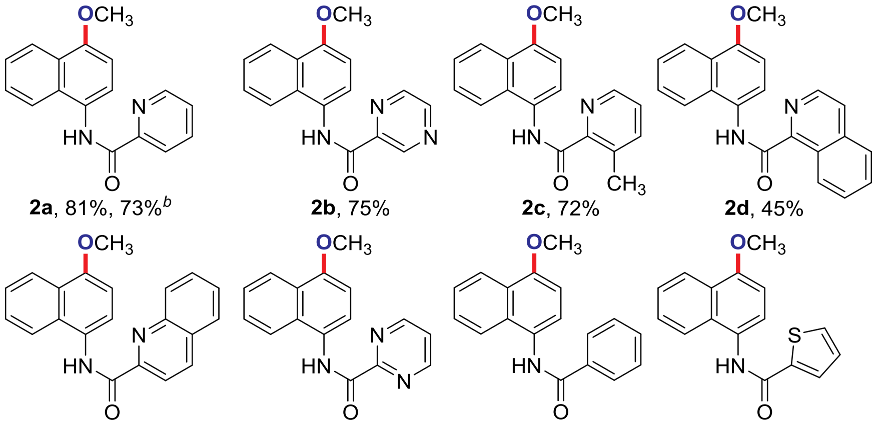


Entry	Catalyst	Additive	Oxidant	Yield [%][b]
1	Pd/SiO$_2$	–	PhI(OAc)$_2$	29
2	Pt/SiO$_2$	–	PhI(OAc)$_2$	69
3	Ru/SiO$_2$	–	PhI(OAc)$_2$	trace
4	Cu/SiO$_2$	–	PhI(OAc)$_2$	trace
5	SiO$_2$	–	PhI(OAc)$_2$	0
6	Pt/SiO$_2$	–	–	0
7	Pt/SiO$_2$	C$_6$H$_5$I	K$_2$S$_2$O$_8$	trace
8	Pt/SiO$_2$	C$_6$H$_5$I	*m*-CPBA	31
9	Pt/SiO$_2$	C$_6$H$_5$I	TBHP	trace
10	Pt/SiO$_2$	C$_6$H$_5$I	H$_2$O$_2$	trace
11	Pt/SiO$_2$	C$_6$H$_5$I	AcOOH	59
12	Pt/SiO$_2$	C$_6$F$_5$I	AcOOH	22
13	Pt/SiO$_2$	4-Me-C$_6$H$_4$I	AcOOH	81
14	Pt/SiO$_2$	4-Br-C$_6$H$_4$I	AcOOH	65
15	Pt/SiO$_2$	4-F-C$_6$H$_4$I	AcOOH	43
16	Pt/SiO$_2$	4-MeO-C$_6$H$_4$I	AcOOH	70
17[c]	Pt/SiO$_2$	4-Me-C$_6$H$_4$I	AcOOH	79
18[d]	Pt/SiO$_2$	4-Me-C$_6$H$_4$I	AcOOH	80
19	PtCl$_2$	4-Me-C$_6$H$_4$I	AcOOH	82

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (loading 1 mol%), additive (0.2 equiv.), oxidant (2 equiv.), MeOH (1 mL), stirred at room temperature for 12 h.
[b] Isolated yields.
[c] Stirred at 70 °C. [d] Under N$_2$ atmosphere.

Table 2
Investigation of the directing group[a].





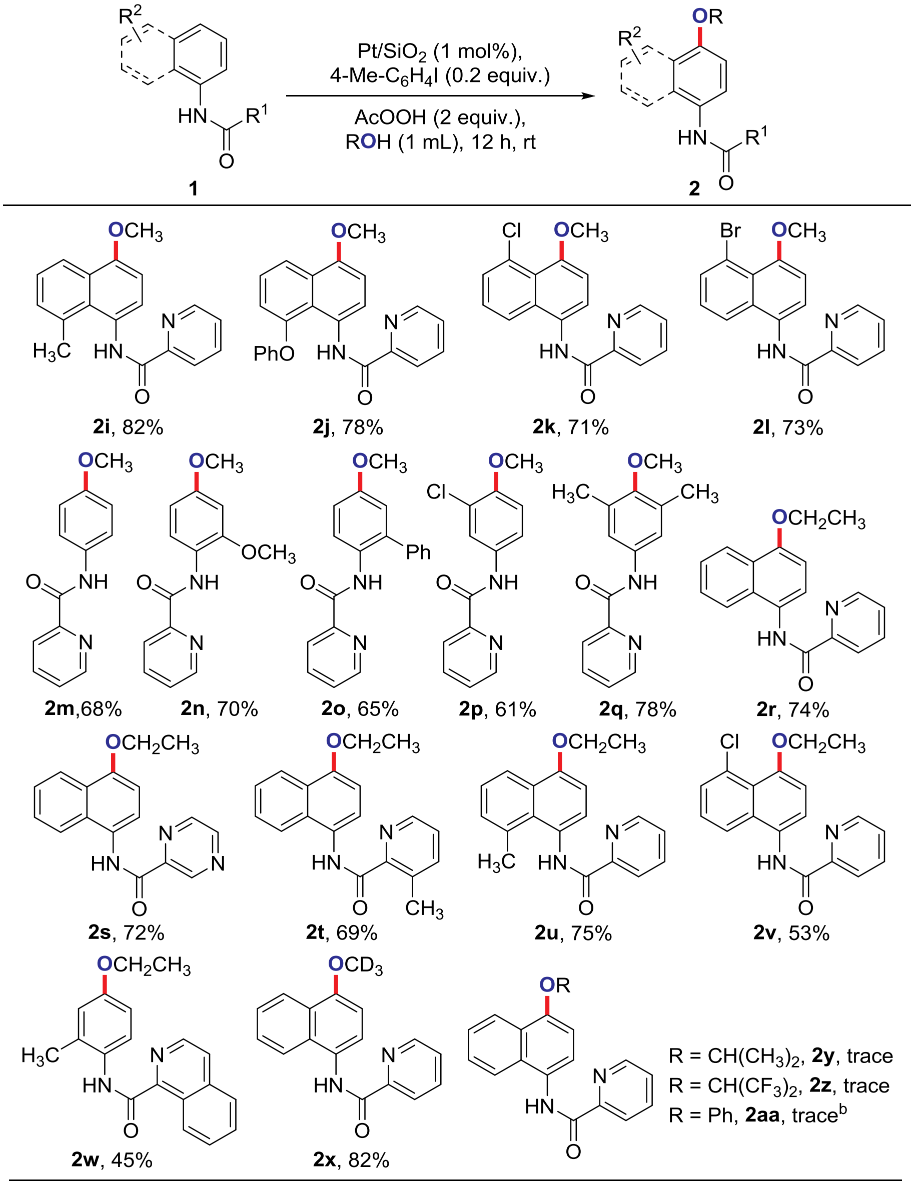
2a, 81%, 73%[b] **2b**, 75% **2c**, 72% **2d**, 45%

2e, 61% **2f**, 55% **2g**, 0% **2h**, 0%

[a]Reaction conditions: **1** (0.2 mmol), Pt/SiO$_2$ (loading 1 mol%), 4-Me-C$_6$H$_4$I (0.2 equiv.), AcOOH (2 equiv.), CH$_3$OH (1 mL), stirred at room temperature for 12 h, isolated yields. [b] gram-scale synthesis (5 mmol of **1a** was used).

methanol (CH$_3$OH) was replaced by ethanol (CH$_3$CH$_2$OH), giving the corresponding products (**2r–w**) in moderate to good yields. When deuterated methanol was employed as the solvent, product **2**× was generated in 82% yield, highlighting that this method is a useful tool for the synthesis of deuterated compounds, which is common in new pharmaceuticals. Unfortunately, the reaction could not occur when

Table 3
Substrate scope[a].



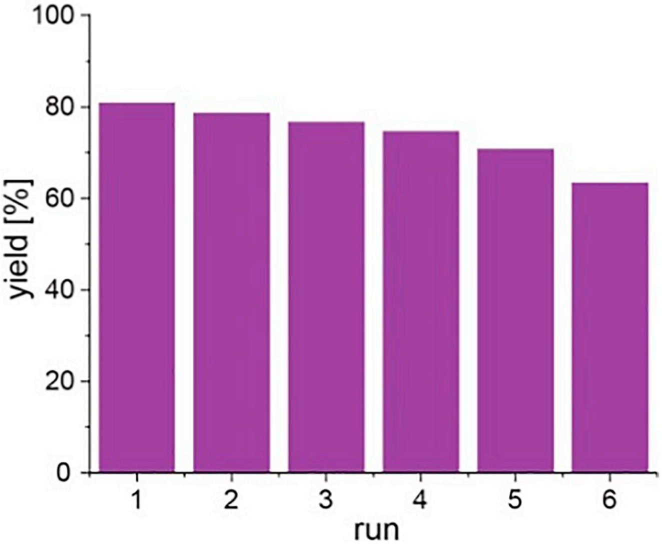
[a]Reaction conditions: **1** (0.2 mmol), Pt/SiO_2 (loading 1 mol%), 4-Me-C_6H_4I (0.2 equiv.), AcOOH (2 equiv.), ROH (1 mL), stirred at room temperature for 12 h, isolated yields. [b] Stirred at 70 °C.

isopropanol ($(CH_3)_2CHOH$), hexafluoroisopropanol ($(CF_3)_2CHOH$), or phenol (PhOH) was used as the solvent and reactant. We suspected that the large steric hindrance of these reactants prevented this transformation.

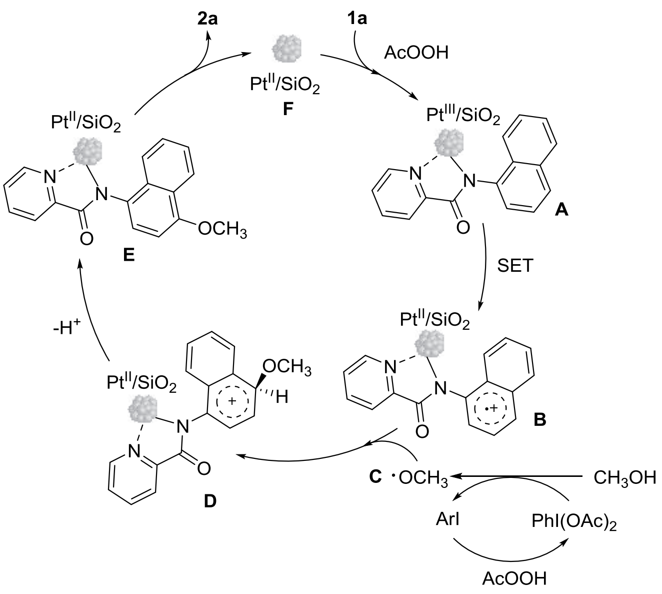
Then, gram-scale synthesis was performed, resulting in the final product **2a** in 73% yield (Table 2). This result demonstrated that this method has potential application prospect in organic synthesis. Furthermore, the application value of the solid-supported Pt catalyst was emphasized by its facile recovery and reuse after the reaction. Even after performing six times of recycling experiments, the catalytic activity of the solid-supported Pt catalyst remained stable (Scheme 2).

The reaction mechanism was subsequently investigated (Scheme 3). First, some analogues (**1n–p**) of substrate **1a** were employed as the starting material. However, no product was obtained. This result further indicated that the N of pyridine and amide group with free NH was indispensable in this reaction (Scheme 3a). The reaction was suppressed if TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) (Scheme 3b) or DPE (1,1-diphenyl ethylene) (Scheme 3c) was used as the radical inhibitor. Furthermore, adduct (**II**) was detected by high-resolution mass spectrometry (HRMS). These results suggest that a radical pathway is involved in the reaction. The kinetic isotope effect experiment was also performed; the low ratio (k = 1.14) indicated that the O—H bond cleavage process was not the rate-determining step (see Supporting Information, Scheme S1). In addition, the reaction with the solution after hot filtration at approximately 50% yield essentially stopped, strongly suggesting that the active catalytic species exist in the heterogeneous substance (Fig. S1) [30]. This conclusion is strengthened by the Hg(0) poisoning test (Scheme 3d). After this, the reaction kinetics were measured. It was observed that similar plots were obtained for the reactions under different stirring speeds (Fig. S2).

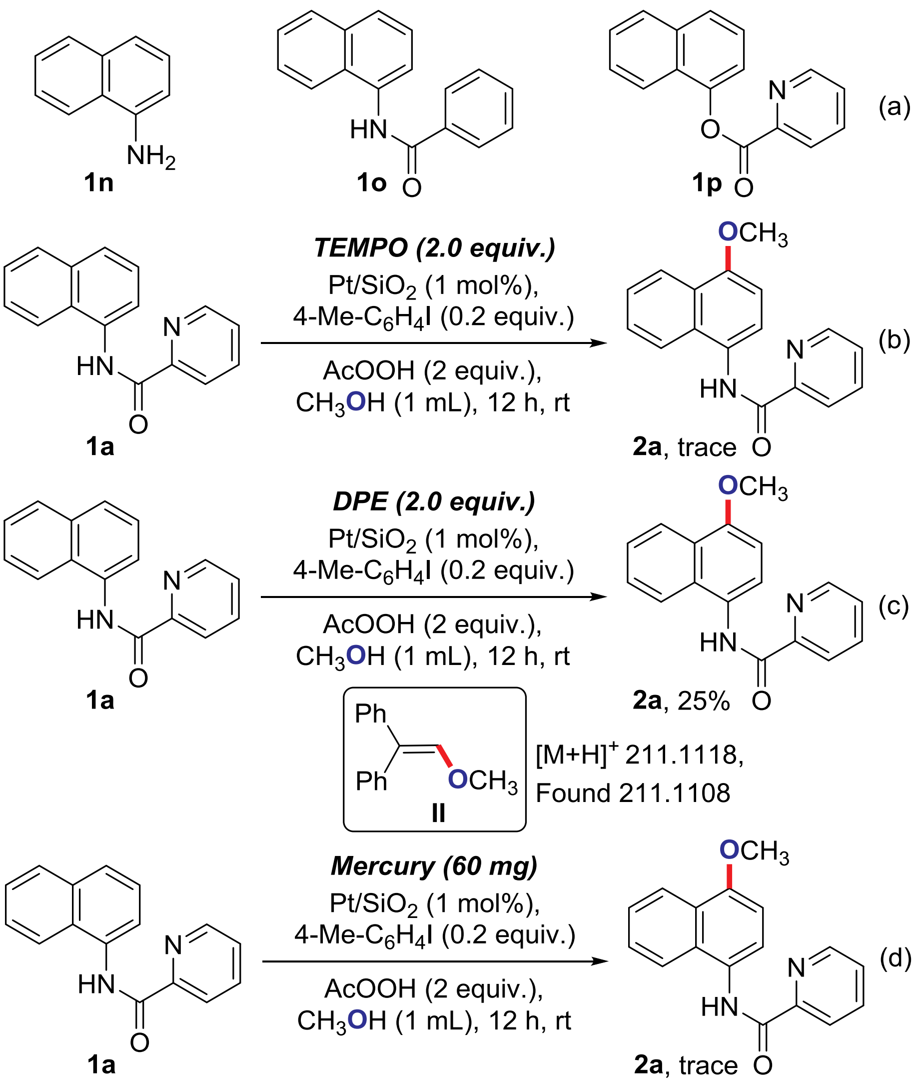
Finally, a possible mechanism for the reaction of solid-supported Pt-catalyzed remote C—H etherification of arylamines was proposed



Scheme 2. Recycling and reuse of the catalyst Pt/SiO$_2$



Scheme 4. Plausible mechanism



Scheme 3. Investigation of the mechanism

(Scheme 4) [16–20,22]. First, substrate **1a** coordinated with Pt^{II}/SiO_2 to form complex (**A**) in the presence of AcOOH. Subsequently, complex (**A**) was converted to complex (**B**) through the single-electron transfer process between amide and the solid-supported Pt catalyst. Further, methoxyl radical (**C**) was generated from methanol in the presence of the *in situ*-formed hypervalent iodine reagent, which attacked complex (**B**) to produce complex (**D**). After the generation of complex (**E**) through deprotonation of complex (**D**), the final product **2a** was obtained through a metal dissociation process.

3. Conclusion

In summary, we have demonstrated a solid-supported Pt-catalyzed strategy for direct remote C—H etherification of arylamines by using alcohol as an alkoxy source, thereby producing desirable products in moderate to good yields. This methodology provided a useful tool for the efficient synthesis of aromatic ethers. Control experiments suggested that there was a radical pathway underlying this reaction.

4. Experimental section

4.1. General information

All the chemicals were obtained commercially and used without any prior purification. All products were isolated by short-column chromatography on a silica gel (200–300 mesh) using petroleum ether (60–90 °C) and ethyl acetate. ^1H and ^{13}C NMR spectra were recorded using a Bruker Advance 500 spectrometer at ambient temperature, with $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. TEM tests were performed using a JEOL transmission electron microscope. Elemental information was recorded by X-ray photoelectron spectroscopy (XPS). The Pt content of Pt/SiO_2 was determined using an inductively coupled plasma optical emission spectrometer (ICP-OES) (Shimadzu, OPTIMA 2100 DV). Analytical thin-layer chromatography (TLC) was performed using Merck precoated TLC (silica gel 60 F_{254}) plates.

4.2. Catalyst preparation and characterization

The Pt/SiO_2 catalyst was prepared according to a modified literature procedure [31,32]. $H_2PtCl_6{\cdot}6H_2O$ (85 mg) was dissolved in distilled water (5 mL) under ultrasonication for 15 min in a beaker. A homogeneous solution was obtained. Then, other reagents such as ethanol (20 mL) and tetraethyl orthosilicate (20.8 g) were added to the solution under vigorous stirring. Then, the mixture was stirred at 338 K until a solid gel was obtained. After aging at room temperature for 12 h, the obtained xerogel was dried at 343 K for 6 h, 373 K for 6 h, and 393 K for 4 h. Finally, the catalyst precursor was calcined at 673 K in air for 4 h to obtain the final catalyst. Pd/SiO_2, Ru/SiO_2, and Cu/SiO_2 were also prepared in the same way as that for Pt/SiO_2. The Pt/SiO_2 catalyst was characterized before and after the reaction by Brunauer–-Emmett–Teller (BET) surface area analysis (Table S1). The dispersion of the Pt/SiO_2 catalyst before and after the reaction was observed by transmission scanning electron microscopy (TEM) (Fig. S3), where no significant changes were observed. The Pt content was found to be 0.5%, which was determined using an ICP-OES. XPS showed that Pt nanoparticles existed as PtO on the SiO_2 support (Fig. S4) [33–35].

4.3. General procedure for the synthesis of product 2

Amide **1** (0.2 mmol), Pt/SiO_2 (loading 1 mol%), 4-Me-C_6H_4I (0.2 equiv.), AcOOH (2 equiv.), and ROH (1 mL) were added into a reaction tube. The mixture was then stirred for 12 h at room temperature. After the conversion was completed, the catalyst was filtered off and the filtrate was poured into water (5 mL), extracted with EtOAc (5 mL × 3), and dried with Na_2SO_4, and the solvent was removed under reduced pressure. Product **2** was purified by flash column chromatography using PE/EtOAc as an eluent.

4.4. General procedure for the gram-scale synthesis of product 2a

Amide **1** (5 mmol), Pt/SiO_2 (loading 1 mol%), 4-Me-C_6H_4I (0.2 equiv.), AcOOH (2 equiv.), and ROH (20 mL) were added into a reaction flask. The mixture was then stirred for 12 h at room temperature. After the conversion was completed, the catalyst was filtered off and the filtrate was poured into water (50 mL), extracted with EtOAc (25 mL × 3), and dried with Na_2SO_4, and the solvent was removed under reduced pressure. Product **2a** was purified by flash column chromatography using PE/EtOAc as an eluent.

4.5. Catalyst recycling experiment

Amide **1a** (0.2 mmol), Pt/SiO_2 (loading 1 mol%), 4-Me-C_6H_4I (0.2 equiv.), AcOOH (2 equiv.), and CH_3OH (1 mL) were added into a reaction tube. The mixture was then stirred for 12 h at room temperature. After conversion was completed, the catalyst was filtered off, washed with ethyl acetate and water twice, and then dried for 12 h at 65 °C. Then, the catalyst was reused for the subsequent reaction.

4.6. General procedure for radical suppression experiment

Following the synthetic procedure for product **2a**, the reaction of amide **1a** (0.2 mmol) was performed in the presence of Pt/SiO_2 (loading 1 mol%), 4-Me-C_6H_4I (0.2 equiv.), AcOOH (2 equiv.), and TEMPO or DPE (2 equiv.) in CH_3OH (1 mL) for 12 h at room temperature.

4.7. General procedure for mercury poisoning experiment

Following the synthetic procedure for product **2a**, the reaction of amide **1a** (0.2 mmol) was performed in the presence of Pt/SiO_2 (loading 1 mol%), 4-Me-C_6H_4I (0.2 equiv.), AcOOH (2 equiv.), and mercury (60 mg) in CH_3OH (1 mL) for 12 h at room temperature.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.catcom.2019.105722.

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