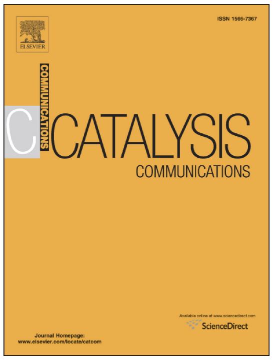

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PII: S1566-7367(18)30557-0
DOI: doi:10.1016/j.catcom.2018.10.026
Reference: CATCOM 5537

To appear in: *Catalysis Communications*

Received date: 28 July 2018
Revised date: 24 October 2018
Accepted date: 25 October 2018

Please cite this article as: Qian-Qian Chen, Hui-Xian Zhang, Jian-Xin Yang , Pd(OAc)2-catalyzed synthesis of benzyl phenyl ether derivatives with H2O2 as an oxidant in neat water. Catcom (2018), doi:10.1016/j.catcom.2018.10.026

Pd(OAc)$_2$-catalyzed synthesis of benzyl phenyl ether derivatives with H_2O_2 as an oxidant in neat water

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Abstract

A new protocol for Pd(OAc)$_2$-catalyzed reactions of different benzyl bromides and various arylboronic acids has been developed to form functionalized benzyl phenyl ethers. This method represents the first instance where arylboronic acid is used as a reaction substrate for benzyl phenyl ether synthesis with H_2O_2 as the green oxidant under atmospheric oxygen and pure H_2O as an environmental friendly solvent without the requirement for phosphine- and N-based ligands, remarkable functional group tolerance, and considerable yield.

Keywords: Pd(OAc)$_2$ catalyst, arylboronic acid, benzyl phenyl ethers, H_2O_2, H_2O

1. Introduction

Benzyl phenyl ethers are important building blocks in pharmaceuticals, as well as in biologically active compounds. Benzyl phenyl ether diamidines with trypanocidal activity [1], benzyl phenyl ether diamidine derivatives with antiprotozoal activity [2], benzyloxybenzaldehyde derivatives with anticancer activity [3], and benzyloxyacetophenone derivatives as inhibitors of monoamine oxidase B [4] are highly in demand for various synthetic approaches toward benzyl phenyl ether derivatives.

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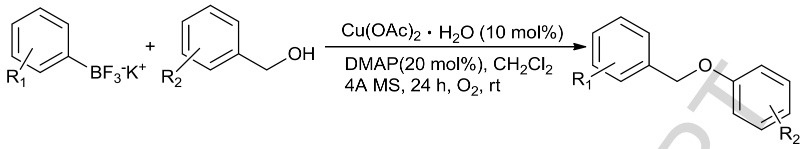
The most conventional approach to synthesize benzyl phenyl ether derivatives is phenol benzylation, which was first reported by McKillop by using dichloromethane as a solvent in 1974 [5]. Various synthetic strategies have been developed for the efficient synthesis of benzyl phenyl ether derivatives. These synthetic strategies include the use of crown ethers [6], phase-transfer catalysis [7-8], ionic liquids [9], etc. [10]. However, the use of high temperature and strong base as well as toxic, volatile, and flammable organic solvent significantly decreases the appeal of these strategies. In C-O ether bond formation, Pd- or Cu-catalyzed etherifications of alcohols or phenols with organometalloid reagents, such as organo-Bi [11], -Sn [12], and -B [13-15], have received considerable attention. The advantages of organoboron reagents, such as low toxicity, tolerance toward various functional groups, availability, inert properties toward H_2O and oxygen [16], and the synthesis of benzyl phenyl ether derivatives from the catalytic coupling of organoboron compounds with benzyl alcohols, have been reported by Batey [17]. This reaction is limited by the fact that 10% of $Cu(OAc)_2$ and 20% of ligand are required, and dichloromethane is used as a solvent (Scheme 1). Consequently, the development of economical, accessible, and low catalytic amount of ligand-free Pd(II) catalytic systems for the synthesis of benzyl phenyl ethers is urgently needed. Water is also the leading candidate in the synthesis of benzyl phenyl ether derivatives because of its low cost, nonflammability, nontoxicity, and low environmental concerns [18]. Herein, we report the first $Pd(OAc)_2$-catalyzed reaction that uses benzyl halides as coupling partners by using arylboronic acids as the aryl source and H_2O_2 as the green oxidant for the synthesis of benzyl phenyl ethers under atmospheric oxygen in pure H_2O (Scheme 2). Although this new protocol is less cost effective than the well-established phenol benzylation with benzyl halides, benzyl alcohol coupling with aryl halide, and the

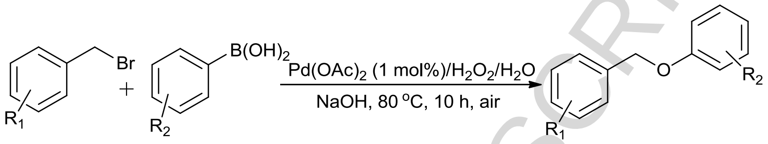
Chan-Lam-Evans coupling of benzyl alcohol and arylboronic acid for benzyl phenyl ether synthesis, the current system represents a novel alternative to the existing methodologies and can be useful for the synthetic literature.

Batey's work [17]:



Scheme 1

Our work:



Scheme 2

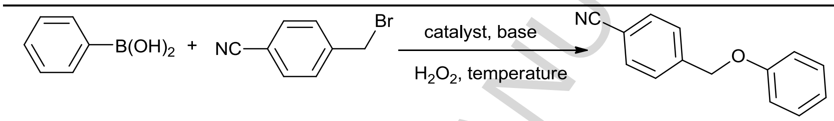
2. Results and discussion

2.1 Optimization of the reaction conditions

4-Cyanobenzylbenzyl bromide and phenylboronic acid were first examined as standard substrates in the presence of a catalytic amount of Pd(OAc)$_2$ by using H_2O_2 (30% aq.) as the oxidant under atmospheric oxygen in pure H_2O. After stirring for 10 h in 80 °C oil bath, a yield of 85% 4-(phenoxymethyl)benzonitrile was obtained with 1 mol% Pd(OAc)$_2$ and 0.2 mL of H_2O_2 (Table 1, Entry 2). Then, the effect of the amount of H_2O_2 on the reaction was examined. Increasing the amount of H_2O_2 from 0.1 mL to 0.3 mL (Table 1, Entries 1-3) decreased the yield, along with 4-(phenoxymethyl)benzonitrile. Small amounts of the corresponding phenol, 4-cyanobenzyl alcohol, 4-cyanobenzaldehyde, biphenyl, and 4-benzylbenzonitrile were detected by GC-MS. Changing the amount of Pd(OAc)$_2$ to 1.2 mol% showed insignificant effect on yield (Table 1, Entry 5). For the further optimization of the reaction conditions with certain amounts of Pd(OAc)$_2$ and H_2O_2 fixed at 1 mol% and 0.1 mL, respectively, survey on the role of bases for this reaction showed that NaOH was the most suitable base (Table 1, Entry 1). KOH and Cs_2CO_3 were also the appropriate choices and resulted in 83% and 85% yields, respectively (Table 1, Entries 6-7). Other bases, such as Na_2CO_3, K_2CO_3, and NEt_3, only obtained yield of the desired product ranging from 57% to 69% (Table 1, Entries 8-10). Decreasing the reaction temperature to 25 °C decreased the yield to 43%, and increasing the temperature to 100 °C showed insignificant effect on yield (Table 1, Entries 11-13). Prolonging the reaction time from 5 h to 15 h (Table 1, Entries 14-15) resulted in the highest yield of the desired product for 10 h (Table 1, Entry 1).

Table 1

Optimization of the reaction conditions[a]



Entry	H_2O_2 (mL)	Base (0.8 mmol)	Pd(OAc) (mol%)	Temperature (°C)	Time (h)	Yield[b] (%)
1	0.1	NaOH	1.0	80	10	89
2	0.2	NaOH	1.0	80	10	85
3	0.3	NaOH	1.0	80	10	56
4	0.1	NaOH	0.5	80	10	71
5	0.1	NaOH	1.2	80	10	90
6	0.1	KOH	1.0	80	10	83
7	0.1	Cs_2CO_3	1.0	80	10	85
8	0.1	NEt_3	1.0	80	10	69
9	0.1	Na_2CO_3	1.0	80	10	57
10	0.1	K_2CO_3	1.0	80	10	64
11	0.1	NaOH	1.0	25	10	43
12	0.1	NaOH	1.0	60	10	78
13	0.1	NaOH	1.0	100	10	87
14	0.1	NaOH	1.0	80	5	78
15	0.1	NaOH	1.0	80	15	87

[a] Reaction conditions: 0.5 mmol of 4-cyanobenzylbenzyl bromide, 0.6 mmol of phenylboronic acid, 3.0 mL of H_2O, air.

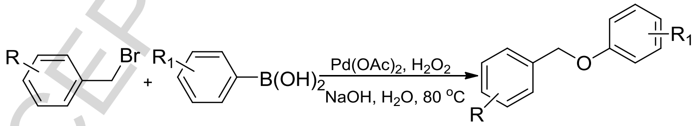
[b] Isolated yield.

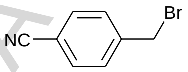
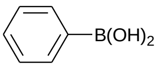
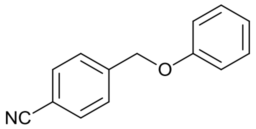
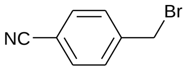
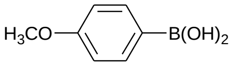
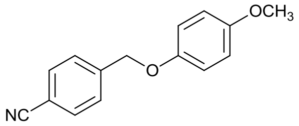
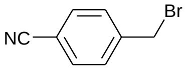
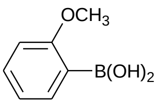
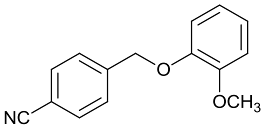
2.2 Scope and limitations of substrates

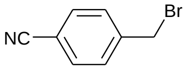
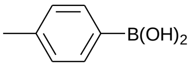
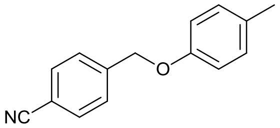
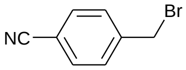
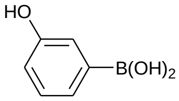
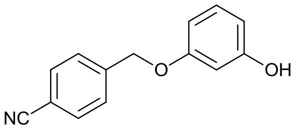
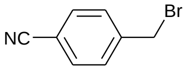
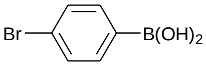
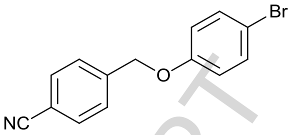
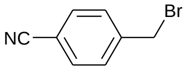
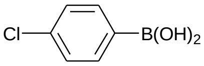
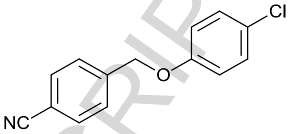
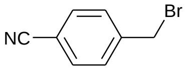
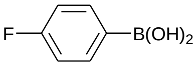
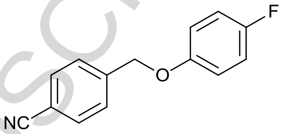
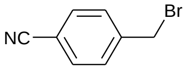
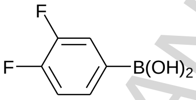
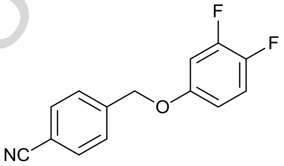
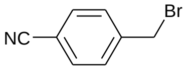
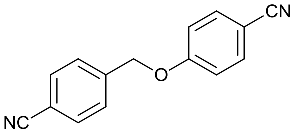
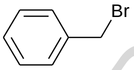
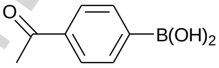
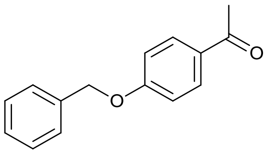
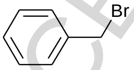
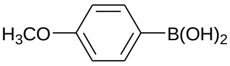
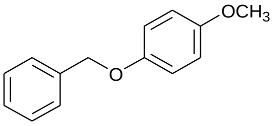
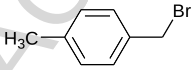
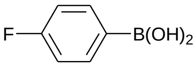
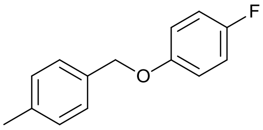
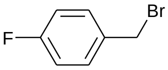
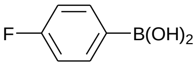
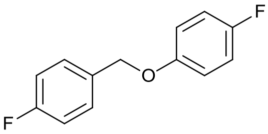
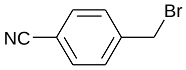
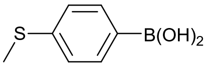
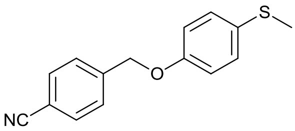
In order to clarify the scope and limitations of this reaction, we conducted a series of reactions of different benzyl bromides and various arylboronic acids under optimized conditions. As shown in Table 2, the substituted arylboronic acids examined bearing electron-donating or -withdrawing groups on either *ortho*-, *metra*-, or *para*-position and reacted readily with 4-cyanobenzylbenzyl bromide to obtain considerable yield of the corresponding benzyl phenyl ethers. (Table 2, Entries 2-10), *Ortho*-substituted arylboronic acids increased the effectivity of the reaction with the isolated yield of 74% because steric hindrance prevented the self-coupling of arylboronic acid identified by GC-MS (Table 2, Entry 3). Then, the substituted benzyl bromides were investigated. Compared with the reactions of benzyl bromides with minimal electron-withdrawing or -donating groups, such as fluro and methyl group with 4-flurophenylboronic acid (Table 2, Entries 13-14), benzyl bromides with strong electron-withdrawing or -donating groups, such as cyano and methoxy group, were the suitable substrates to obtain high yields (Table 2, Entry 8). When arylboronic acid with sensitive functional group, such as thioether group, reacted with 4-cyanobenzylbenzyl bromide under oxidation condition, the yield of the desired product also increased up to 83% (Entry 15).

Table 2

Pd(OAc)$_2$-catalyzed synthesis of benzyl phenyl ether derivatives: Substrate scope[a]



Entry	Benzyl bromides	Arylboronic acids	Products	Yield[b]
1				89
2				72
3				74

4				74
5				71
6				80
7				83
8				85
9				82
10				92
11				85
12				81
13				68
14				66
15				83

[a] Reaction conditions: conducted with 0.5 mmol of benzyl bromide, 0.6 mmol of arylboronic acid, 1 mol% $Pd(OAc)_2$, 0.1 mL of H_2O_2, 0.8 mmol of NaOH, 3.0 mL of H_2O at 80 °C in the air for 10 h.

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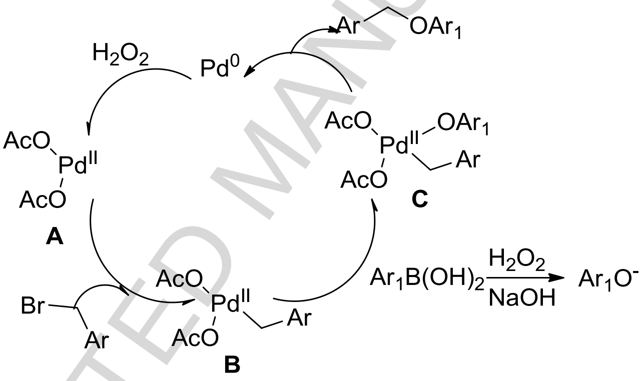
[b] Isolated yield.

A plausible mechanism is envisioned with the aid of previous reports in the literature (Scheme 3). Initially, Pd(OAc)$_2$ **A** was followed by a transmetalation of the benzyl group from benzyl bromide to palladium to form intermediate **B** [19]. Research work by Prakash shows that H_2O_2 equivalents are found to be much safer, convenient, and efficient reagent systems for the *ipso*-hydroxylation of arylboronic acids to the corresponding phenols in high yields at a faster rate [20]. Then, Pd(II) intermediate **C** is produced by the reaction of phenol with intermediate **B**. Reductive elimination ensues to form the products and Pd(0) species, which is then oxidized by H_2O_2 to regenerate the palladium(II) to complete the catalytic cycle.



Scheme 3

3. Experimental

Benzyl bromides, arylboronic acids, and Pd(OAc)$_2$ were obtained commercially from Alfa Aesar and used without further purification. ^{1}H and ^{13}C NMR were recorded on a Bruker Avance III (400 MHz) spectrometer by using tetramethylsilane as the internal standard and $CDCl_3$ as the solvent. All benzyl bromide and arylboronic acid reactions were conducted in air. A reaction tube was charged with 0.5 mmol of benzyl bromide, 0.6 mmol of arylboronic acid, 0.005 mmol of Pd(OAc)$_2$, 0.8 mmol of NaOH, and 3 mL of H_2O. This mixture was added with 0.1 mL of H_2O_2 (30%),,and then the mixture was stirred at 80 °C in the air for 10 h and cooled to room temperature. Then, saturated NH_4Cl was added, and the resulting mixture was extracted with AcOEt (3 × 10 mL). The combined organic layers were dried with Na_2SO_4. The solution was filtered and evaporated in a vacuum, and the residue was purified through flash chromatography (hexane/AcOEt) to obtain the product.

4. Conclusions

We have developed a new and efficient reaction of benzyl bromides and arylboronic acids to generate benzyl phenyl ether derivatives by using ligand-free $Pd(OAc)_2$ as the catalyst and H_2O_2 as the oxidant. The reaction was completed smoothly, and we obtained considerable yields of the corresponding substituted benzyl phenyl ethers. Remarkable advantages of this protocol include the use of H_2O_2 as the green oxidant under atmospheric oxygen and pure H_2O as an environmental friendly solvent without the need for phosphine- and N-based ligands and remarkable functional group tolerance. The described reactions of benzyl bromides and arylboronic acids should be efficient and indicate substantial improvement to the known synthesis methods for benzyl phenyl ethers because of these advantages. Further detailed investigations on this reaction mechanism and synthetic applications are ongoing in our laboratory.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (no. 51663009).

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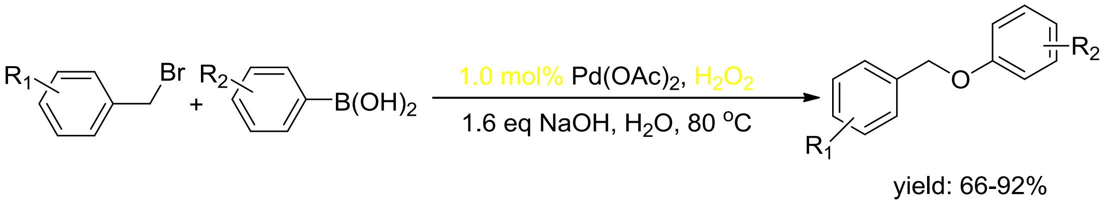

Graphical abstract

Highlights:

1. A new protocol for $Pd(OAc)_2$-catalyzed synthesis of benzyl phenyl ethers.
2. H_2O_2 as the green oxidant.
3. Pure H_2O as an environmentally friendly solvent.
4. Without the requirement for phosphine- and N-based ligands.
5. Remarkable functional group tolerance and considerable yield.