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Palladium/P(t-Bu)$_3$-catalyzed synthesis of aryl t-butyl ethers and application to the first synthesis of 4-chlorobenzofuran

Makoto Watanabe,* Masakazu Nishiyama and Yasuyuki Koie

Yokkaichi Research Laboratory, Tosoh Corporation, 1-8 Kasumi, Yokkaichi, Mie 510-8540, Japan

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Abstract

Pd/P(t-Bu)$_3$ catalyzed reaction of aryl halides with sodium t-butoxide effectively to give aryl t-butyl ethers. The high catalytic activity realized the formation of aryl t-butyl ethers from not only electron-deficient aryl halides but also electron-rich aryl halides. Moreover, the first synthesis of 4-chlorobenzofuran was attained utilizing the selective mono-t-butoxylation of aryl dihalide.

Keywords: alkoxylation; aryl halides; benzofurans; ethers; palladium catalysts.

The palladium-catalyzed carbon–oxygen bond formation from aryl halides with oxygen nucleophilic reagents could be a useful synthetic method for the preparation of aryl ethers, which are important compounds as pharmaceuticals and protected phenols.[1] Although the conventional copper-catalyzed synthesis of aryl ethers were extensively utilized, the harsh reaction conditions and employment of highly polar aprotic solvents such as DMF, HMPA, and DMSO limited the applicability of the methodology.[2]

Recently, palladium-catalyzed formation of aryl ethers was reported by Mann and Hartwig and Buchwald et al.[3] These efforts, however, were mostly successful in reactions employing electron-deficient aryl halides in the presence of a large amount of the catalyst and there are no examples using aryl halides with electron-donating substituents such as a methoxy group. Although they also examined electron-rich bulky phosphine ligands mainly for the preparation of diaryl ethers, the examination of the synthesis of aryl ethers such as aryl t-butyl ethers was quite limited.[4] These reports prompted us to disclose our own results on the synthesis of aryl t-butyl ethers from various aryl halides and sodium t-butoxide using Pd/P(t-Bu)$_3$.

We first demonstrated that a P(t-Bu)$_3$-ligated palladium catalyst gave exceedingly high catalytic activity on animation of aryl halides with piperazine[5a] and diarylamines.[5b] We herein report that this catalytic system is applicable to the synthesis of aryl t-butyl ethers from both electron-deficient and -rich aryl halides (Eq. 1). The synthesis of novel 4-chlorobenzofuran utilizing the catalytic system is also reported.

* Corresponding author. Tel: +81 593 63 1374; fax: +81 593 63 2641; e-mail: m_wata@tosoh.co.jp

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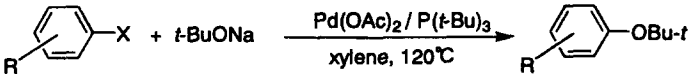


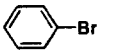
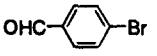
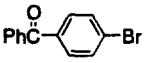
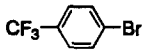
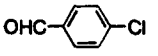
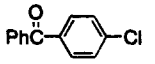
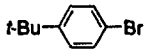
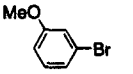
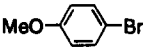
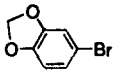
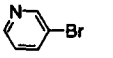
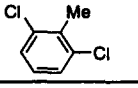
(1)

We investigated the formation of aryl ethers employing a variety of aryl halides with electronically different characters. Reaction of aryl halides with sodium *t*-butoxide was carried out in xylene in the presence of $Pd(OAc)_2$ and $P(t\text{-}Bu)_3$ by heating the mixture (Table 1). The catalytic system was so active that electron-neutral bromobenzene could be consumed in 2 h at 120°C in the presence of 1 mol% of $Pd(OAc)_2$ to afford 89% yield of *t*-butyl phenyl ether (run 1). The ratio of ether:benzene:biphenyl was 95:3:2.[6] Under the same reaction conditions, Pd/PCy_3 and Pd/DPPF were much less reactive, giving 5% yields after 10 h, respectively [PCy_3=tri(cyclohexyl)phosphine, DPPF=1,1′-bis(diphenylphosphino)ferrocene]. Electron-withdrawing substituents such as formyl, benzoyl, and trifluoromethyl greatly accelerated C–O bond formation in the presence of a small amount of the catalyst (runs 2, 3,[7] and 4). Aryl chlorides could also be converted (runs 5[8] and 6). Reaction of *p*-bromo-*t*-butylbenzene afforded the corresponding aryl *t*-butyl ether in both high yield and high selectivity in the presence of 2 mol% of the catalyst (run 7). *m*-Bromoanisole was converted to the desired product in 82% yield (run 8). Whereas the rate of reaction with *p*-bromoanisole decelerated and considerable debromination took place, the aryl ether was obtained in 48% yield (run 9). Even reaction of 1,2-methylenedioxy-4-bromobenzene, which has a strong electron-donating nature, took place (run 10). In this case, the product was isolated as sesamol (3,4-methylenedioxyphenol) after acidic hydrolysis. Furthermore, 3-bromopyridine was converted to 3-*t*-butoxypyridine (run 11). The results shown here are the unprecedented examples of palladium complexes containing both electron-rich aryl groups and *t*-butoxy group undergoing C–O bond-forming reductive elimination.

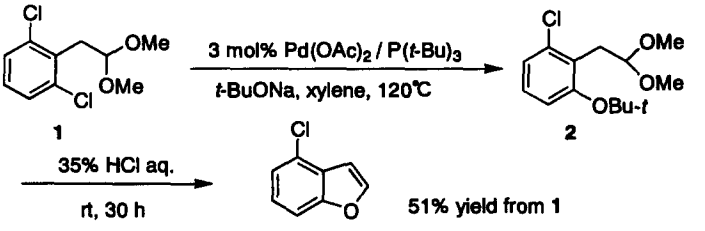
Then, we examined the mono-*t*-butoxylation of 2,6-dichlorotoluene. Reaction employing 1.0:1 ratio of dichlorotoluene:*t*-BuONa gave a 6.8:1 ratio of 2-*t*-butoxy-6-chlorotoluene:2,6-di-*t*-butoxytoluene at 82% conversion of dichlorotoluene. When the ratio of the starting materials was increased to 1.5:1, the product ratio rose to 15.2:1 (run 12). After acidic treatment, 2-hydroxy-6-chlorotoluene was obtained in 64% yield. Although the selectivity of mono-*t*-butoxylation depends mainly on the ratio of reactants, this catalytic system rendered as feasible the selective formation of mono-*t*-butyl ether from aryl dichloride.[9]

The feature of the mono-*t*-butoxylation of 2,6-dichlorotoluene was directed to the synthesis of 4-chlorobenzofuran (Eq. 2). Some halobenzofurans such as 5-chloro- and 7-chlorobenzofuran were prepared by cyclization of phenol derivatives.[10] However, to our knowledge, synthesis of 4-chlorobenzofuran has not been reported due to the difficulty of the synthesis. We chose 2,6-dichlorophenylacetaldehyde dimethylacetal (**1**) as a substrate, which was prepared in 82% yield after distillation by treatment of 2,6-dichlorophenylacetaldehyde[11] with methanol in the presence of 1 mol% of TsOH. Reaction of **1** with 1.1 equivalent of *t*-BuONa gave 9.0:1 ratio of the desired mono-*t*-butoxylated arene **2**/bis-*t*-butoxylated arene at 86% conversion of **1**. Whereas, the formation of the bis-*t*-butoxylated arene was highly suppressed compared with *t*-butoxylation of 2,6-dichlorotoluene, dechlorination of both **1** and **2** occurred, giving 7.5:1 ratio of **2**/dechlorinated products.[12] We examined the acidic hydrolysis of the resulting reaction mixture and found that the use of an excess amount of hydrochloric acid[13] gave 4-chlorobenzofuran in 51% yield from **1**.[14] Because the electron-rich $Pd/P(t\text{-}Bu)_3$ activates unreactive aryl chlorides, 4-chlorobenzofuran is capable of being a versatile synthetic intermediate for various 4-substituted benzofurans by using $P(t\text{-}Bu)_3$-ligated palladium-catalyzed reactions such as amination,[5] Suzuki coupling, and vinylation.[15]

Table 1
Pd/P(*t*-Bu)$_3$-catalyzed synthesis of aryl *t*-butyl ethers[a]

Entry	Aryl halide	Pd(OAc)$_2$/mol%	Time/h	AE/A/B[b]	Yield/%
1		1.0	2	95/3/2	89[c]
2		0.5	1	99.5/0.5/0	91[c]
3		0.5	1	100/0/0	94[c]
4		0.5	1	99/1/0	88[d]
5		1.0	2	95/5/0	60[d]
6		1.0	3	99.5/0.5/0	92[c]
7		2.0	3	94/4/2	85[e]
8		3.0	3	96/2/2	82[c]
9		6.0	8	70/26/4	48[f]
10		3.0	6	71/17/12	20[e]
11		6.0	22	90/4/6	30[f]
12		1.0	2	91/6/3[g]	64[e]

[a]Reaction conditions: Pd(OAc)$_2$/P(*t*-Bu)$_3$ = 1/3, 1 equiv of ArX, 1.2 equiv of *t*-BuONa, 120℃, solvent; xylene.
[b]Aryl ether/Arene/Biaryl. The ratio was determined by GC analysis.
[c]Isolated yield by bulb-to-bulb distillation.
[d]Determined by GC analysis using *n*-butyl phenyl ether as internal standard.
[e]Conc. HCl was added to the crude reaction mixture and stirred for 1d (run 7), 1h (run 10), and 14 h (run 12), and after extractive work-up phenol derivatives were isolated.
[f]Isolated yield by column chromatography on Al_2O_3 (hexane/AcOEt).
[g]*t*-Butoxychlorotoluene/Di-*t*-butoxytoluene/Chlorotoluene.



(2)

In conclusion, a catalytic system consisting of palladium and P(*t*-Bu)$_3$ is shown to be very useful for the coupling of a variety of aryl halides with *t*-butoxide. It is proposed that bulky and electron-rich P(*t*-Bu)$_3$

is responsible for facilitating not only the oxidative addition of aryl halide to palladium but also the reductive elimination from the Pd-complex. Further, the methodology of selective mono *t*-butoxylation of aryl dihalide was extended to the synthesis of novel 4-chlorobenzofuran.

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6. $Pd_2(dba)_3$ showed the same reactivity and selectivity.
7. *t*-Butyl(dimethyl)silyl aryl ether was also obtained by reaction between TBDMSONa and 4-bromobenzophenone in 94% yield.
8. This case resulted in the by-production of 10% yield of *t*-butyl *p*-chlorobenzoate which may arise from β-hydride elimination of a Pd–hemiacetal intermediate from reaction of the aldehyde group with *t*-butoxide.
9. The catalytic system consisting of 1 mol% of $Pd(OAc)_2$ and BINAP gave a sluggish reaction of 2,6-dichlorotoluene with *t*-BuONa and lost its catalytic activity at 10% conversion of the substrate at 120°C.
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11. This aldehyde was prepared from easily available 2,6-dichlorobenzyl chloride as follows: The corresponding benzyl Grignard reagent prepared in Et_2O was treated with DMF. Quenching by acid and recrystallization from MTBE gave the aldehyde in 62% yield. ^1H NMR (400 MHz, $CDCl_3$): δ=4.12 (s, 2H), 7.20 (t, *J*=8.1 Hz, 1H), 7.36 (d, *J*=8.7 Hz, 2H), 9.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=45.90, 128.27, 129.34, 129.86, 136.14, 196.71.
12. When the acetal protected by ethylene glycol was used instead of **1**, the ratio of the desired product:dechlorinated products decreased to 5.0:1.
13. Fifty percent H_2SO_4 gave only a trace amount of 4-chlorobenzofuran.
14. Procedure: A mixture of $Pd(OAc)_2$ (0.06 mmol), P(*t*-Bu)$_3$ (0.18 mmol), **1** (2 mmol), sodium *t*-butoxide (2.2 mmol), and xylene (5 ml) was heated at 120°C for 4 h under N_2. After addition of water and extractive work-up, the solvent was stripped off in vacuo. To the residue was added conc. hydrochloric acid (4.5 g) and the reaction mixture was stirred for 30 h at room temperature. After extractive work-up, 4-chlorobenzofuran (156 mg, 1.02 mmol) was isolated by bulb-to-bulb distillation in 51% yield. ^1H NMR (400 MHz, $CDCl_3$): δ=6.86 (d, *J*=2.0 Hz, 1H), 7.20–7.24 (m, 2H), 7.40 (dd, *J*=6.1, 2.0 Hz, 1H), 7.63 (d, *J*=2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=105.40, 110.09, 122.78, 124.92, 126.33, 127.04, 145.49, 155.31.
15. After we reported high catalytic activity and selectivity of P(*t*-Bu)$_3$-ligated palladium on amination of aryl halides (Ref. 5), biaryl synthesis based on Suzuki couplings and vinylation of aryl halides were reported using the same catalytic system, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3387 for Suzuki coupling, and Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10 for vinylation.