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One-pot synthesis of 2-substituted benzo[*b*]furans *via* Pd–tetraphosphine catalyzed coupling of 2-halophenols with alkynes†

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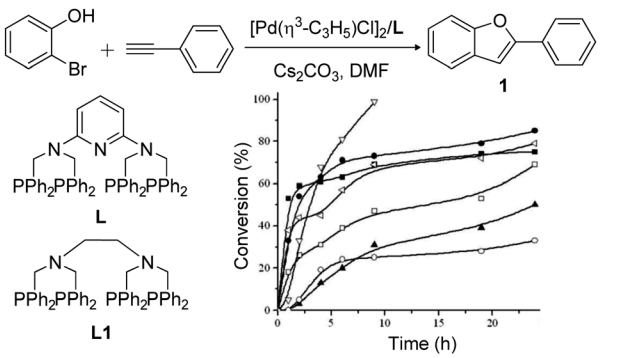
A catalyst composed of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and *N*,*N*,*N*′,*N*′-tetra(diphenylphosphinomethyl)pyridine-2,6-diamine (L) was found to be effective for one-pot synthesis of 2-substituted benzo[*b*]furans from 2-halophenols and alkynes. For 2-bromo-3-hydroxypyridine, the catalyst loading could be as low as 1 ppm and the turnover number (TON) was up to 870 000.

2-Substituted benzo[*b*]furan is a ubiquitous framework in natural products and pharmaceuticals.[1] Various methods have been developed for the synthesis of benzo[*b*]furan derivatives. Pd-catalyzed one-pot synthesis of benzo[*b*]furans from 2-halophenols and terminal alkynes by a Sonogashira coupling–cyclization sequence is a classical, useful and reliable way.[2] Typically this reaction is performed using a palladium phosphine catalyst in the presence of a copper salt as a co-catalyst.[2a,3] However, this reaction commonly employs 2-iodo-[1a,4] or 2-bromophenols[2a,f,3d,5] as substrates and there are a few reports on the use of 2-chlorophenols.[6] Recently, K. Manabe found $PdCl_2(CH_3CN)_2$/HTP (hydroxyterphenylphosphine) to be an



Scheme 1 Effect of the ligand on the reaction of 2-bromophenol and phenylacetylene (▽: **L**, ●: PPh_3, ◁: dppb, ■: no ligand, □: dppe, ▲: P-Phos, ◦: **L1**).

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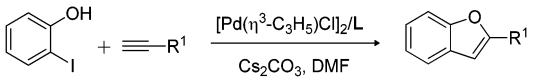
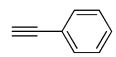
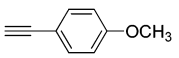
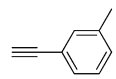
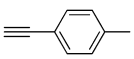
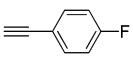
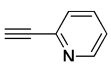
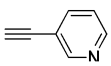
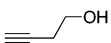
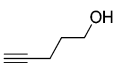
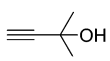
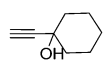
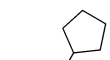
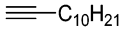
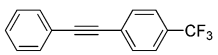
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc00815d

Table 1 Synthesis of 2-substituted benzo[*b*]furans using 2-iodophenol and alkynes[a]



Entry	Alkyne	Time (h)	Product	Yield (%)
1		1	**1**	99
2		1	**2**	99
3		3	**3**	99
4		3	**4**	99
5		3	**5**	78
6		24	—	Trace
7		4	**6**	58
8		24	**7**	93
9		24	**8**	82
10		24	**9**	33
11		20	**10**	99
12		20	**11**	96
13		20	**12**	97
14		24	**27**	70[b]

[a] Conditions: 2-iodophenol 0.5 mmol, alkynes 0.6 mmol, DMF 2 mL, Cs_2CO_3 1 mmol, 130 °C, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ 2.5×10^{-4} mmol, **L** 5×10^{-4} mmol, isolated yield. [b] $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ 2.5×10^{-3} mmol, **L** 5×10^{-3} mmol.

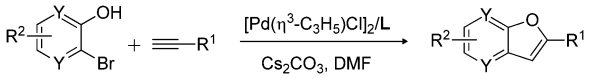
effective catalyst for one-pot benzo[*b*]furan synthesis from 2-chlorophenols and alkynes, and then developed another ligand DHTP (dihydroxyterphenylphosphine) to overcome the drawbacks of the former system such as a long reaction time, narrow substrate scope and the need for a sealed tube for the reaction.[6d] But all of them required a high amount of palladium (2–10 mol%). Therefore, the development of a simple and highly efficient catalytic system is highly desired.

We previously reported the Pd–tetraphosphine (**L**) catalytic system for Cu-free Sonogashira reaction, and found that aryl bromides and even aryl chlorides were successfully alkynylated at low palladium loading on water.[7] In this respect, we applied this catalyst to achieve the synthesis of 2-substituted benzo[*b*]furans.

Herein we present the palladium catalyzed one-pot synthesis of 2-substituted benzo[*b*]furans from 2-halophenols and alkynes using tetraphosphine **L** as the ligand. Firstly we tried to obtain 2-substituted benzo[*b*]furan **1** using 2-bromophenol and phenylacetylene as model reactants under the copper-free conditions, and found that the catalyst $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$–**L** gave the desired product in a yield of 99% (see the ESI,† Table S1). To optimize conditions, the effect of various reaction parameters (palladium precursor, base and solvent) on the outcome of the reaction was explored. It was found that $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was the most effective under otherwise identical conditions. Furthermore, Cs_2CO_3 was much more effective than other bases. In our previous work,[7] water was the most effective solvent in copper-free Sonogashira reaction, but it failed to give the product, and DMF was the suitable solvent (Table S1, ESI,† entries 14–18). In order to explore the role of the ligand, the relationship between conversions and reaction time in different phosphine systems was investigated (Scheme 1). It was found that in PPh_3 or no ligand system, the initial rate was much faster than in the ligand **L** system. But the rate of reaction slowed down after 2 h due to the formation of palladium black. In diphosphines and **L1** systems, the increase of conversion became very slow after 6 h. But the activity of the catalytic system containing **L** was retained for the complete conversion of the substrate obviously. Ligand **L** played a key role in this system because it can maintain the stability of the palladium active species.

Under the optimized reaction conditions, 2-halophenols and alkynes smoothly underwent transformation to produce 2-substituted benzo[*b*]furans in good to excellent yields. First, the reactions of 2-iodophenol with various alkynes were tested with a low palladium loading of 0.1 mol% (Table 1). With either electron-rich or electron-poor aryl acetylenes as substrates, 2-iodophenol was completely converted into desired products (Table 1, entries 1–5). The reaction with 2-pyridylacetylene was found to be difficult because of the formation of a stable Pd-alkyne intermediate (Table 1, entry 6).[7] In this system, alkynes bearing electron-rich groups were more susceptible to undergo coupling–cyclization reaction than alkynes bearing electron-poor groups. Even aliphatic alkynes, such as 3-butyn-1-ol, 4-pentyn-1-ol, 1-entynyl-1-cyclohexanol and 3-cyclopentyl-1-propyne, could give desired products **7–8** and **10–12** in high yields (Table 1, entries 8–9, 11–13). To our knowledge, **10** and **11** were synthesized for the first time. 2-Methyl-3-butyn-2-ol gave **9** in a low yield of 33% (Table 1, entry 10). Furthermore the

Table 2 Synthesis of benzo[*b*]furans using 2-bromophenols and alkynes[a]



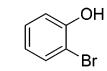
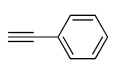
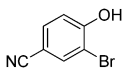
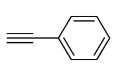
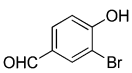
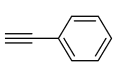
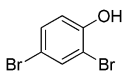
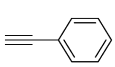
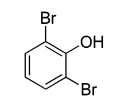
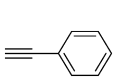
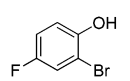
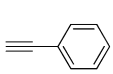
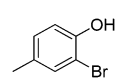
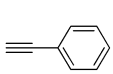
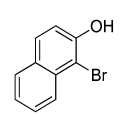
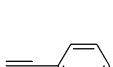
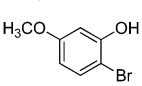
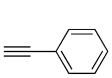
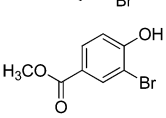
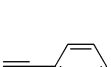
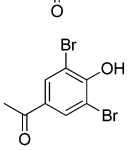
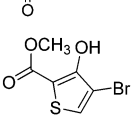
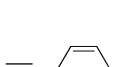
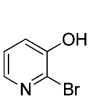
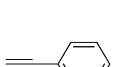
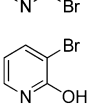
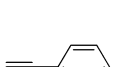
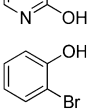
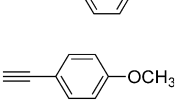
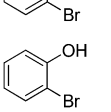
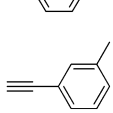
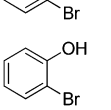
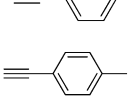
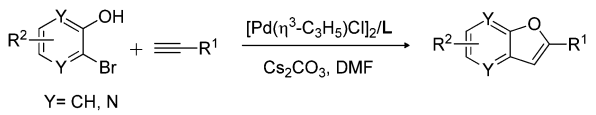
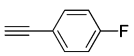
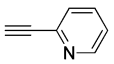
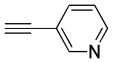
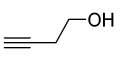
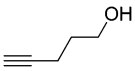
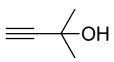
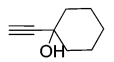
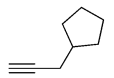
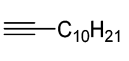
Entry	2-Bromophenol	Alkyne	S/C	Time (h)	Product	Yield (%)
1			1000	9	**1**	95
2			1000	24	**13**	96
3			1000	24	**14**	87
4			1000	24	**15**	75
5			1000	24	**16**	27
6			1000	24	**17**	82
7			1000	24	**18**	31
8			1000	24	**19**	78
9			1000	24	**20**	73
10			1000	24	**21**	98
11			1000	24	**22**	97
12			1000 100	24 24	**23**	7.5[b] 43
13			1000 10 000 100 000 1000 000	1 9 20 40	**24**	99 >99[b] >99[b] 87[b]
14			1000	5	**25**	99
15			1000	6	**2**	83
16			1000	48	**3**	74
17			1000	48	**4**	70

Table 2 (*continued*)



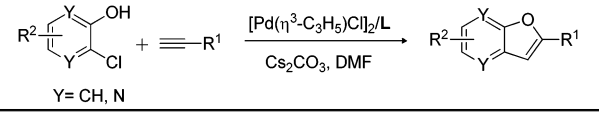
Entry	2-Bromo-phenol	Alkyne	S/C	Time (h)	Product	Yield (%)
18			1000	48	**5**	29
19			1000	48	—	Trace[b]
20			1000	24	**6**	99
21			1000	24	**7**	23
22			1000	24	**8**	30
23			1000	24	**9**	27
24			1000	24	**10**	64
25			1000	24	**11**	81
26			1000	48	**12**	92

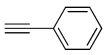
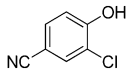
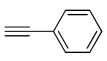
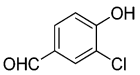
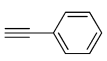
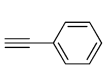
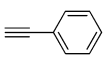
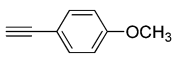
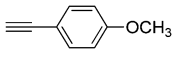
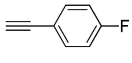
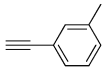
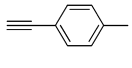
[a] Conditions: 2-bromophenols 0.5 mmol, alkynes 0.6 mmol, DMF 2 mL, Cs_2CO_3 1 mmol, 130 °C, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ 2.5 × 10^{-4} mmol, **L** 5 × 10^{-4} mmol, isolated yield. [b] GC yield.

inner alkyne 1-(phenylethynyl)-4-(trifluoromethyl)benzene was heteroannulated with a yield of 70% (Table 1, entry 14).

Next, the reactions of various 2-bromophenols with terminal alkynes were investigated (Table 2). 2-Bromophenols bearing –CN, –CHO, –Br, $–OCH_3$, $–COOCH_3$, $–COCH_3$ and –F groups all reacted smoothly and produced desired compounds **13–15**, **17**, **20–22** in good to excellent yields: 73–98% (Table 2, entries 2–4, 6, 9–11). The success in the synthesis of 4-bromobenzo[*b*]furan indicated that the Sonogashira coupling step site-selectively occurred at the 2-position in accordance with the literature (Table 2, entry 4).[6b] Due to hindrance, only 27% of 2,6-dibromophenol was transformed into product **16** (Table 2, entry 5). 1-Bromo-2-naphthol gave the corresponding benzo[*b*]furan **19** in a yield of 78%, while 4-methyl-2-bromophenol afforded product **18** in 31% yield (Table 2, entries 7–8). The results showed that 2-bromophenols containing electron-rich groups inhibited the reaction because the electron deficient phenoxide ion was more likely to make an attack on the triple bond resulting in the formation of the benzo[*b*]furans. 2-Bromo-3-hydroxypyridine reacted with phenylacetylene to form quickly product **24** in the presence of 0.05 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ for

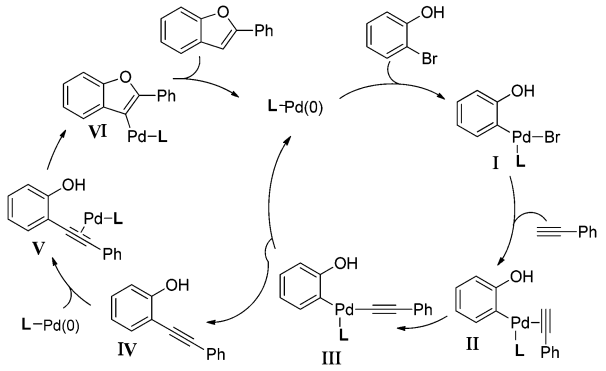
Table 3 Synthesis of benzo[*b*]furans using 2-chlorophenols and alkynes[a]



Entry	2-Chloro-phenol	Alkyne	S/C	Time (h)	Product	Yield (%)
1			1000	24	**1**	70
2			1000	2	**13**	98
3			1000	48	**14**	Trace[b]
4			100 1000 10 000 100 000	24 8 20 40	**24**	Trace[b] 86 >99[b] 63[b]
5			1000	8	**25**	90
6			1000	2	**26**	95
7			1000	48	**2**	46
8			1000	48	**5**	10
9			1000	48	**3**	23
10			1000	48	**4**	48
11			1000	48	**6**	36
12			1000	48	**10**	Trace[b]
13			1000	48	**11**	17[b]

[a] Conditions: 2-chlorophenols 0.5 mmol, alkynes 0.6 mmol, DMF 2 mL, Cs_2CO_3 1 mmol, 130 °C, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ 2.5 × 10^{-4} mmol, **L** 5 × 10^{-4} mmol, isolated yield. [b] GC yield.

1 h (Table 2, entry 13). To test the efficiency and longevity of the catalyst, as low as 1 × 10^{-4} mol% of palladium was used in the reaction of 2-bromo-3-hydroxypyridine. The expected coupling product was obtained in 87% yield after 40 h and the TON was up to 870 000, which is the best result reported in the literature.[8] Substrates derived from alkynes with either electron-donating or withdrawing groups were able to undergo an intramolecular cyclization reaction and generated the corresponding products **2–5** in 29–83% yields (Table 2, entries 15–18). Good to excellent yields of the desired products (64–92%) were obtained for aliphatic alkynes (Table 2, entries 24–26).



Scheme 2 A proposed mechanism for palladium-catalyzed Sonogashira coupling–cyclization reaction.

Futhermore, 2-chlorophenol, which is reported scarcely,[6] inexpensive, and readily available as the starting material, was examined in this system. The electron-poor 3-chloro-4-hydroxybenzonitrile was transformed into product **13** in an excellent yield of 98% in the presence of 0.05 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ after 2 h (Table 3, entry 2). But another electron-poor substrate 3-chloro-4-hydroxybenzaldehyde failed to give the desired product albeit increasing palladium loading to 1 mol% (Table 3, entry 3). 2-Chloro-3-hydroxypyridine and 3-chloro-2-hydroxypyridine smoothly underwent the reaction and produced desired compounds **24** and **25** in good yields of 86% and 90%, respectively. For 2-chloro-3-hydroxypyridine, even if as low as 0.0005 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was used, the yield of 63% was still achieved with a TON of 63 000, which is much higher than the best value reported in the literature.[6b] With ethynyl-3-methylbenzene, ethynyl-4-methylbenzene and 3-pyridylacetylene, 2-chlorophenols can still transform into the corresponding products in the yields of 23–48% (Table 3, entries 9–11). Product **11** was obtained in 17% yield when 3-cyclopentyl-1-propyne was used as the substrate.

Based on the experimental fact and the reported results,[9] a mechanism for palladium-catalyzed one-pot synthesis of 2-substituted benzo[*b*]furan from 2-halophenols and alkynes is proposed in Scheme 2. It consists of two steps: the Sonogashira coupling of 2-halophenol with alkyne and the subsequent cyclization of 2-alkynylphenols. The acyclic compound **IV** was detected using GC/MS in the reaction mixture of 2-bromophenol and phenylacetylene after 0.5 h. The relative intensities of cyclic and acyclic compounds were 3 : 1 after 2 h, an increase in the reaction time up to 7 h changed the intensity ratio to 20 : 1, with the complete conversion of starting 2-bromophenol. This fact is in good agreement with the literature in which the proportion of the cyclic compound to the acyclic intermediate in the course of domino synthesis of benzo[*b*]furan increased with reaction time.[9]

In summary, we developed a highly efficient catalyst system $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$–**L** for the one-pot systhesis of 2-substituted benzo[*b*]furans from 2-halophenols and alkynes. This system tolerates a wide range of functional groups and gives the desired products in good to excellent yields at low catalyst loading even if as low as 1 ppm palladium is used.

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