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COMMUNICATION

One-pot Synthesis of 2-Substituted Benzo[*b*]furan via Pd/Tetraphosphine Catalyzed Coupling of 2-Halophenols with Alkynes

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Hua Chen^a and Rui-xiang Li^{a*}

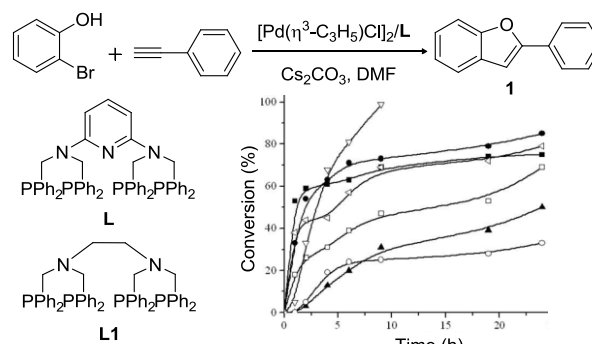
A catalyst composed of [Pd(η^3 -C₃H₅)Cl]₂ and N,N,N',N'-tetra(diphenylphosphinomethyl)pyridine-2,6-diamine (L**) was found to be effective for one-pot synthesis of 2-substituted benzo[*b*]furan from 2-halophenols and alkynes. For 2-bromo-3-hydroxypyridine, the catalyst loading could be as low as 1 ppm 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 from 2-halophenols and terminal alkynes by a Sonogashira coupling-cyclization sequence is a classical, useful and reliable way.² Typically these reactions are performed with a palladium phosphine catalyst in the presence of a copper salt as co-catalyst.^{2a, 3} However, these reactions commonly employ 2-iodo-^{1a, 4} or 2-bromophenols^{2a, 2f, 3d, 5} as substrates and a few reports of the use of 2-chlorophenols.⁶ Recently, K. Manabe found PdCl₂(CH₃CN)₂/HTP (hydroxyterphenylphosphine) is an effective catalyst for one-pot benzo[*b*]furan synthesis from 2-chlorophenols and alkynes, and then developed another ligand DHTP (dihydroxyterphenylphosphine) to overcome the former system's drawbacks such as long reaction time, narrow substrate scope and the need of a sealed tube for the reaction.^{6d} But all of them required a high amount of palladium (2-10 mol%). Thereby, the development of a simple and high efficient catalytic system is highly desired.

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

Herein we presented the palladium catalyzed one-pot synthesis of 2-substituted benzo[*b*]furan from 2-halophenols and alkynes using tetraphosphine **L** as the ligand. Firstly we tried to obtain 2-substituted benzo[*b*]furan **1** with 2-bromophenol and phenylacetylene as model reactants under the condition of copper-free, and found that the catalyst [Pd(η^3 -C₃H₅)Cl]₂/**L** gave the desired product in a yield of 99% (see the Supporting Information, 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(η^3 -C₃H₅)Cl]₂ was the most effective under otherwise identical conditions. Furthermore,

Cs₂CO₃ was much more effective than other bases. In our previous works,⁷ water was the most effective solvent in copper-free Sonogashira reaction, but it was failed to give the product, and DMF was the suitable solvent (Table S1, entries 14-18). In order to explore the role of ligand, the relationship between conversions and reaction time in different phosphine systems was investigated (scheme 1). It was found that in PPh₃ or no ligand system, the initial rate was much faster than in ligand **L** system. But the rate of reaction slowed down after 2 h due to the formation of palladium back. In diphosphines and **L1** system, the increase of conversions became very slow after 6 h. But the activity of catalytic system containing **L** was kept to the complete conversion of substrate obviously. Ligand **L** played a key role in this system because it can maintain the stability of the palladium active species.

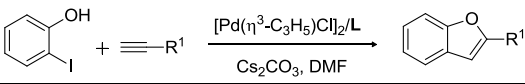


Scheme 1. Effect of ligand on the reaction of 2-bromophenol and phenylacetylene (∇ **L**, \bullet PPh₃, \triangle dppb, \blacksquare no ligand, \square dppe, \blacktriangle P-Phos, \circ **L1**)

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). Either electron-rich or electron-poor aryl acetylenes as substrates, 2-iodophenol was completely converted into desired products (Table 1, entries 1-5). 2-pyridylacetylene was difficult to undergo because of the formation of stable Pd-alkyne intermediate (Table 1, entry 6).⁷ In this system,

alkynes bearing electron-rich groups were more susceptible to occur coupling-cyclization reaction than bearing electron-poor groups. Even aliphatic alkynes, such as 3-butyne-1-ol, 4-pentyn-1-ol, 1-entynyl-1-cyclohexanol and 3-cyclopentyl-1-propyne, could also give desired products **7-8**, **10-12** in high yields (Table 1, entries 8-9, 11-13). To our knowledge, it is the first time to synthesize **10**, **11** up to now. 2-methyl-3-butyne-2-ol gave **9** in a low yield of 33% (Table 1, entry 10). Furthermore the inner alkyne 1-(phenylethynyl)-4-(trifluoromethyl)benzene has been heteroannulated with a yield of 70% (Table 1, entry 14).

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



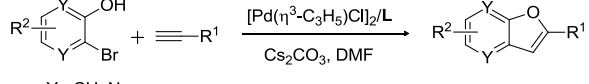
Entry	Alkyne	Time (h)	Product	Yield (%)
1		1	1	99
2		1	2	99
3		3	3	99
4		3	4	99
5		3	5	78
6		24	--	trace
7		4	6	58
8		24	7	93
9		24	8	82
10		24	9	33
11		20	10	99
12		20	11	96
13		20	12	97
14		24	27	70 ^b

^aCondition: 2-iodophenol 0.5 mmol, alkynes 0.6 mmol, DMF 2 mL, Cs₂CO₃ 1mmol, 130 °C, [Pd(η³-C₃H₅)Cl]₂ 2.5*10⁻⁴ mmol, L 5*10⁻⁴ mmol, isolated yield; ^b [Pd(η³-C₃H₅)Cl]₂ 2.5*10⁻³ mmol, L 5*10⁻³ mmol.


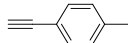

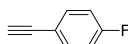

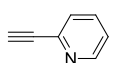

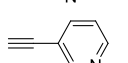

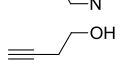



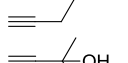

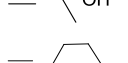

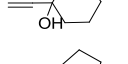

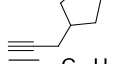
Next, the reactions of various 2-bromophenols with terminal alkynes were investigated (Table 2). 2-bromophenols bearing -CN, -CHO, -Br, -OCH₃, -COOCH₃, -COCH₃ and -F group all reacted smoothly and produced desired compounds **13-15**, **17**, **20-22** in good to excellent yields:73-98% (Table 2, entries 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 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 concluded that 2-bromophenols contained electron-rich groups inhibited the proceeding of reaction because the deficient electronic phenoxide ion was more likely to make an attack on the triple bond resulted 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(η³-C₃H₅)Cl]₂ for 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).

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




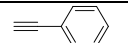

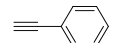

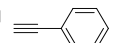


Entry	2-Bromophenol	Alkyne	S/C	Time (h)	Product	Yield (%)
1			1,000	9	1	95
2			1,000	24	13	96
3			1,000	24	14	87
4			1,000	24	15	75
5			1,000	24	16	27
6			1,000	24	17	82
7			1,000	24	18	31
8			1,000	24	19	78
9			1,000	24	20	73
10			1,000	24	21	98
11			1,000	24	22	97
12			1,000	24	23	7.5 ^b
			100	24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


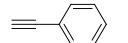

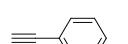

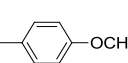

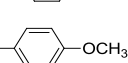

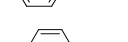

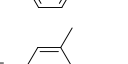

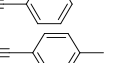

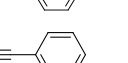

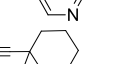

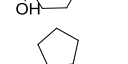
17			1,000	48	4	70
18			1,000	48	5	29
19			1,000	48	--	trace ^b
20			1,000	24	6	99
21			1,000	24	7	23
22			1,000	24	8	30
23			1,000	24	9	27
24			1,000	24	10	64
25			1,000	24	11	81
26			1,000	48	12	92

^aCondition: 2-bromophenols 0.5 mmol, alkynes 0.6 mmol, DMF 2 mL, Cs₂CO₃ 1 mmol, 130 °C, [Pd(η³-C₃H₅)Cl]₂ 2.5*10⁻⁴ mmol, L 5*10⁻⁴ mmol, isolated yield; ^bGC yield.

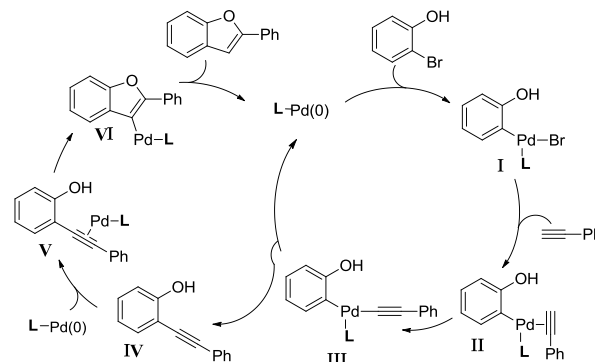
Futhermore, 2-chlorophenols, which are few reported,⁶ inexpensive, and readily available as the starting material, were examined in this system. The electron-poor 3-chloro-4-hydroxybenzotrile was transformed into product **13** in an excellent yield of 98% in the presence of 0.05 mol% [Pd(η³-C₃H₅)Cl]₂ after 2 h (Table 3, entry 2). But another electron-poor substrate 3-chloro-4-hydroxybenzaldehyde failed to get the desired product albeit increasing palladium loading to 1 mol% (Table 3, entry 3). 2-chloro-3-hydroxypyridine and 3-chloro-2-hydroxypyridine underwent smoothly and produced desired compounds **24**, **25** in good yields of 86% and 90%, respectively. For 2-chloro-3-hydroxypyridine, even if as low as 0.0005 mol% [Pd(η³-C₃H₅)Cl]₂, 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). The product **11** was obtained in 17% yield when 3-cyclopentyl-1-propyne as substrate.

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

Entry	2-Chlorophenol	Alkyne	S/C	Time (h)	Product	Yield (%)
1			1,000	24	1	70
2			1,000	2	13	98
3			1,000	48	14	trace ^b
			100	24	14	trace ^b

4			1,000	8	24	86
			10,000	20		>99 ^b
			100,000	40		63 ^b
5			1,000	8	25	90
6			1,000	2	26	95
7			1,000	48	2	46
8			1,000	48	5	10
9			1,000	48	3	23
10			1,000	48	4	48
11			1,000	48	6	36
12			1,000	48	10	trace ^b
13			1,000	48	11	17 ^b

^aCondition: 2-chlorophenols 0.5 mmol, alkynes 0.6 mmol, DMF 2 mL, Cs₂CO₃ 1 mmol, 130 °C, [Pd(η³-C₃H₅)Cl]₂ 2.5*10⁻⁴ mmol, L 5*10⁻⁴ mmol, isolated yield; ^bGC yield.



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

Based on the experimental fact and the reported results, 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 good agreement with the literature in which the proportion of cyclic compound to acyclic intermediate in the course of domino synthesis of benzo[*b*]furan was increasing with reaction time.⁹

Conclusions

In summary, we developed a highly efficient catalyst system [Pd(η³-C₃H₅)Cl]₂/L for one-pot synthesis of 2-substituted benzo[*b*]furan 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.

Notes and references

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