Phosphazene base-catalyzed intramolecular cyclization for efficient synthesis of benzofurans *via* carbon–carbon bond formation†

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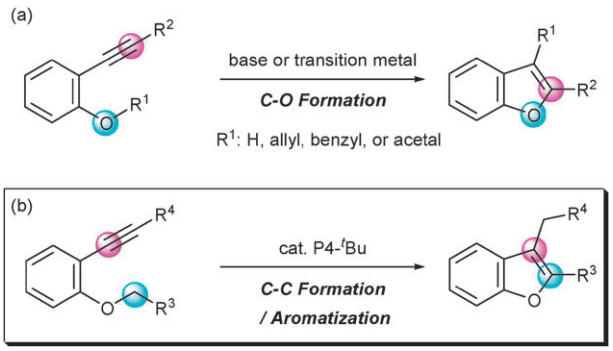
Received (in College Park, MD, USA) 8th July 2009, Accepted 23rd July 2009
First published as an Advance Article on the web 7th August 2009
DOI: 10.1039/b913588j

An organic superbase, phosphazene P4-^{t}Bu, functioned as an active catalyst for intramolecular cyclization of *o*-alkynylphenyl ethers *via* carbon–carbon bond formation to provide an efficient synthetic method for 2,3-disubstituted benzofurans derivatives under mild reaction conditions without the need for a metal catalyst.

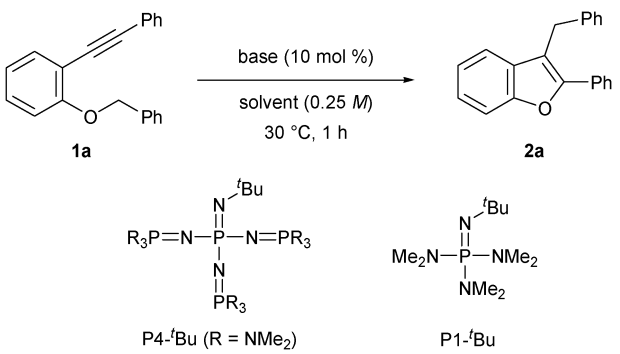
Alkynylbenzene derivatives having a nucleophilic site at the *ortho*-position are widely utilized as efficient precursors for constructing heterocyclic compounds. The intramolecular cyclization reaction of *o*-alkynylphenols or *o*-alkynylphenyl ethers *via* a carbon–oxygen bond (C–O) formation is one of most simple and efficient methods for preparing benzofurans (Scheme 1a),[1–3] a very important class of heterocycles, as versatile building blocks for naturally occurring and biologically active compounds. A number of methodologies using bases or transition metal catalysts have been established on the basis of C–O cyclization. However, to the best of our knowledge, there have been no previous reports on benzofuran syntheses from alkynylbenzene derivatives *via* carbon–carbon bond (C–C) cyclization (Scheme 1b),[4,5] as an alternative strategy (Scheme 1a). Herein we report catalytic intramolecular cyclization of *o*-alkynylphenyl ethers *via* C–C forming reactions to provide 2,3-disubstituted benzofuran derivatives in high yields (Scheme 1b). The present unprecedented cyclization was successfully demonstrated using an organic superbase, phosphazene P4-^{t}Bu, as the catalyst.[6] The method enables efficient access to substituted benzofuran derivatives without the need for a metal catalyst.



Scheme 1 Intramolecular cyclization of *o*-alkynylphenyl ethers.

We began by investigating the catalytic cyclization reaction of *o*-alkynylphenyl benzyl ether (**1a**) in the presence of a base catalyst. As shown in Table 1, P4-^{t}Bu acts as an efficient and unique catalyst in the present cyclization reaction.[7] For example, the reaction of **1a** in the presence of P4-^{t}Bu (10 mol%) in DMSO at 30 °C afforded the desired benzofuran derivative (**2a**) in excellent yield (Table 1, entry 1). A screening of other bases, such as KHMDS, ^{n}BuLi, and ^{t}BuONa, demonstrated that these typical strong bases did not promote the reaction at all, or as efficiently, under the same reaction conditions (entries 2–4). The phosphazene base P1-^{t}Bu, which is less basic than P4-^{t}Bu, was also ineffective (entry 5). Further screening of other solvents revealed that their basicity is more important in promoting the reaction efficiently than the polarity of the solvents employed;‡[8,9] the reaction proceeded smoothly in basic solvents such as DMSO and DMF (entries 1 and 8), while in less basic solvents, such as THF or MeCN, the reaction resulted in much less or nil product formation (entries 6 and 7). The system with P4-^{t}Bu as the catalyst and DMSO as the solvent accelerated the cyclization reaction

Table 1 Catalytic intramolecular cyclization of **1a**[a]



Entry	Base	Solvent	Yield[b] (%)
1	P4-^{t}Bu	DMSO	95
2	KHMDS	DMSO	20
3	^{n}BuLi	DMSO	No reaction
4	^{t}BuONa	DMSO	No reaction
5	P1-^{t}Bu	DMSO	No reaction
6	P4-^{t}Bu	THF	9
7	P4-^{t}Bu	CH_3CN	No reaction
8	P4-^{t}Bu	DMF	89
9[c]	P4-^{t}Bu	DMSO	(95)[d]

[a] Unless otherwise noted, all reactions were carried out using 10 mol% of base at 30 °C for 1 h. [b] ^{1}H NMR yield. [c] 5 mol% of P4-^{t}Bu. [d] Isolated yield.

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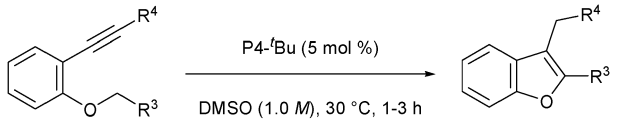
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data of relevant compounds. See DOI: 10.1039/b913588j

efficiently[10] and allowed the catalyst loading to be reduced to 5 mol% without compromising the chemical yield (entry 9).

Having identified suitable reaction conditions and a promising catalyst, P4-^{t}Bu, we next investigated the scope and limitations of the present cyclization reaction (Table 2). Both electron-donating and electron-withdrawing aryl groups were tolerated for the substituents (R^3) at the alkoxy terminus (entries 1 and 2), although higher reaction temperature and catalyst loading were required in the reaction of **1c** bearing the electron-donating *p*-methoxyphenyl substituent (entry 2). In contrast, the sterically demanding 1-naphthyl substituent was applicable without any difficulties (entry 3). Further investigation of the R^4 substituent at the alkynyl terminus revealed that the electron-donating *p*-methoxyphenyl and the sterically hindered 1-naphthyl substituents promoted the attainment of the corresponding benzofurans in high yields (entries 4 and 5). However, the reaction of the alkyl substituted **1g** resulted in a complex mixture (entry 6).

Table 2 P4-^{t}Bu-catalyzed intramolecular cyclization of various **1**[a]



Entry	1	R^3	R^4	2	Yield[b] (%)
1[c]	**1b**	*p*-$O_2NC_6H_4$	Ph	**2b**	62
2[d]	**1c**	*p*-$MeOC_6H_4$	Ph	**2c**	72
3	**1d**	1-Naphthyl	Ph	**2d**	89
4	**1e**	Ph	*p*-$MeOC_6H_4$	**2e**	91
5	**1f**	Ph	1-Naphthyl	**2f**	86
6	**1g**	Ph	^{n}Pr	**2g**	[e]

[a] Unless otherwise noted, all reactions were carried out using 5 mol% of P4-^{t}Bu at 30 °C for 1–3 h in DMSO (1.0 M). [b] Isolated yield. [c] 10 mol% of P4-^{t}Bu. [d] 15 mol% of P4-^{t}Bu. At 100 °C for 6 h. [e] Complex mixture.

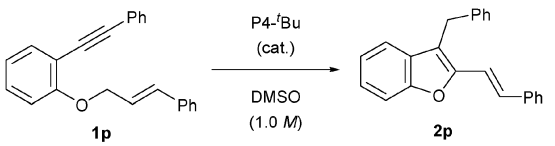
The present catalytic cyclization can also be applied to *o*-alkynylphenyl ethers having carbonyl groups at the alkoxy terminus (R^3). As shown in Table 3, the P4-^{t}Bu catalyst exhibited excellent performance for these substrates and the corresponding products were obtained in high yields (entries 1–3), with the exception of the nitrile substituent, which gave the product (**2k**) in low yield as a result of overreaction between the nitrile moiety of **2k** and intermediary carbanion species (entry 4).§ A variety of R^4 substituents were tolerated at the alkynyl terminus in the present cyclization reaction (entries 5–8). The corresponding products were obtained in good yield, irrespective of the electronic properties of the aryl groups (entries 5 and 6). It is noteworthy that substrates having both alkenyl and alkyl groups were good candidates for the present catalytic reactions (entries 7 and 8).

Table 3 Intramolecular cyclization of **1** having carbonyl groups at the alkoxy terminus[a]

Entry	1	R^3	R^4	2	Yield[b] (%)
1	**1h**	CO_2Et	Ph	**2h**	86
2	**1i**	$CO_2{}^t$Bu	Ph	**2i**	70
3	**1j**	COPh	Ph	**2j**	76
4	**1k**	CN	Ph	**2k**	14
5	**1l**	CO_2Et	*p*-$MeOC_6H_4$	**2l**	88
6	**1m**	CO_2Et	*p*-$CF_3C_6H_4$	**2m**	87
7	**1n**	CO_2Et	1-Cyclohexenyl	**2n**	83
8[c]	**1o**	CO_2Et	^{n}Pr	**2o**	59

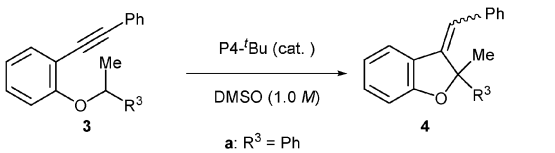
[a] Unless otherwise noted, all reactions were carried out using 5 mol% of P4-^{t}Bu at 30 °C for 1–2 h in DMSO (1.0 M). [b] Isolated yield. [c] 15 mol% of P4-^{t}Bu. At 100 °C for 6 h.

Finally, we applied the present catalytic method to a vinylogous analogue of **1a**, that is, *o*-alkynylphenyl allyl ether (**1p**) (eqn (1)), and **3**, which has a methine carbon at the alkoxy group (eqn (2)). Unfortunately, the reaction of the vinylogous **1p** yielded an oligomeric product under standard reaction conditions. However, this problem could be circumvented by addition of excess water[11] and the desired product (**2p**) was obtained in good yield (eqn (1)). On the other hand, the reaction of **3** yielded geometrical mixtures of 3-benzylidene-2,3-dihydrobenzofurans (**4**) with a quaternary carbon atom (eqn (2)). In the reaction of **3a** (R^3 = Ph), relatively harsh conditions, including high catalyst loading, high temperature, and prolonged reaction, were required to obtain the corresponding product (**4a**) in good yield. Without any additive, moderate (*E*)-selectivity (*E* : *Z* = 2 : 1) was observed, while addition of excess ^{t}BuOH resulted in the formation of the opposite (*Z*)-isomer as the major product (*E* : *Z* = 1 : 3.5), albeit with low chemical yield.[7,11] In contrast, the reaction of **3b** (R^3 = CO_2Et) proceeded smoothly under the standard reaction conditions to give (*Z*)-**4b** predominantly (*E* : *Z* = 1 : 4). The (*Z*)-selectivity could be improved (*E* : *Z* = 1 : 25) by adding excess ethanol, although elevated temperature and a prolonged reaction period were required to achieve high chemical yield.[7,11]



(1)

P4-^{t}Bu (5 mol %) no additive 30 °C, 1.5 h oligomerization
P4-^{t}Bu (15 mol %) 10 equiv H_2O 100 °C, 6 h 82%



(2)

3a P4-^{t}Bu (20 mol %) no additive 100 °C, 6 h 81% (*E*:*Z* = 2:1)
3a P4-^{t}Bu (20 mol %) 10 equiv ^{t}BuOH 120 °C, 9 h 24% (*E*:*Z* = 1:3.5)
3b P4-^{t}Bu (10 mol %) no additive 30 °C, 1 h 93% (*E*:*Z* = 1:4)
3b P4-^{t}Bu (10 mol %) 10 equiv EtOH 80 °C, 4 h 90% (*E*:*Z* = 1:25)

A plausible mechanism of the P4-^{t}Bu-catalyzed cyclization is depicted in Fig. 1. Deprotonation of **1** by P4-^{t}Bu to generate anion **A**, followed by 5-*exo* intramolecular cyclization, would give vinyl anion intermediate **B**.[10] Subsequent protonation of **B** would take place by the conjugate acid [P4-^{t}BuH]$^+$, as supported by the catalytic reaction proceeding smoothly even in DMF (Table 1, entry 8), although DMSO or the substrate (**1**), having a carbonyl group at the alkoxy terminus, cannot be

ruled out as the proton source. The protonation provides the intermediate **C** while also regenerating P4-^{t}Bu for further catalytic cycles. Heteroaromatization of **C** finally gives the benzofuran (**2**).

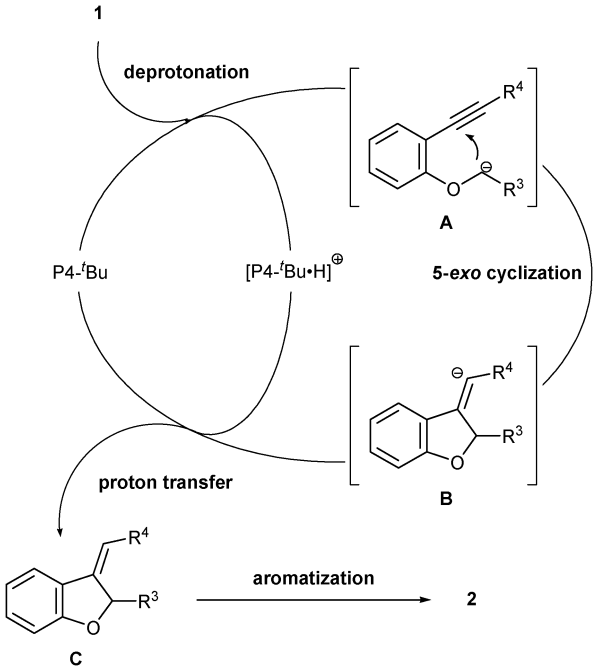


Fig. 1 Plausible catalytic cycles.

In conclusion, we have demonstrated a novel efficient synthetic method for substituted benzofurans starting from *o*-alkynylphenyl ethers. The use of P4-^{t}Bu as the catalyst in DMSO as a solvent is crucial for the present unprecedented reaction, which enables cyclization *via* carbon–carbon bond formation. Further application of the present method is in progress with the aim of developing efficient syntheses of not only heterocyclic compounds but also carbocyclic varieties.

We acknowledge Research Fellowships from the Japan Society for the Promotion of Science for Young Scientists (C.K.).

Notes and references

‡ Normalized donor numbers (DN^N) of the solvents employed: DMSO: 0.768, DMF: 0.686, THF: 0.515, CH_3CN: 0.363, see ref. 8. Normalized solvent polarity values (E_T^N) of the solvents employed: DMSO: 0.444, DMF: 0.404, THF: 0.207, CH_3CN: 0.460, see ref. 9.
§ Mass spectroscopic analysis of crude mixtures obtained from the reaction of **1k** exhibited molecular ion peaks at nearly, but not exactly, twice as much as the molecular mass of **2k**, although we have not determined yet the structures of these dimeric side-products.

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