

Phosphazene-Base-Catalyzed Tandem Addition–Cyclization Reaction of *o*-Alkynylbenzaldehyde with Oxygen and Nitrogen Nucleophiles

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Abstract: The tandem addition–cyclization reaction between *o*-alkynylbenzaldehyde and nucleophile catalyzed by P4'-Bu, a phosphazene base, is demonstrated. The nucleophilic cyclization is efficiently triggered not only by alcohols, including sterically demanding ones, but also by nitrogen nucleophiles, such as amide and pyrrole, under the influence of a catalytic amount of P4'-Bu. The method enables efficient access to isobenzofuran derivatives under mild conditions.

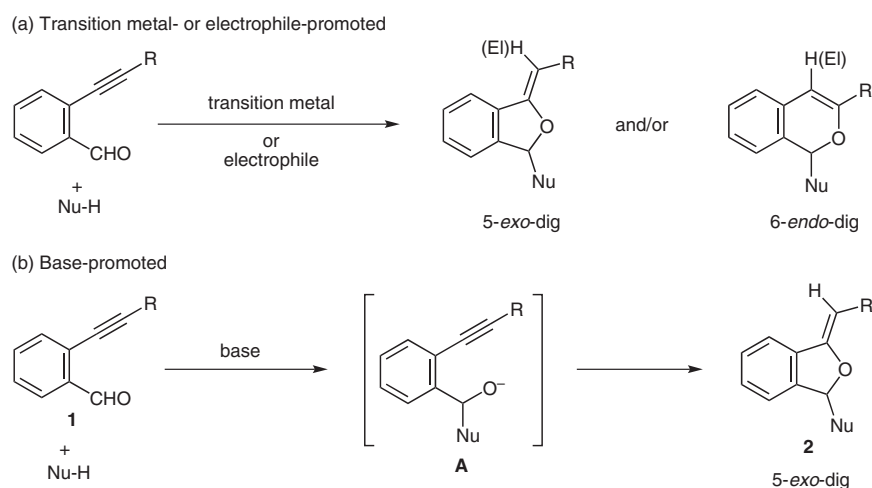
Key words: phosphazene, tandem reaction, cyclization, isobenzofuran, *o*-alkynylbenzaldehyde

The intramolecular cyclization reaction of *o*-alkynyl-substituted arene carbonyl compounds with nucleophilic components is a powerful and atom-efficient strategy for the construction of substituted oxygen heterocycles.^{1–3} A variety of activating agents, such as metallic catalysts¹ and iodine or related electrophiles,² have been extensively investigated for their potential to promote the cyclization via electrophilic activation of alkynes (Scheme 1, a). Under electrophilic conditions, various nucleophiles, such as alcohol and carbon-centered ones, have been employed to afford densely functionalized oxygen heterocycles, and it was shown that the predominance of the cyclization mode, 6-*endo*-dig or 5-*exo*-dig, is highly dependent on the

starting *o*-alkynyl-substituted arene carbonyl compounds and activating agents.^{1,2}

The analogous cyclization of heteroaromatic aldehydes having an *o*-alkynyl substituent was recently reported by Belmont and co-workers^{3a} and Cikotiene et al.^{3b} using K₂CO₃ or alkoxide as base promoter to activate nucleophilic components. However, this type of nucleophilic cyclization, namely, the base-mediated tandem addition–cyclization reaction, remains largely unexplored despite exclusive formation of a furan ring via the 5-*exo*-dig cyclization mode (Scheme 1, b).³ Alcohols are the only nucleophiles reported to date and neither secondary nor tertiary alcohols promote the nucleophilic cyclization effectively. Primary alcohols are the sole nucleophile that triggers the cyclization efficiently. In addition, a large excess of alcohol (generally used as solvent) is required to obtain the corresponding heterocycles in good yields.

Recently, we demonstrated the intramolecular cyclization of *o*-alkynylbenzoic acid catalyzed by organic bases to afford isobenzofuranone derivatives via the 5-*exo*-dig cyclization mode.⁴ In our continuing effort to develop base-catalyzed intramolecular cyclization reactions of *o*-alkynyl-substituted arene carbonyl compounds, we have aimed to expand the synthetic utility of the tandem addi-



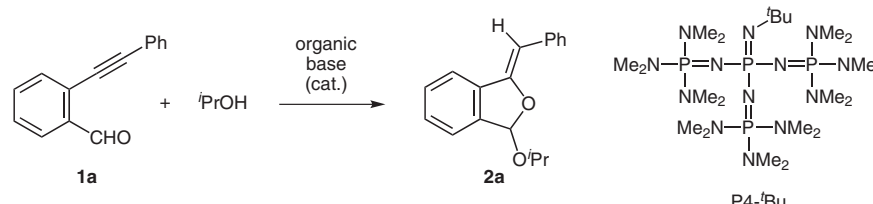
Scheme 1 Tandem addition–cyclization reaction of *o*-alkynyl-substituted arene carbonyl compounds with nucleophiles

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Table 1 Screening of Bases and Optimization of Reaction Conditions^a


Entry	Base (mol%)	<i>i</i> -PrOH (equiv)	Solvent	Conditions	Yield (%) ^b
1	DBU (10)	2	DMSO	80 °C, 3 h	0 ^c
2	TMG (10)	2	DMSO	80 °C, 3 h	0 ^c
3	P4- ^t Bu (20)	2	DMSO	40 °C, 1 h	77
4	P4- ^t Bu (10)	1.5	DMSO	30 °C, 3 h	60
5	P4- ^t Bu (10)	4	DMSO	30 °C, 0.5 h	88
6	P4- ^t Bu (10)	–	<i>i</i> -PrOH	30 °C, 1 h	23
7	P4- ^t Bu (10)	4	toluene	30 °C, 1 h	57
8	P4- ^t Bu (10)	4	MeCN	30 °C, 1 h	trace
9	P4- ^t Bu (10)	4	THF	30 °C, 1 h	(90)

^a All reactions were carried out using 0.2 mmol of **1a**, the indicated equivalent of *i*-PrOH, and catalyst in 0.4 mL of solvent (0.5 M) under argon atmosphere for the time indicated.

^b NMR yield. Isolated yield is in parentheses.

^c Compound **1a** was recovered.

tion–cyclization sequence triggered by nucleophiles. Herein we report the organic-base-catalyzed 5-*exo*-dig cyclization of *o*-alkynylbenzaldehyde derivatives **1** with not only oxygen but also nitrogen nucleophiles, yielding isobenzofuran derivatives **2**. The proposed nucleophilic cyclization was found to proceed smoothly under mild conditions using a catalytic amount of phosphazene base P4-^tBu.⁵

An initial experiment was performed using *o*-alkynylbenzaldehyde **1a** with *i*-PrOH as the nucleophilic component (2 equiv), a catalytic amount of organic base {10 mol% 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)}, and DMSO as solvent, at 80 °C under argon atmosphere. As shown in Table 1, despite using DBU, a relatively strong organic base, and following reaction conditions similar to those used in the base-catalyzed cyclization of *o*-alkynylbenzoic acids,⁴ no desired product was obtained (entry 1). Tetramethylguanidine (TMG) was also ineffective and **1a** was recovered in a nearly quantitative manner (entry 2). We hence turned our attention to using much stronger organic bases, such as phosphazene bases. The organic base P4-^tBu, a member of the phosphazene family, is known as one of the strongest metal-free bases.⁵ Taking advantage of its unique properties, intriguing transformations using a catalytic amount of P4-^tBu have been accomplished.⁶ We therefore attempted to employ P4-^tBu in the present tandem reaction. The reaction of **1a** with *i*-PrOH (2 equiv)

was conducted in the presence of 20 mol% P4-^tBu at 40 °C (entry 3). Delightfully, the reaction proceeded smoothly and corresponding product **2a** was obtained in an acceptable yield within one hour. Optimization of the reaction conditions allowed us to reduce the catalyst load to 10 mol% and to decrease the reaction temperature to 30 °C (entry 5), even though 4 equivalents *i*-PrOH was necessary to achieve a high chemical yield. Further screening for solvents revealed that the catalytic efficiency is markedly dependent on the solvent employed (entries 6–9). Interestingly, a significant reduction in chemical yield was observed when *i*-PrOH was used as solvent (entry 6). A less polar solvent, toluene, was also useful for the present reaction albeit the moderate yield (entry 7), while in the presence of more polar acetonitrile, **1a** was recovered in a nearly quantitative manner (entry 8). Among the solvents tested, THF was found to be the best in terms of chemical yield (entry 9). Desired product **2a** was isolated in 90% yield.

With the optimal conditions in hand, a series of nucleophiles including nitrogen ones were investigated for their suitability in the tandem addition–cyclization reaction. As shown in Table 2, the present catalytic method is applicable not only to oxygen nucleophiles but also to nitrogen ones. The reactions of primary alcohols, *n*-BuOH, BnOH, and allyl alcohol, proceeded smoothly to give corresponding products **2b–d** in high yields (entries 1–3).

Table 2 Tandem Addition–Cyclization Reaction of **1a** with Various Nucleophiles^a

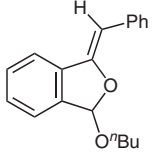
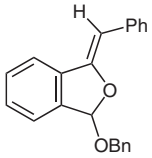
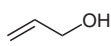
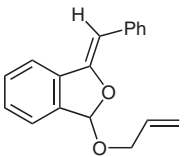
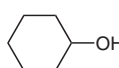
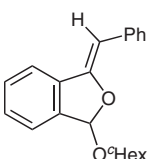
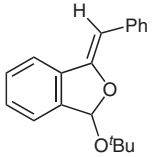
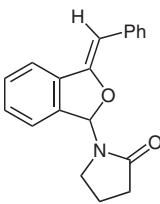
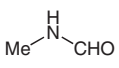
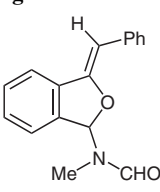
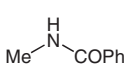
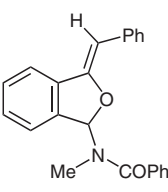
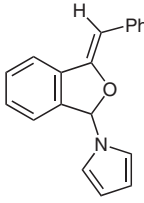
Entry	Nucleophile	Conditions	2	Yield (%) ^b
1	<i>n</i> -BuOH	30 °C, 2 h	 2b	90
2	BnOH	60 °C, 3 h	 2c	93
3		60 °C, 3 h	 2d	91
4		30 °C, 1 h	 2e	99
5 ^c	<i>t</i> -BuOH	80 °C, 18 h	 2f	70
6	2-pyrrolidinone	30 °C, 1 h	 2g	90
7		30 °C, 1 h	 2h	90
8		80 °C, 12 h	 2i	67 ^d

Table 2 Tandem Addition–Cyclization Reaction of **1a** with Various Nucleophiles^a (continued)

Entry	Nucleophile	Conditions	2	Yield (%) ^b
9	pyrrole	30 °C, 1 h		95
10	phthalimide	100 °C, 8 h	–	n.r. ^e
11	benzamide	100 °C, 8 h	–	n.r. ^e

^a The reaction of **1a** (0.2 mmol) with nucleophile (4 equiv) was conducted in THF (0.5 M) in the presence of P4-^tBu (20 μmol, 20 μL of 1 M solution in hexane) under argon atmosphere for the time indicated.

^b Isolated yield.

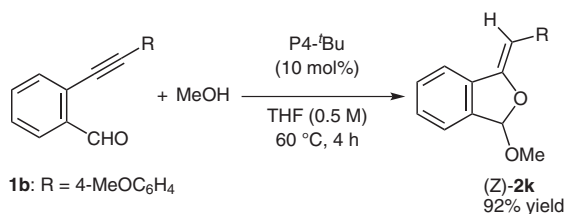
^c The amount of 15 mol% of P4-^tBu was used.

^d Recovery of **1a** in 20%.

^e n.r. = no reaction.

A cyclic secondary alcohol, cyclohexanol, is also applicable giving the corresponding product **2e** in a nearly quantitative yield (entry 4). It is noteworthy that the sterically demanding tertiary alcohol, *t*-BuOH, could be utilized as an effective trigger for the present reaction; desired product **2f** was obtained in satisfactory yield when catalyst load was increased to 15 mol% and the reaction temperature elevated to 80 °C (entry 5). It markedly contrasts the trace or limited amounts of desired products formed in previous methods reported so far.³ Nitrogen nucleophiles as well as alcohols functioned as an effective trigger for the present tandem addition–cyclization sequence. 2-Pyrrolidinone, *N*-methylformamide, *N*-methylbenzamide, and 1-*H* pyrrole provided corresponding products **2g–j** in good to excellent yields (entries 6–9). However, neither phthalimide nor benzamide gave the product (entries 10 and 11), presumably due to the instability of anionic intermediate **A** (Scheme 1).⁷

The tandem addition–cyclization reaction afforded product **2** as the sole geometrical isomer. The geometry of the newly generated double bond was determined to be *Z* after comparing with stereochemically known compound (*Z*)-**2k**.^{1f} Thus, the reaction of *o*-alkynylbenzaldehyde **1b** with MeOH was conducted under modified optimum conditions (Equation 1). Product **2k** was obtained as the sole geometrical isomer in 92% yield and its ¹H NMR and ¹³C NMR data were consistent with those reported by Wu et al.^{1f}

**Equation 1****Table 3** Scope of Substituents on Alkynyl Terminus^a

Entry	1 (R)	Time (h)	2	Yield (%) ^b
1	1b 4-MeOC ₆ H ₄	3	2l	83
2	1c 4-MeC ₆ H ₄	2	2m	78
3	1d 4-F ₃ CC ₆ H ₄	1	2n	65 ^c
4	1e CO ₂ Et	1	2o	75 ^d
5	1f <i>n</i> -Bu	4	–	dec.
6	1g TMS	5	–	dec.
7	1h H	3	–	dec.

^a The reaction of **1** (0.2 mmol) with *i*-PrOH (4 equiv) was conducted in THF (0.5 M) in the presence of P4-^tBu (20 μmol, 20 μL of 1 M solution in hexane) under argon atmosphere for the time indicated.

^b Isolated yield.

^c Trace amount of (*E*)-**2n** was obtained.

^d Combined yield of (*Z*)- and (*E*)-**2o**; *Z*/*E* = 72:28.

Finally, the scope of substituents on the alkynyl terminus was investigated using *i*-PrOH as the nucleophilic component (Table 3). Although the introduction of electron-donating groups to the terminal benzene ring prolonged the reaction time (entries 1 and 2), products **2l** and **2m** were obtained in good yields. The reaction of **1d** having an electron-withdrawing substituent, trifluoromethyl moiety, gave (*Z*)-**2n** in an acceptable yield, accompanied by a trace amount of the geometrical isomer, (*E*)-**2n** (entry 3). The formation of the geometrical isomer was detected markedly in the reaction of **1e** in which electron-withdrawing ethoxycarbonyl was directly introduced to the alkynyl terminus (entry 4). The isomerization at the double bond could be attributed to the fact that vinylic anion intermediates, generated at the cyclization step, were stabilized by these electron-withdrawing groups. Further investigation of terminal substituents, such as alkyl, trimethylsilyl, and hydrogen, showed that decomposition of

the starting *o*-alkynylbenzaldehyde occurred and no desired product was obtained (entries 5–7).

In conclusion, we have demonstrated the organic-base-catalyzed tandem addition–cyclization reaction of *o*-alkynylbenzaldehyde with various nucleophiles. The organic base P4-*t*Bu was found to be an efficient catalyst for the tandem reaction. Most notably is the fact that sterically demanding alcohols are capable of triggering the nucleophilic cyclization efficiently under the influence of a catalytic amount of P4-*t*Bu. We showed for the first time that nitrogen nucleophiles, such as amide and pyrrole, are applicable to the nucleophilic cyclization. The method enables efficient access to isobenzofuran derivatives under mild conditions. Further studies on base-catalyzed nucleophilic cyclization are under way in our laboratory.

Typical Procedure for P4-*t*Bu-Catalyzed Tandem Addition–Cyclization Reaction between *o*-Alkynylbenzaldehyde **1a** and *i*-PrOH

To a THF solution (0.4 mL, 0.5 M) of *o*-(2-phenylethynyl)benzaldehyde **1a** (41.2 mg, 0.2 mmol) and *i*-PrOH (61 mL, 0.8 mmol) was added P4-*t*Bu (20 mL, 20 mmol; 1.0 M solution in hexane) at 30 °C under argon atmosphere. After the consumption of **1a**, the reaction mixture was filtered through a short Florisil pad and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, *n*-hexane–EtOAc, 50:1 to 15:1) to afford product **2a** in 90% yield (37.1 mg).

Analytical Data of **2a**

White solid. ¹H NMR (270 MHz, CDCl₃): δ = 1.36 (6 H, d, *J* = 6.0 Hz), 4.22 (1 H, sept, *J* = 6.0 Hz), 5.98 (1 H, s), 6.67 (1 H, s), 7.17 (1 H, tt, *J* = 7.0, 1.0 Hz), 7.32–7.46 (5 H, m), 7.55–7.59 (1 H, m), 7.75–7.80 (2 H, m). ¹³C NMR (68 MHz, CDCl₃): δ = 22.69, 23.61, 71.85, 97.81, 106.21, 119.74, 123.05, 125.68, 128.15, 128.33, 128.88, 129.67, 135.41, 136.02, 137.89, 153.04. IR (neat): 3053, 2972, 2927, 1658, 1489, 1463, 1365, 1084, 1033, 1014, 942, 904, 822 cm^{−1}. ESI-HRMS: *m/z* calcd for C₁₈H₁₈O₂ [M⁺ + Na]: 289.1199; found: 289.1197.

Analytical Data of **2g**

White solid. ¹H NMR (500 MHz, CDCl₃): δ = 1.88–2.60 (2 H, m), 2.54 (2 H, m), 2.83–2.88 (1 H, m), 3.18 (1 H, tt, *J* = 7.0, 11.0 Hz), 5.98 (1 H, s), 7.18 (1 H, dd, *J* = 6.0 Hz), 7.26–7.48 (6 H, m), 7.61 (1 H, d, *J* = 8.0 Hz), 7.74 (2 H, d, *J* = 7.0 Hz). ¹³C NMR (125 MHz, CDCl₃): δ = 17.65, 31.40, 41.50, 85.99, 97.68, 119.95, 122.36, 125.85, 128.26, 128.35, 129.13, 129.66, 135.54, 135.64, 136.01, 153.16, 176.04. IR (neat): 3726, 3707, 3624, 3599, 2891, 1695, 1665, 1491, 1411, 1359, 1271, 1226, 1038, 942 cm^{−1}. ESI-HRMS: *m/z* calcd for C₁₉H₁₇NO₂ [M⁺ + Na]: 314.1151; found: 314.1150.

Analytical Data of **2j**

White solid. ¹H NMR (500 MHz, CDCl₃): δ = 6.05 (1 H, s), 6.25 (2 H, s), 6.74 (2 H, s), 7.17 (1 H, dd, *J* = 7.0 Hz), 7.26–7.35 (3 H, m), 7.41 (1 H, dd, *J* = 7.0 Hz), 7.52 (1 H, dd, *J* = 7.0 Hz), 7.67 (1 H, d, *J* = 7.0 Hz), 7.71 (3 H, d, *J* = 7.0 Hz). ¹³C NMR (125 MHz, CDCl₃): δ = 91.78, 98.45, 109.86, 119.90, 119.91, 123.17, 126.01, 128.33, 128.35, 129.23, 130.06, 135.32, 135.52, 136.60, 152.61. IR (neat): 2923, 1689, 1596, 1487, 1307, 1082, 1033, 1016, 960, 760 cm^{−1}.

ESI-HRMS: *m/z* calcd for C₁₉H₁₅NO [M⁺ + Na]: 296.1046; found: 296.1045.

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- (7) Other nucleophiles, such as phenol, 1-butanethiol, dimethyl malonate, and phenylacetylene did not give desired product.

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