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Dichotomous Control of *E*/*Z*-Geometry in Intramolecular Cyclization of *o*-Alkynylbenzamide Derivatives Catalyzed by Organic Superbase P4-*t*Bu in the Presence/Absence of Water

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Synthetic studies on heterocyclic compounds have been a continuous theme in organic chemistry and hence a considerable number of synthetic methods have been reported to date. Among these methodologies, intramolecular cyclization of alkynylbenzene derivatives having a nucleophilic substituent at the *ortho*-position is a simple and powerful strategy to construct a variety of heterocyclic compounds. Intramolecular cyclization of *o*-alkynylbenzoic acid[1] and *o*-alkynylbenzamide,[2,3] as well as their derivatives,[4] represents one of the most efficient and well-investigated methodologies for constructing oxygen and nitrogen heterocycles, respectively (Figure 1). In particular, palladium-catalyzed[2] or iodine-promoted[3e] intramolecular cyclization of *o*-alkynylbenzamides, which proceeds through electrophilic activation of an alkyne moiety via 5-*exo* or 6-*endo* cyclization, is a well documented method to provide five- or six-membered nitrogen heterocycles, many of which are potentially useful as pharmaceuticals or other biologically active compounds. An alternative strategy to electrophilic activation is intramolecular cyclization via activation of a nucleophilic site through the addition of a catalytic or stoichiometric amount of a base (Figure 1). However, such base-catalyzed intramolecular reactions have not been well exploited.[2c,e,3c,d] Herein we report the organic base-catalyzed intramolecular cyclization of *o*-alkynylbenzamide (**1**) to provide efficient access to isoindolinone derivatives (**2**), in which dichotomous control of the geometry at the *exo*-vinylidene moiety was established using the organic superbase P4-*t*Bu (**3**), a member of the phosphazene family.[5,6] The presence/absence of water

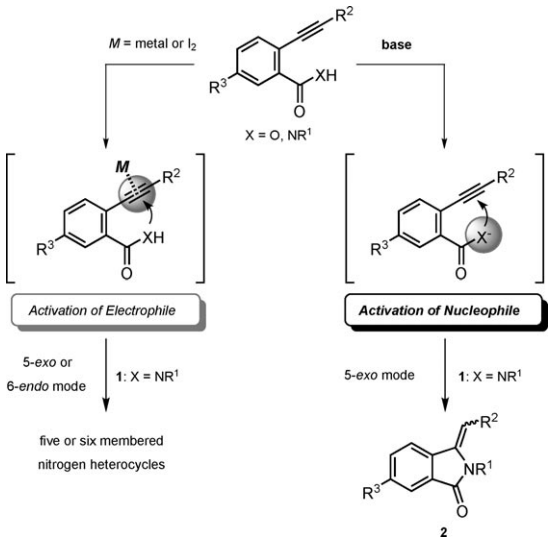

Figure 1. Intramolecular cyclization of *o*-alkynylbenzene derivatives.

along with the use of P4-*t*Bu (**3**) was found to provide the necessary control of the *E*/*Z*-geometry at the double bond.

The use of water as a controlling element in the final geometry obtained at the double bond was inspired by the results of an initial screening for organic bases under water-free conditions.[7] The base-catalyzed intramolecular cyclization reactions of the parent compound *o*-alkynylbenzamide (**1a**) were performed using a catalytic amount (10 mol%) of a common organic base, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), or a phosphazene superbase, P4-*t*Bu (**3**), in acetonitrile or DMSO under an argon atmosphere. As shown in Table 1, the reaction of *o*-alkynylbenzamide (**1a**) proceeded smoothly and *E*/*Z*-geometrical mixtures of the isoindolinone derivative (**2a**) were obtained in excellent chemical yield in all cases. It is noteworthy that the *E*/*Z*-selectivity of **2a** was markedly dependent not only on the solvents and organic bases employed, but also on the concentration of the reactants. When acetonitrile was employed as a solvent, higher *Z*-selectivity was observed than that in DMSO (Table 1,

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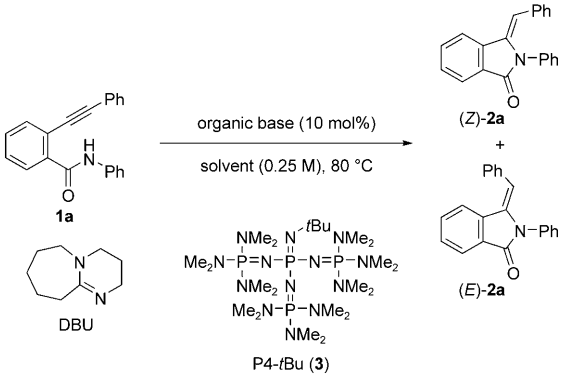
Table 1. Screening of catalysts, solvents, and concentration of intramolecular cyclization of **1a**.[a]



Entry	Organic base	Solvent	*t* [h]	Yield [%][b]	*E*/*Z*[c]
1	DBU	MeCN (0.25 M)	6	99	10:90
2	DBU	DMSO (0.25 M)	6	99	50:50
3	**3**	DMSO (0.25 M)	2	99	70:30
4	**3**	DMSO (0.125 M)	2	99	81:19

[a] Unless otherwise noted, all reactions were carried out using 0.2 mmol of **1a** and 20 μmol of an organic base (10 mol%) in the indicated solvent (0.8 mL: 0.25 M or 1.6 mL: 0.125 M) at 80 °C. [b] ^{1}H NMR yield. [c] *E*/*Z* ratio was detemined by ^{1}H NMR.

entry 2 vs 1).[8,9] The use of the much stronger base P4-*t*Bu (**3**), instead of DBU, was found to provide the opposite geometrical isomer, (*E*)-**2a**, as the major product, albeit in moderate selectivity (Table 1, entry 3). Further screening of the reaction conditions while changing the concentration (Table 1, entry 4) revealed a considerable concentration effect in the catalysis by P4-*t*Bu (**3**) (Table 1, entry 4 vs 3); at a lower concentration, the *E*-selectivity increased (Table 1, entry 4), reaching 81% *E* for a 0.125 M solution of **1a**.

Recently we reported the analogous intramolecular cyclization of *o*-alkynylbenzoic acids (**4**) catalyzed by organic bases to afford phthalide derivatives (**5**) in excellent *Z*-selectivity (Figure 2).[1b,10] In the previous carboxylic acid system,

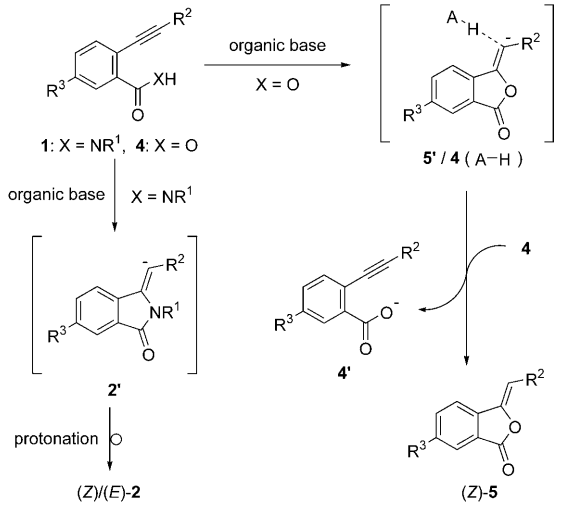
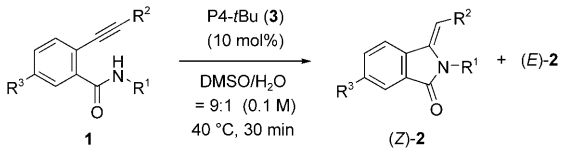


Figure 2. Intramolecular cyclization of *o*-alkynylbenzoic acids and *o*-alkynylbenzamides catalyzed by organic base.

we proposed that an intermediary carbanion (**5**′) was effectively quenched by the acidic proton delivered from the carboxylic acid fragment of **4**.[10,11] In contrast to the cyclization of the carboxylic acid system, the acidity of the amide proton is presumed to be insufficient to enable it to be an effective proton source in the present system. Therefore, it seems likely that the intriguing dependence of the *E*/*Z*-selectivity on the concentration and properties of the organic bases can be ascribed to the absence or presence of an efficient proton source for quenching of the intermediary carbanion species (**2**′). If a more acidic proton source existed in the reaction media, the intermediary carbanion (**2**′) could be protonated immediately, and hence it is anticipated that (*Z*)-**2** would be formed predominantly as in the case of the carboxylic acid system. In order to validate this hypothesis, we therefore attempted the reaction using water as the facile proton source coupled with the more basic P4-*t*Bu (**3**) as the catalyst.[12]

The proposed *Z*-selective cyclization of **1a** was performed in a DMSO/H_2O (v/v = 9:1) co-solvent system in the presence of P4-*t*Bu (**3**) (10 mol%). The representative results are summarized in Table 2. As expected, the *Z*-isomer was

Table 2. *Z*-Selective cyclization reaction catalyzed by P4-*t*Bu in DMSO/H_2O co-solvent system.[a]



Entry	1	R^1	R^2	R^3	Yield [%][b]	*E*/*Z*
1[c]	**1a**	Ph	Ph	H	87	<2:>98
2[c]	**1b**	Bn	Ph	H	96	<2:>98
3[c]	**1c**	allyl	Ph	H	99	<2:>98
4[c]	**1d**	MPM	Ph	H	95	<2:>98
5[c]	**1e**	MPM	*p*-$MeOC_6H_4$	H	97	<2:>98
6	**1f**	MPM	*p*-$CF_3C_6H_4$	H	99	24:76
7	**1g**	MPM	1-naphthyl	H	99	11:89
8	**1h**	MPM	TMS	H	91	–[d]
9	**1i**	MPM	*n*Pr	H	97	53:47
10	**1j**	MPM	Ph	Ac	61	67:33
11[c]	**1k**	MPM	Ph	MeO	92	<2:>98

[a] Unless otherwise noted, all reactions were carried out using 0.2 mmol of **1** and 20 μmol of **3** (10 mol%) in 1.8 mL of DMSO and 0.2 mL of H_2O at 40 °C for 30 min. [b] Isolated yield. [c] Only trace amount of (*E*)-**2** was obtained in crude ^{1}H NMR or was not obtained. [d] Desilylated product (**2r**) was obtained.

obtained as the major product in the DMSO/H_2O co-solvent system in most cases. It is noteworthy that a catalytic amount of P4-*t*Bu (**3**) worked very well even in the presence of water and gave the corresponding isoindolinone derivatives (**2**) in excellent yield, albeit at a lower reaction temperature (40 °C).[13] A variety of substituents (R^1) at the nitrogen atom, including phenyl, benzyl, allyl, and *p*-methoxyphenylmethyl (MPM) groups, were applicable to the present DMSO/H_2O system, providing the *Z*-isomers exclusively in excellent yield (Table 2, entries 1–4). We further investigated

the scope and limitations of the *Z*-selective cyclization using a series of *o*-alkynylbenzamide derivatives (**1**) bearing a MPM moiety at the nitrogen atom (Table 2, entries 5–11). The introduction of an electron-donating methoxy group to either the terminal or backbone aromatic ring provided excellent *Z*-selectivities (Table 2, entries 5 and 11). In contrast, the introduction of an electron-withdrawing group on either ring led to a decrease in the *Z*-selectivity (Table 2, entries 6 and 10). In particular, introduction of an acetyl group to the backbone aromatic ring provided the opposite *E*-isomer as the major product (Table 2, entry 10). Further screening of sterically demanding substituents at the alkynyl terminus revealed that the 1-naphthyl substituent was able to provide a high level of *Z*-selectivity (Table 2, entry 7), while the cyclization of **1h**, having a trimethylsilyl (TMS) group, afforded the desilylated product (**2r**), although in high yield (Table 2, entry 8). The aliphatic substituent was also applicable but compromised the selective formation of *Z*-isomers (Table 2, entry 9).

We next turned our attention to developing *E*-selective cyclization reactions using the same catalyst, P4-*t*Bu (**3**), but under water-free conditions. As shown in Table 3, *E*/*Z*-selectivities were substantially dependent on the substituents (R^1) introduced at the nitrogen atom (Table 3, entries 1–4). Among the substituents examined, the MPM group was found to be the best with respect to both reactivity and selectivity (Table 3, entry 4), with the cyclization product obtained quantitatively in high *E*-selectivity.[14] We further investigated the scope and limitations of the present *E*-selective cyclization under the P4-*t*Bu/DMSO system in the absence of water. In summary, it was found that the electronic properties and steric demand of the substituents (R^2 and R^3) had a marked impact on the *E*/*Z*-selectivities. Substitution by an electron-donating group at the terminal or backbone phenyl ring compromised the formation of *E*-isomers (Table 3, entries 5 and 11), while substitution of an electron-withdrawing group afforded the *E*-isomers predominantly (Table 3, entries 6 and 10), albeit in low yield for the acetyl substituent owing to side reactions (Table 3, entry 10). The most sterically hindered substituents, TMS and 1-naphthyl, exhibited high *E*-selectivities (Table 3, entries 7 and 8). Introduction of an aliphatic group at the alkynyl terminus led to a decrease in chemical yield, but gave rise to the *E*-isomer in a highly selective manner (Table 3, entry 9).

Table 3. *E*-Selective cyclization reaction catalyzed by P4-*t*Bu under water-free conditions.[a]

Entry	**1**	R^1	R^2	R^3	Yield [%][b]	*E*/*Z*
1[c]	**1a**	Ph	Ph	H	98	80:20
2[c]	**1b**	Bn	Ph	H	70	91:9
3[c]	**1c**	allyl	Ph	H	72	53:47
4	**1d**	MPM	Ph	H	99	87:13
5	**1e**	MPM	*p*-$MeOC_6H_4$	H	99	51:49
6	**1f**	MPM	*p*-$CF_3C_6H_4$	H	90	89:11
7	**1g**	MPM	1-naphthyl	H	93	94:6
8	**1h**	MPM	TMS	H	58	>98:<2
9	**1i**	MPM	*n*Pr	H	62	94:6
10	**1j**	MPM	Ph	Ac	30	87:13
11	**1k**	MPM	Ph	MeO	92	28:72

[a] Unless otherwise noted, all reactions were carried out using 0.2 mmol of **1** and 20 μmol of **3** (10 mol%) in dried DMSO (1.6 mL) at 40 °C for 1–2 h. [b] Isolated yield. [c] Reactions were carried out at 60 °C.

A plausible mechanism for the dichotomous control of *E*/*Z*-geometry is depicted in Figure 3. An anionic intermediate

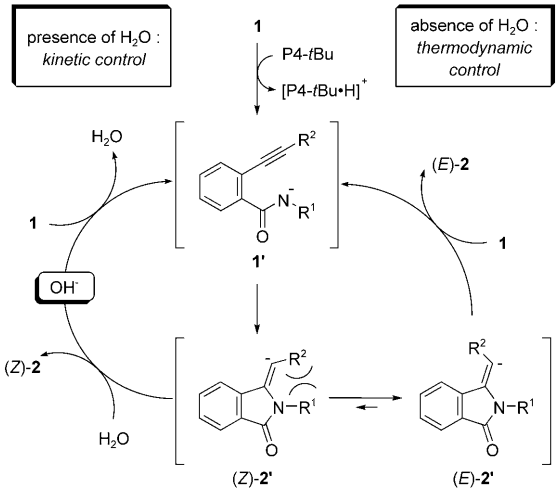
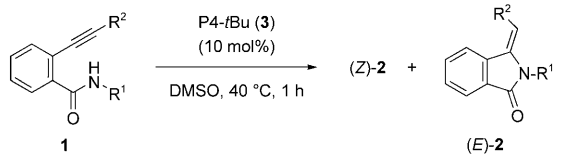


Figure 3. Plausible mechanism of dichotomous control of *E*/*Z*-geometry in intramolecular cyclization reaction catalyzed by P4-*t*Bu.

1′ generated by deprotonation of **1** undergoes intramolecular cyclization to form a vinyl anion intermediate, (*Z*)-**2′**. In the presence of water, the intermediary (*Z*)-**2′** would be protonated immediately by water to provide (*Z*)-**2** as the kinetically favored product with high selectivity. After protonation, a hydroxide is also formed, which serves as a base to reproduce **1′** for subsequent catalytic cycles. In contrast, in the absence of water, an efficient proton source is not present during the course of the reaction, because the conjugate acid of P4-*t*Bu, that is, $[P4\text{-}tBu{\cdot}H]^+$, and the amide proton of **1** are less acidic.[12] Hence a repulsive interaction between R^1 and R^2 would enforce the geometrical isomerization from anion (*Z*)-**2′** to the thermodynamically favored (*E*)-**2′** before protonation occurs.[15] After isomerization to (*E*)-**2′** as the major geometrical isomer, the intermediary anion (**2′**) would be protonated by the less acidic **1**, accompanied by the generation of anion (**1′**) for further catalytic cycles.

Finally we attempted to increase the *E*-selectivity under water-free conditions on the basis of the above mechanistic considerations. If the repulsive interaction between R^1 and R^2 were critical for determining the relative stability between *E*/*Z*-geometrical isomers of the anions (**2′**), it can be anticipated that the *E*-selectivity would be enhanced by introduction of a more sterically congested substituent at the R^1 group. As expected, substitution by the bulky benzhydryl or *tert*-butyl moiety at the nitrogen atom gave rise to a higher *E*-selectivity (Table 4, entries 1 and 2). The *tert*-butyl substituent is particularly effective[16] and applicable to a series of *o*-alkynylbenzamide derivatives (**1**), providing the

Table 4. *E*-Selective cyclization of **1** having bulky R^1 substituents under water-free conditions.[a]



1 (*E*)-**2**

Entry	**1**	R^1	R^2	Yield [%][b]	*E*/*Z*
1	**1l**	Ph_2CH-	Ph	93	92:8
2	**1m**	*t*Bu	Ph	93	>98:<2
3	**1n**	*t*Bu	*p*-$MeOC_6H_4$	93	>98:<2
4	**1o**	*t*Bu	*p*-$CF_3C_6H_4$	91	>98:<2
5	**1p**	*t*Bu	1-naphthyl	90	>98:<2
6	**1q**	*t*Bu	*n*Pr	11	>98:<2

[a] Unless otherwise noted, all reactions were carried out using 0.2 mmol of **1** and 20 μmol of **3** (10 mol%) in DMSO (1.6 mL) at 40°C for 1 h. [b] Isolated yield.

E-isomers exclusively (Table 4, entries 3–6), even in the reaction of **1n**, which has a *p*-methoxyphenyl substituent at the alkynyl terminus (Table 4, entry 3). The excellent *E*-selectivity achieved in the reaction of **1n** deserves attention, because the MPM-substituted **1e**, which also has a *p*-methoxyphenyl terminus, yielded a 1:1 mixture of *E*/*Z*-isomers under water-free conditions (see Table 3, entry 5). The compound **1q**, bearing an aliphatic substituent, afforded the *E*-product exclusively, albeit in low chemical yield owing to the formation of byproducts (Table 4, entry 6).

In conclusion, we have developed an intramolecular cyclization reaction of *o*-alkynylbenzamides that allows dichotomous control of the *E*/*Z*-geometry when catalyzed by an organic superbase, P4-*t*Bu. The presence/absence of water along with the use of P4-*t*Bu was found to be crucial in controlling the geometry at the double bond. In the presence of water, the kinetically favoured *Z*-isomers were formed in a highly selective manner in most cases, while in the absence of water, the steric interaction of the substituents introduced at the alkynyl terminus and the nitrogen atom were responsible for the high *E*-selectivity. These methods provide efficient access to isoindolinone derivatives, an important class of biologically active molecules, without the need for a metal catalyst. Further studies on the applicability of the present method, which combines the use of an organic superbase and water, are underway in our laboratory to selected organic syntheses.

Experimental Section

Typical procedure for *Z*-selective cyclization: To water (0.2 mL) and *N*-(4-*m*ethoxyphenylmethyl)-2-(2′-phenylethynyl)benzamide (**1d**) (68.3 mg, 0.2 mmol) was added DMSO (1.8 mL), and then phosphazene base P4-*t*Bu (1 M solution in hexane, 20 μL, 20 μmol) under an Ar atmosphere. The solution was stirred at 40°C for 1 h. After the consumption of **1d**, the reaction mixture was extracted with AcOEt. The combined organic layers were washed with water and brine, and dried over $MgSO_4$. After the solvent was removed by rotary evaporation, the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt 40:1—3:1 as eluent) to give (*Z*)-3-benzylidene-*N*-(*p*-methoxyphenylmethyl)-isoindolin-1-one [(*Z*)-**2d**, yellow oil] in 95% yield.

Typical procedure for *E*-selective cyclization: To a DMSO solution (1.6 mL) of *N*-(*p*-methoxyphenylmethyl)-2-(2′-phenylethynyl)benzamide (**1d**) (68.3 mg, 0.2 mmol) was added phosphazene base P4-*t*Bu (1 M solution in hexane, 20 μL, 20 μmol) under an Ar atmosphere. The solution was stirred at 40°C for 1.5 h. After the consumption of **1d**, the reaction mixture was extracted with AcOEt. The combined organic layers were washed with water and brine, and dried over $MgSO_4$. After the solvent was removed by rotary evaporator, the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt 10:1—1:1 as eluent) to give (*Z*)-3-benzylidene-*N*-(*p*-methoxyphenylmethyl)-isoindolin-1-one [(*Z*)-**2d**, yellow oil] and (*E*)-3-benzylidene-*N*-(*p*-methoxyphenylmethyl)-isoindolin-1-one [(*E*)-**2d**, yellow solid] in 13% and 87% yield, respectively.

Acknowledgements

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Keywords: intramolecular cyclization · organocatalysis · phosphazenes · superbase

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[7] Acetonitrile and DMSO were dried over 3 Å molecular sieves.

[8] Other solvents, such as DMF, toluene, 1,4-dioxane were investigated using 10 mol% of DBU as the catalyst, however these solvents were less effective in terms of either *E*/*Z*-selectivities or chemical yields; DMF: 96% yield, 47% *Z*; toluene: 19% yield, >98% *Z*; 1,4-dioxane: 16% yield, >98% *Z*.

[9] The structure of the major isomer of **2a** was determined to be *Z* by X-ray crystallographic analysis. See the Supporting Information for details.

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[11] Theoretical studies on the carboxylic acid system revealed that the participation of the carboxylic acid fragment reduced the activation energy of the transition states significantly and led to the exclusive formation of the *Z*-isomer. See, Ref. [10].

[12] When DBU is employed as the catalyst, it is considered that the conjugate acid, $[DBU{\cdot}H]^+$, would serve as the proton source, thus providing (*Z*)-**2a** predominantly (Table 1, entries 1–3). To prove our hypothesis, we performed the reaction using P4-*t*Bu (**3**), because this stronger base generates a much less acidic conjugate acid, $[P4\text{-}t\mathrm{Bu}{\cdot}H]^+$.

[13] The reaction of **1a** ($R^1=R^2=$Ph, $R^3=$H) in a DMSO/H_2O co-solvent system provided a trace amount of **2a** at 60 °C for 3 h when DBU was employed as the catalyst. An elevated temperature and prolonged reaction time were required to obtain the desired product in good yield (at 80 °C for 1 h: 89% yield, >98% *Z*).

[14] The structure of the major isomer of **2d** was determined to be *E* by X-ray crystallographic analysis. See the Supporting Information for details.

[15] Neither (*Z*)-**2d** nor (*E*)-**2d** isomerized to opposite geometrical stereoisomer in the presence of 10 mol% P4-*t*Bu in dried DMSO (0.125 M) at 40 °C for 2 h.

[16] The reaction of **1m** ($R^1=t$Bu, $R^2=$Ph, $R^3=$H) in a DMSO/H_2O co-solvent system gave a 1:1 mixture of *E*/*Z*-isomers in 95% yield. This result strongly suggests that the *t*Bu substituent effectively accelerates the isomerization of (*Z*)-**2′** into (*E*)-**2′** (see Table 2, entries 1–4).

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