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Cyclization reactions of 2-alkynylbenzyl alcohol and 2-alkynylbenzylamine derivatives promoted by tetrabutylammonium fluoride

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Abstract—The regioselectivity of the cyclization reaction of 2-ethynylbenzyl alcohol and 2-ethynylbenzylamine derivatives promoted by TBAF was investigated. Six-membered ring derivatives were obtained from the compounds, which have a butyl group on the triple bond. Whereas five-membered ring products were afforded from the substrates having hydrogen or aromatic substituents on the acetylene moiety. It was also concluded that both the tetrabutylammonium cation and fluoride anion were essential for the cyclization. Thus, the actual mechanism and catalytic cycle were also suggested. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Intramolecular ring closure reactions, which can be carried out between the nucleophilic part and carbon–carbon multibond in the same molecules, are one of the useful methods for constructing cyclic compounds and have been used for natural product syntheses.[1] Sometimes, the ring size of the products from the ring closure reaction could be predicted by the famous Baldwin's rule,[2] which was an empirically proposed rule based on stereoelectronic effects. For example, for the substrates (**1**) which have a triple bond as the counterpart, both the '6-*endo-dig*' mode (→**2**) and '5-*exo-dig*' mode (→**3**) are allowed by Baldwin's rule (Fig. 1). In fact, both of the cyclized products for the 2-ethynylphenyl derivatives had been shown in the literature, e.g. indoles,[3,4] benzo[*b*]furans,[3,5] isoquinolines,[6] 3-alkylidenephthalides vs. 3-substituted isocoumarins,[3,7] 1-alkylideneisobenzofurans vs. 3-substituted 1*H*-2-benzopyrans,[7b,8] and 3-alkylideneisoindolin-1-ones vs. 3-substituted isoquinolin-1-ones (Fig. 2).[7f,9] Particularly, the regioselective cyclizations for the latter three cases have also been reported.[8,9] However, in spite of the many reports about such reactions, there has not been well-documented the reasons for the regioselectivity.

Tetrabutylammonium fluoride (TBAF) is a well known reagent for the cleavage of silyl ethers.[10] Commercially available TBAF usually contains H_2O as crystal water or ca. 5 wt% in THF solution and the difficulty in removing H_2O was also reported.[11] Recently, TBAF has sometimes been used not only as a deprotection reagent, but also as effective reagents for the aldol-type condensation reaction,[12a] the Michael-type reaction,[11a,12b] nucleophilic substitution[11a] and addition reaction,[12c] fluorination,[11c] desulfonylation,[12d,e] and promoter for the homocoupling of aryl halides.[12f]

In 1992, Jacobi and Rajeswari reported the first TBAF promoted 5-*exo-dig* cyclization reaction.[13a] After this report, they applied this cyclization reaction to synthesize various kind of 5-membered cyclic enamide.[13b–d] However, in spite of the efficiency, the applications of TBAF promoted cyclization toward the other heterocyclic ring system syntheses have not been reported.

As part of our program directed toward the development of new synthetic methods for heterocyclic compounds, we have already published a mild and efficient indole cyclization method mediated by TBAF.[4d] In this paper, we report the TBAF-mediated cyclization reaction of 2-ethynylbenzyl alcohol derivatives and 2-ethynylbenzylamine derivatives and the mechanistic studies of this cyclization reaction.

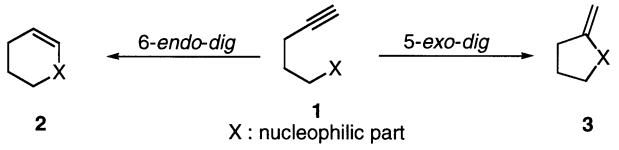

Figure 1.

Keywords: TBAF; 5-*exo-dig*; 6-*endo-dig*; isobenzofurans; benzopyrans; cyclization reactions.

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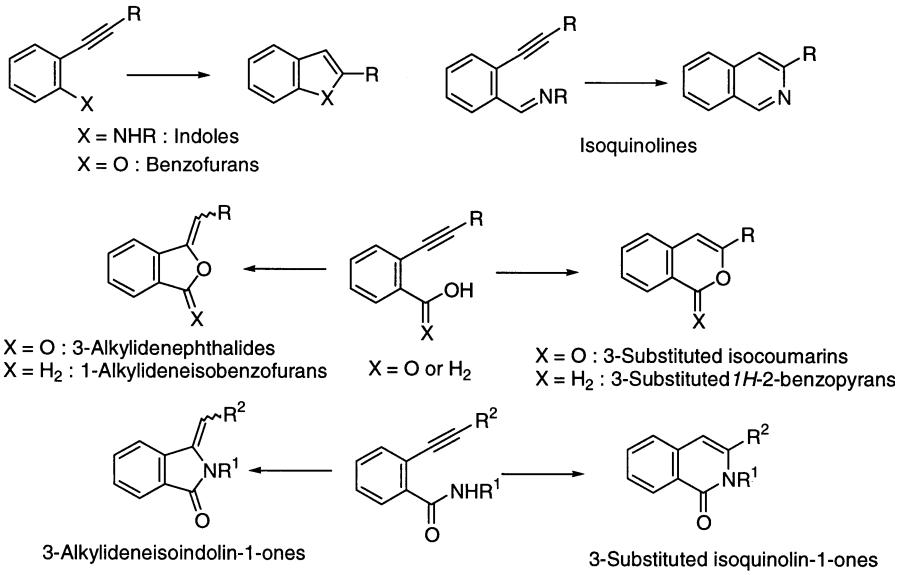


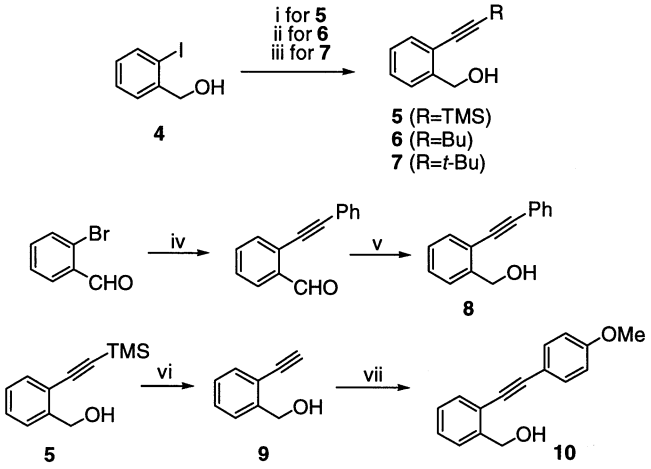
Figure 2.

2. Results and discussion

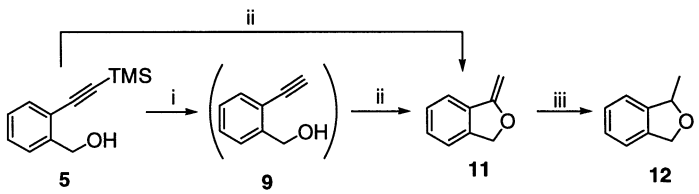
2.1. Cyclization reactions of 2-ethynylbenzyl alcohol and 2-ethynylbenzylamine derivatives

The trimethylsilyl and alkyl substituted 2-ethynylbenzyl alcohol derivatives (**5**, **6**, **7**) were synthesized from 2-iodobenzyl alcohol (**4**) and corresponding alkynes using Sonogashira coupling reaction (Scheme 1).[14] The phenylacetylene derivative (**8**)[8c,d] was synthesized from 2-bromobenzaldehyde and phenylacetylene by the coupling reaction, followed by $NaBH_4$ reduction. The 4-methoxyphenyl derivative (**10**) was synthesized from 2-ethynylbenzyl alcohol (**9**), which was obtained from the detrimethylsilyl reaction of **5**, by the coupling reaction with 4-iodoanisole (Scheme 1).

When the trimethylsilyl substituted benzyl alcohol (**5**) was treated with TBAF in THF at room temperature, only the detrimethylsilyl reaction proceeded to afford **9** as the sole

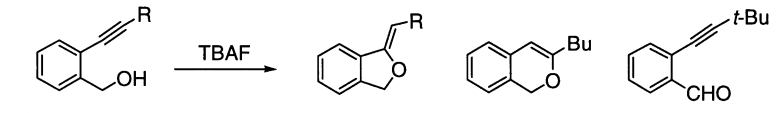


Scheme 1. *Reagents and conditions*: (i) $PdCl_2(PPh_3)_2$, CuI, trimethylsilylacetylene, Et_3N, 0°C–rt, 3 h, 83%; (ii) $PdCl_2(PPh_3)_2$, CuI, 1-hexyne, *i*-Pr_2NH, 0°C–rt, 6 h, 90%; (iii) $PdCl_2(PPh_3)_2$, CuI, 3,3-dimethyl-1-butyne, Et_3N, 0°C–rt, 3.5 h, 91%; (iv) $PdCl_2(PPh_3)_2$, CuI, phenylacetylene, Et_3N, rt, 6 h; (v) $NaBH_4$, MeOH, 0°C, 80% (two steps); (vi) TBAF·$3H_2O$, THF, rt, 1 h; (vii) $PdCl_2(PPh_2)_2$, CuI, 4-iodoanisole, Et_3N, rt, 3.5 h, 64% (two steps).



Scheme 2. *Reagents and conditions*: (i) TBAF, THF, rt, 1.5 h, 62%; (ii) TBAF, THF, reflux; (iii) H_2, Pd–C, toluene, 24 h, 47% (two steps).

Table 1. TBAF promoted cyclization reactions of 2-ethynylbenzyl alcohol derivatives



5 (R=TMS)
6 (R=Bu)
7 (R=*t*-Bu)
8 (R=Ph)
9 (R=H)
10 (R=4-MeOC$_6$H$_4$)

11 (R=H)
13 (R=Ph)
14 (R=4-MeOC$_6$H$_4$)

15

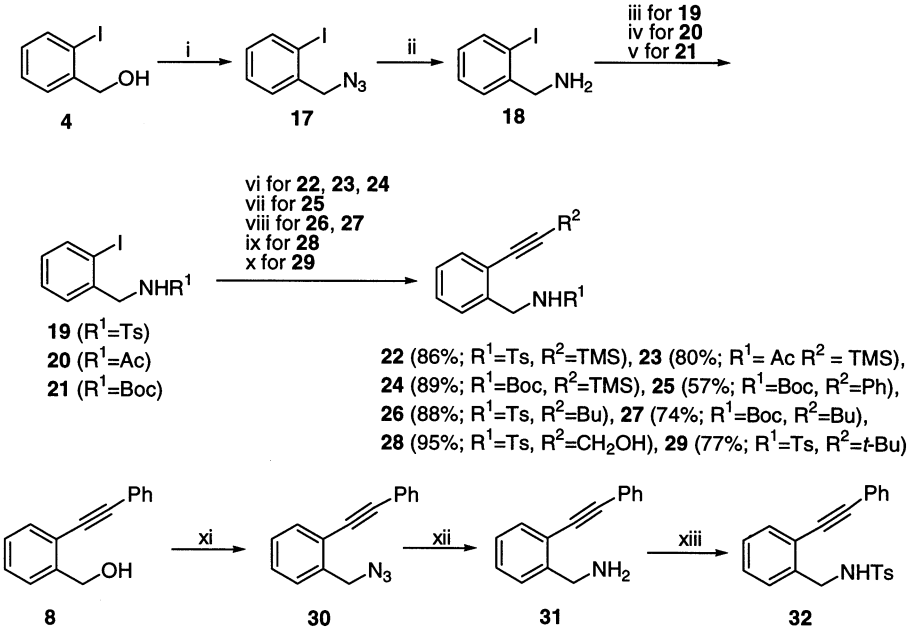
16

Entry	R	Solvent	Temperature	Time	Yield (compound number) (%)		
					5-*exo*-*dig*	6-*endo*-*dig*	**16**
1	TMS (**5**)	THF	Reflux	1.5 h	Quant[a] (**11**)	–	–
2	H (**9**)	THF	Reflux	2 h	Quant[a] (**11**)	–	–
3	Ph (**8**)	THF	Reflux	2 h	80 (**13**)	–	–
4	4-Methoxyphenyl (**10**)	THF	Reflux	4 h	95 (**14**)	–	–
5	Bu (**6**)	THF	Reflux	24 h	–	–	–
6	Bu (**6**)	THF-DMF (4:1)	Reflux	60 h	–	10 (**15**)	–
7	*t*-Bu (**7**)	THF	100°C	6 d	–	–	20[b]

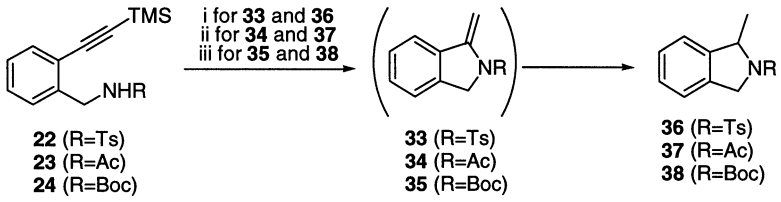
[a] Only **11** was detected by ^{1}H NMR analysis of the crude mixture.
[b] 49% of **7** was recovered.

product. However, when the reaction mixture was heated under reflux, elimination of trimethylsilyl group was observed at first by TLC, then the produced 2-ethynylbenzyl alcohol (**9**) was cyclized to give the compound (**11**). Because of the instability of **11**, the structure of **11** was confirmed as its reduced form (**12**) obtained by the H_2/Pd–C reduction (Scheme 2).[15,16] The results with the other substrates are summarized on Table 1. Briefly, the cyclization reactions produced not only R=H, but also R=Ph and the 4-methoxyphenyl group in good yields to afford only the five-membered products (**11**,[15] **13**,[7b,8a,c,d,15,17] **14**) (Table 1: entries 1–4). However, for R=Bu, the cyclization reaction did not proceed in THF, but in THF–DMF (4:1), the six-membered ring compound (**15**) was isolated as the sole product, but yield was poor (Table 1: entry 5 and 6). When 7 (R=*t*-Bu) was used as the starting material, the cyclized compound could not be isolated at all, instead the oxidized aldehyde (**16**) was obtained (Table 1: entry 7). The detail mechanism of this oxidation is not clear yet, but it can be considered as an air oxidation.

The substituted 2-ethynylbenzylamine derivatives (**22**–**29**)



Scheme 3. *Reagents and conditions*: (i) $(PhO)_2PON_3$, DBU, toluene, rt, 1 h, 90%;[20] (ii) PPh_3, THF, 0°C–rt, 16 h, then 3N NaOH, rt, 1 h; (iii) *p*-TsCl, Et_3N, THF, 0°C–rt, 2 h; (iv) Ac_2O, pyridine, rt, 2 h; (v) Boc_2O, THF, rt, 2 h; (vi) $PdCl_2(PPh_3)_2$, CuI, trimethylsilylacetylene, Et_3N–THF, rt, 3 h for **22** and **23**, Et_3N, rt, 2 h for **24**; (vii) $PdCl_2(PPh_3)_2$, CuI, phenylacetylene, *i*-Pr_2NH, THF, 0°C–rt, 12 h; (viii) $PdCl_2(PPh_3)_2$, CuI, 1-hexyne, *i*-Pr_2NH, THF, 0°C–rt, 12, 5 h for **26**, 2.5 h for **27**; (ix) $PdCl_2(PPh_3)_2$, CuI, propargyl alcohol, *i*-Pr_2NH, rt, 6 h; (x) $PdCl_2(PPh_3)_2$, CuI, 3,3-dimethyl-1-butyne, Et_3N–THF, 0°C–rt, 2.5 h; (xi) $(PhO)_2PON_3$, DBU, toluene, rt, 12 h;[20] (xii) PPh_3, THF, rt–40°C, 6 h, then 3N NaOH, rt, 2 h; (xiii) *p*-TsCl, Et_3N, THF, 0°C–rt, 30 h, 46% (three steps).



Scheme 4. *Reagents and conditions*: (i) TBAF·3H$_2$O, THF, rt, 9 h, then H$_2$, Pd–C, THF, 18.5 h, 86%; (ii) TBAF·3H$_2$O, THF, reflux, 8 h, then H$_2$, Pd–C, THF, 13 h, 91%; (iii) TBAF·3H$_2$O, THF, reflux, 25 h, then H$_2$, Pd–C, THF, 18 h, 73%.

were synthesized by the coupling reaction with **19**, **20**, and **21** that could be synthesized from 2-iodobenzyl alcohol (**4**) through the azide (**17**) and the benzylamine (**18**) (Scheme 3). The results of the Sonogashira coupling reaction[14] between the iodides (**19**, **20**, and **21**) and the various acetylenes are summarized in Scheme 3.

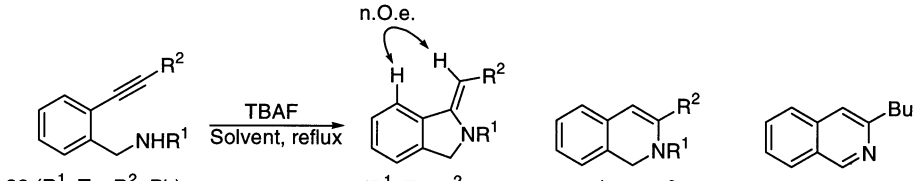
The tosylamide (**32**) was synthesized from the benzyl alcohol (**8**) shown by Scheme 3 in good overall yield.

When **22**, **23**, and **24** were refluxed in THF in the presence of TBAF, elimination of the trimethylsilyl group on the terminal alkyne first occurred as the reaction of the benzyl alcohol (**5**), and then the cyclization smoothly proceeded to give the cyclized products (**33**, **34**,[9g] and **35**). As the products (**33**, **34**, and **35**) were also unstable like **11**, determination of the structures was carried out after being converted to their reduced forms by the catalytic hydrogenation (Scheme 4). Among the tested compounds, the tosylamide (**22**) had the highest reactivity compared with the acetamide (**23**) and the *t*-butyl carbamate (**24**) (rt vs. THF reflux). These results may be ascribed to the difference in the pK_a value of the N–H proton.

The results of the other substrates, which have the Ph, Bu, CH_2OH, and *t*-Bu groups on the terminal alkyne are summarized in Table 2.

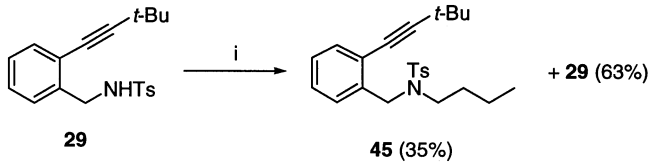
For R^2=Ph, the compound having both R^1=Ts (**32**) and Boc (**25**), only the five-membered products (**39**[9b] and **40**) were produced in THF under reflux (Table 2: entries 1 and 2). The geometry of the double bond of **39** and **40** were determined by n.O.e. experiments between the olefinic proton and aromatic proton shown in the figure of Table 2. When the substrates, which have R^2=Bu (**26**), were reacted with TBAF in THF or dioxane–THF, the spontaneous E2 elimination of the sulfinic acid occurred from almost half of the product to afford a mixture of **42** and 3-butylisoquinoline (**44**)[18] (Table 2: entries 3 and 4). However, this side reaction was avoided by changing the solvent to dioxane (Table 2: entry 5). Although there is no obvious evidence, presumably the suppression of the E2 reaction is caused by reducing the polarity of the solvent by changing from THF to dioxane. The reaction of **27** (R^1=Boc, R^2=Bu) did not proceed at all and only the recovering the starting material was observed (Table 2: entry 6). In case of **28** (R^1=Ts, R^2=CH_2OH), in which R^2 group is much smaller than **26** (R^2=Bu), two products (**41** and **43**) were isolated and the structure of the former was characterized for five-membered compound and the latter was six-membered compound by analyzing their

Table 2. TBAF promoted cyclization reactions of 2-ethynylbenzylamine derivatives



Entry	Substrate	Reagent	Solvent	Time (h)	Yield (compound number) (%)		
					5-*exo-dig*	6-*endo-dig*	**44**
1	**32**	TBAF·3H$_2$O	THF	28	32 (**39**)	–	–
2	**25**	TBAF (THF solution)	THF	3	56 (**40**)	–	–
3	**26**	TBAF (THF solution)	THF–DMF (10:1)	12	–	37 (**42**)	45
4	**26**	TBAF (THF solution)	Dioxane	12	–	54 (**42**)	36
5	**26**	TBAF·3H$_2$O	Dioxane	24	–	84 (**42**)	–
6[a]	**27**	TBAF (THF solution)	THF	48	–	–	–
7	**28**	TBAF·3H$_2$O	THF	2.5	66 (**41**)	30 (**43**)	–

[a] 100% of **27** was recovered.



Scheme 5. *Reagents and conditions*: (i) TBAF·$3H_2O$, dioxane, reflux, 2 d.

^{1}H NMR spectra (Table 2: entry 7). When **29** (R^1=Ts, R^2=*t*-Bu) was reacted in dioxane at 100°C, the only isolated product was the butylated compound on the nitrogen atom in place of the cyclization (Scheme 5).

The following results for this cyclization reaction can be used for both the benzyl alcohol derivatives and benzylamine derivatives:

1. These cyclization reactions are sensitive to the bulkiness of the substituents on the terminal alkyne.
2. Generally, the benzylamine derivatives are much more reactive than the benzyl alcohol derivatives.
3. The reactivity is highly depended on the acidity of the proton on the nitrogen atom.
4. Five-membered ring products were observed for the reaction of the substrates having a hydrogen atom or aromatic ring or smaller alkyl chain on the terminal alkyne.
5. Six-membered ring products were afforded for a relatively bulky alkyl group (Bu) at the end of the triple bond.

When 2-ethynylbenzoic acid or amide derivatives were used as the substrates, the observed regioselectivity was highly dependent on the employed reagents. For example, Kundu et al. reported that for the triethylammonium salt promoted cyclization, phthalides and the isoindolin-1-ones are major products irrespective of the substituted group on the end of the triple bond.[7d,9j] On the other hand, substrate independent 6-*endo-dig* selective cyclization reactions were shown by Liao (palladium–zinc chloride catalyze reaction),[7e] Sashida[7f] and Nagarajan[9a] (palladium catalyzed reactions; Sashida reported that benzoic acid derivatives having a bulky substituent on the acetylne gave a mixture of both mode products) and almost the same results were also observed by Bellina et al. for the silver ion catalyzed cyclization reaction.[7g]

In contrast to these results, when the benzyl alcohol derivatives (**5**–**10**) were used as the substrates, the regioselectivity tendency is similar to the reported in the literature.[8] Namely, when a hydrogen or aromatic ring is on the end of the alkyne, cyclization produced the 5-*exo-dig*, but the 6-*endo-dig* product is produced for the alkyl chain substituent. In our cases, the observed selectivity not only of the alcohol, but also the amino derivatives are compatible with the results of Castro and Padwa.[8a,c,d]

If the resonance effect of the 4-methoxyphenyl group contributes to the reaction, the six-membered ring product might be produced to some extent (Fig. 3). However, we could not detect the six-membered product at all for the reaction of the phenyl and 4-methoxyphenyl substrates (Table 1: entries 3 and 4; Table 2: entries 1 and 2). Therefore, at least for the cyclization of the benzyl alcohol and benzylamine derivatives, it seems likely that the electronic nature of the

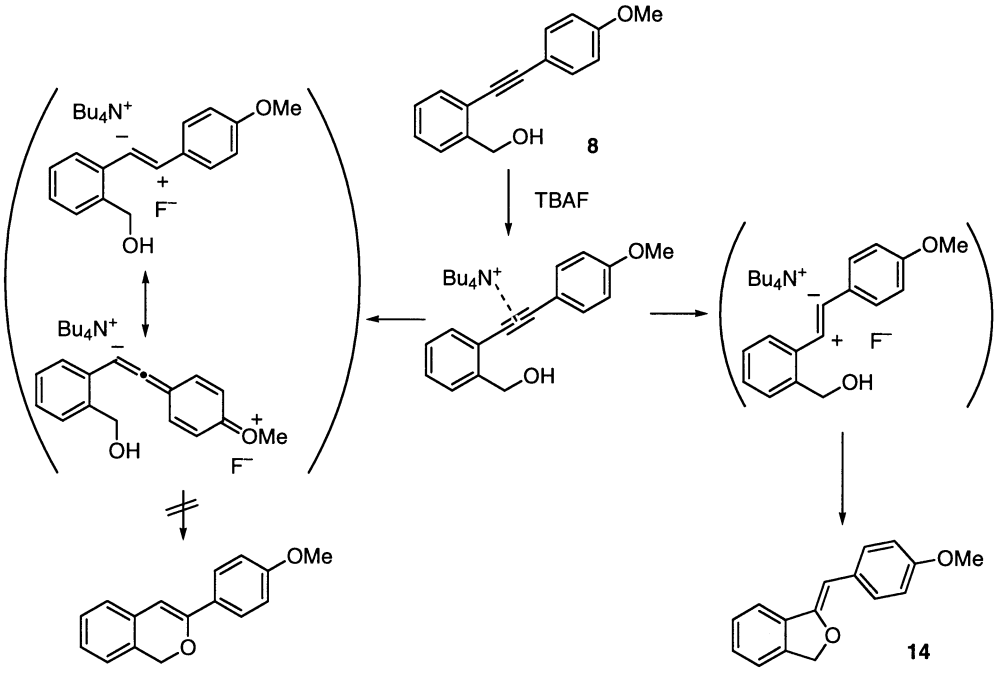


Figure 3.

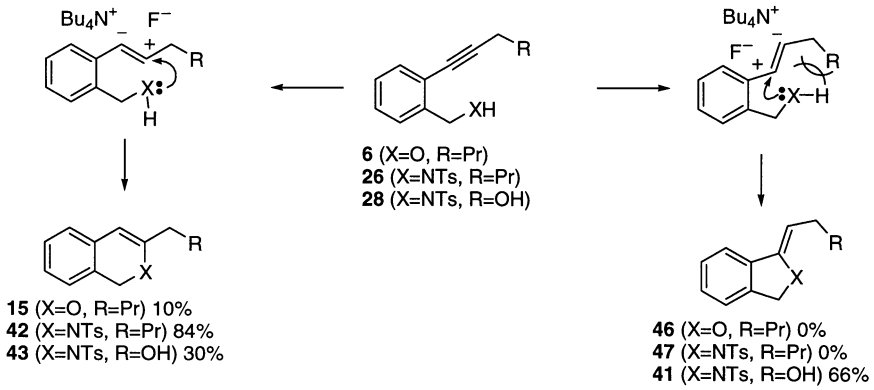


Figure 4.

substituted group on the acetylene terminal is not important for the cyclization mode.

On the other hand, the substrate that has butyl group on the acetylene terminal (**26**) gave exclusively six-membered product (**42**). However, the reaction of the compound having smaller substituent (**28**: CH_2OH) gave the mixture of five-membered (**41**) and six-membered compound (**43**). Therefore, it can be concluded that the observed six-membered ring cyclization selectivity for the alkyl substituents will be due to the steric repulsion at the transition state (Fig. 4).

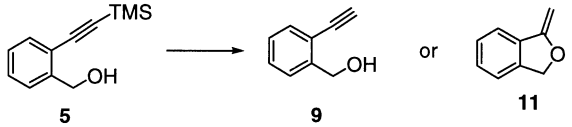
2.2. Mechanistic study of the cyclization reaction mediated by TBAF

To clarify the requirement of this particular cyclization reactions, we next tested various reaction conditions using **5** as the substrate. The product(s) were analyzed by ^1H NMR spectra of the crude reaction mixture and the results are shown in Table 3.

Commercially available TBAF solution in THF is known to be basic, because it contains a small amount of H_2O.[11] As we have already published about the cyclization reaction mediated by the alkoxide anion,[19] we doubted that the cyclization was caused by the alkaline conditions. However, under alkaline conditions decomposition of the starting material (Table 2: entry 2) or only the detrimethylsilyl product were observed (Table 2: entries 1 and 4) and no cyclized product was detected at all. The reaction with tetrabutylammonium chloride (TBACl) did not proceed at all and only the starting material was recovered even at reflux temperature with or without H_2O (Table 2: entries 3 and 4). These results strongly suggest that the fluoride ion is essential for these cyclization reactions.

Next, the effects of the counter cation were investigated. The reaction with KF in THF or MeCN did not give **11**, even at reflux temperature (Table 2: entries 5 and 6). However, when CsF was used as the reagent, only the detrimethylsilyl reaction occurred in THF at rt (Table 2: entry 7) or reflux temperature (Table 2: entry 8), in MeCN at rt (Table 2: entry 9), but a cyclized product was obtained

Table 3. Cyclization reactions of **5** under various conditions



5 **9** **11**

Entry	Reagents	Solvent	Temperature	Time (h)	Product
1	K_2CO_3	MeOH	Rt	11.5	**9**
2	*t*-BuOK	THF	Rt	0.5	Decomposed
3	TBACl	THF	Reflux	6	No reaction
4	TBACl+0.1N NaOH	THF–H_2O	Reflux	2	**9**
5	KF	THF–H_2O	Rt	22.5	No reaction
6	KF·$2H_2O$	MeCN	Reflux	6	**9**
7	CsF	THF	Rt	25	**9**
8	CsF	THF	Reflux	14	**9**
9	CsF	MeCN	Rt	11.5	**9**
10	CsF	MeCN	Reflux	6	**11**
11	TBACl+KF	THF–H_2O	Rt	1	**9**
12	TBACl+KF	THF–H_2O	Reflux	2.5	**9**
13	TBACl+KF·$2H_2O$	MeCN	Reflux	6	**11**
14	TBACl+AgF	THF	Rt	0.5	**9**
15	TBACl+AgF	THF	Reflux	6	**11** (23)[a]
16	TBAF (50 mol%)	THF	Reflux	2.5	**11** (49)[a]
17	TBAF (10 mol%)	THF	Reflux	1.5	**11** (51)[a]

[a] The numbers in the parentheses are isolated yields of **12**, which were obtained after hydrogenation.

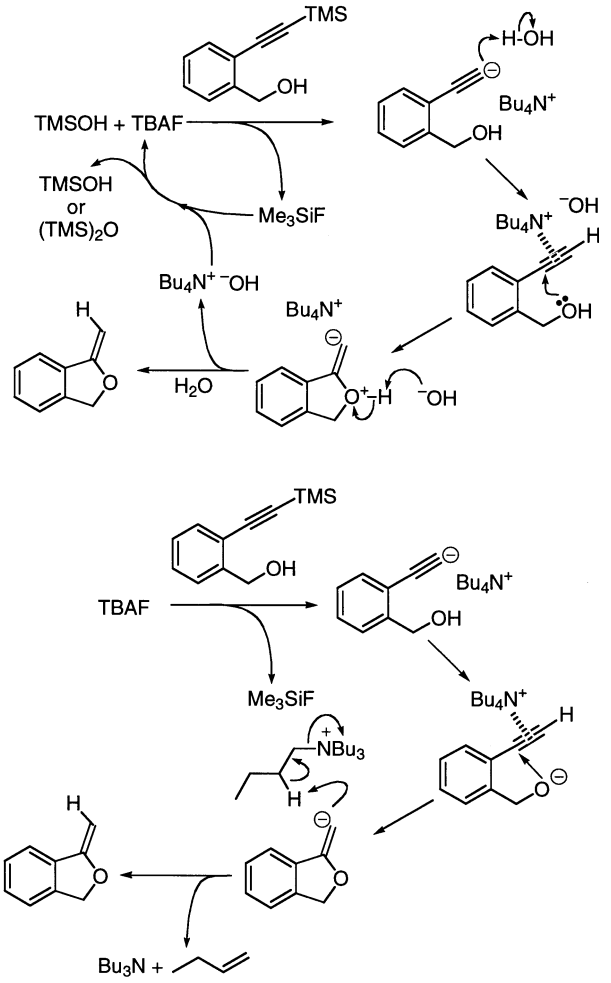


Figure 5.

in MeCN at reflux, although some side products were detected (Table 2: entry 10). These results suggested that a softer cation would be favorable for the cyclization reaction of this substrate.

To demonstrate the hypothesis described above, we next investigated the reaction with TBAF generated in situ. A mixture of **5**, TBACl, and KF in THF at rt or reflux temperature gave only the detrimethylsilyl product (Table 2: entries 11 and 12), but in MeCN, the cyclized product was obtained (Table 2: entry 13). Furthermore, for the reaction with TBACl and AgF in THF, **9** was afforded at rt (Table 2: entry 14), but **11** occurred at reflux temperature (Table 2: entry 15). The evidence described above proves that both the tetrabutylammonium cation and fluoride anion are essential for the efficient cyclization.

Finally, the catalytic reactions were investigated. When 50 mol% (Table 2: entry 16) or 10 mol% (Table 2: entry 17) of TBAF was used, only **11** was detected, which means TBAF worked as a catalyst. Interestingly, the reaction did not terminate and gave the mixture of **9** and **11**, when TBAF solution in THF pre-treated with 4 Å molecular sieves was used. In this case, the signals of Bu_3N were also detected in the ^1H NMR spectrum of the crude product. Therefore, we deduced the possible mechanism for this TBAF promoted cyclization reaction as shown in Fig. 5.

3. Conclusion

For the cyclization reactions promoted by TBAF, a high regioselectivity was observed depending on the substituents on the end of the triple bond. Namely, when the benzyl alcohol or benzylamine derivatives, which have either a hydrogen or aromatic ring on the triple bond, were treated with TBAF, the products always have five-membered ring (5-*exo-dig*). On the other hand, for a smaller alkyl group (CH_2OH), a mixture of the six-membered ring (6-*endo-dig*) and 5-membered ring (5-*exo-dig*) was produced. Furthermore, the compound having bulky alkyl group only gave six-membered ring (6-*endo-dig*). The causes of the observed regioselectivity were suggested not by the electronic nature of the functional group on the triple bond, but by the steric bulkiness. It was also concluded that both the tetrabutylammonium cation and fluoride anion are essential for the efficient cyclization reactions.

4. Experimental

4.1. General

All melting points and boiling points are uncorrected. The IR spectra were measured using a JASCO IR-810 spectrophotometer. The ^1H NMR spectra were recorded on a Varian Gemini 2000 (300 MHz) and JEOL GX-500 (500 MHz) in $CDCl_3$ as the solvent, unless otherwise stated. The chemical shifts are expressed in δ (ppm) values with tetramethylsilane (TMS) as the internal reference and coupling constants (J) are measured in Hz. The mass spectra and high-resolution mass spectra were recorded on JEOL JMS-DX303 and JMS-AX500 instruments, respectively.

4.2. General procedure for the Sonogashira coupling reaction between aryliodides and acetylenes using triethylamine as the solvent

Acetylene, $PdCl_2(PPh_3)_2$, and CuI were successively added to a solution of 2-iodobenzyl alcohol derivatives or 2-iodobenzylamine derivatives in triethylamine at 0°C, then being stirred at room temperature. The mixture was filtered through a pad of Celite®, then the filtrate was diluted with Et_2O. The organic solution was washed successively with H_2O and saturated aq. NaCl solution, then dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography to afford the 2-ethynylbenzyl alcohol derivatives or 2-ethynylbenzylamine derivatives.

4.2.1. 2-(Trimethylsilylethynyl)benzyl alcohol (5). According to the general procedure (Section 4.2), trimethylsilylacetylene (2.70 g, 27.6 mmol), $PdCl_2(PPh_3)_2$ (0.75 g, 1.06 mmol), CuI (0.41 g, 2.14 mmol), and 2-iodobenzyl alcohol (5.00 g, 21.4 mmol) in triethylamine (40 ml) were allowed to react for 3 h. The crude products were purified by silica gel column chromatography eluting with hexane–AcOEt (4:1) to afford an oil, which was further purified by bulb to bulb distillation to afford **5** (3.63 g, 83%) as a

colorless oil, bp 70°C/1 mmHg (Found: C, 70.42; H, 7.75. $C_{12}H_{16}OSi$ requires C, 70.53; H, 7.89%); ν_{max} (film)/cm^{-1} 3400, 2160; δ_H (300 MHz, $CDCl_3$) 0.27 (9H, s), 2.33 (1H, t, J=6.5 Hz), 4.81 (2H, d, J=6.5 Hz), 7.23 (1H, dt, J=1.1, 7.4 Hz), 7.33 (1H, dt, J=1.1, 7.4 Hz), 7.41 (1H, dd, J=1.1, 7.4 Hz), 7.46 (1H, dd, J=1.1, 7.4 Hz); m/z 204 (M^+) (Found: m/z 204.0980, requires $C_{12}H_{16}OSi$: 204.0971).

4.2.2. 2-(1-Hexynyl)benzyl alcohol (6). $PdCl_2(PPh_3)_2$ (0.350 g, 0.5 mmol) and CuI (0.190 g, 1.0 mmol) were added to a solution of 2-iodobenzyl alcohol (2.34 g, 10.0 mmol), 1-hexyne (1.23 g, 15.0 mmol), and i-Pr_2NH (2.00 g, 20.0 mmol) in THF (50 ml) at 0°C. After being stirred for 6 h at room temperature, H_2O was added and the aqueous solution was extracted with AcOEt (×3). The organic solution was dried over $MgSO_4$ and evaporated. The crude oil was purified by silica gel column chromatography [hexane–AcOEt (6:1)] to afford **6** (1.69 g, 90%) as a viscous colorless oil, ν_{max} (film)/cm^{-1} 3363, 2228; δ_H (300 MHz, $CDCl_3$) 0.96 (3H, t, J=7.1 Hz), 1.42–1.67 (4H, m), 2.25 (1H, t, J=6.3 Hz), 2.46 (2H, t, J=6.9 Hz), 4.79 (2H, d, J=6.3 Hz), 7.18–7.31 (2H, m), 7.37–7.42 (2H, m); m/z 188 (M^+) (Found: m/z 188.1209, requires $C_{13}H_{16}O$: 188.1201).

4.2.3. 2-(3,3-Dimethyl-1-butynyl)benzyl alcohol (7). According to the general procedure (Section 4.2), 3,3-dimethyl-1-butyne (0.82 g, 10 mmol), $PdCl_2(PPh_3)_2$ (0.18 g, 0.25 mmol), CuI (95 mg, 0.50 mmol), and 2-iodobenzyl alcohol (1.23 g, 5.26 mmol) in triethylamine (15 ml) were stirred for 3.5 h. The residue was purified by silica gel column chromatography using hexane–AcOEt (6:1) as an eluent to afford **7** (0.99 g, 91%) as a viscous colorless oil, ν_{max} (film)/cm^{-1} 3350, 2230; δ_H (300 MHz, $CDCl_3$) 1.34 (9H, s), 2.22 (1H, t, J=6.6 Hz), 4.79 (2H, d, J=6.6 Hz), 7.22 (1H, dt, J=1.7, 7.5 Hz), 7.28 (1H, dt, J=1.7, 7.5 Hz), 7.37–7.41 (2H, m); m/z 188 (M^+) (Found: m/z 188.1210, requires $C_{13}H_{16}O$: 188.1202).

4.2.4. 2-(2-Phenylethynyl)benzyl alcohol (8).[8c,d] $PdCl_2(PPh_3)_2$ (0.35 g, 0.5 mmol) and CuI (0.19 g, 1.0 mmol) were added to a solution of 2-bromobenzaldehyde (2.00 g, 10.8 mmol) and phenylacetylene (2.20 g, 21.6 mmol) in triethylamine (20 ml) at 0°C. After being stirred for 6 h at room temperature, H_2O (50 ml) was added to the mixture, then extracted with AcOEt (×3). The combined organic solution was dried over $MgSO_4$ and the filtrate was evaporated to afford the crude mixture, which was used to the next reaction without further purification.

$NaBH_4$ (0.113 g, 2.7 mmol) was added to a solution of the crude aldehyde in MeOH (50 ml) at 0°C. After the reaction was terminated, H_2O was added to the reaction mixture and the aqueous phase was extracted with AcOEt (×3). The combined organic solution was dried over $MgSO_4$ and concentrated to afford the crude oil, which was purified by silica gel column chromatography [hexane–AcOEt (6:1)] to afford **8** [1.80 g, 80% (two steps)] as a colorless solid, mp 67–68°C, ν_{max} ($CHCl_3$)/cm^{-1} 3315, 1490, 1454; δ_H (300 MHz, $CDCl_3$) 2.10 (1H, t, J=6.3 Hz), 4.93 (2H, d, J=6.3 Hz), 7.31 (1H, dd, J=1.4, 7.7 Hz), 7.34–7.40 (4H, m), 7.49 (1H, d, J=7.4 Hz), 7.52–7.56 (3H, m); m/z 208 (M^+) (Found: m/z 208.0887, requires $C_{15}H_{12}O$: 208.0888).

4.2.5. 2-Ethynylbenzyl alcohol (9). TBAF·$3H_2O$ (0.30 g, 1.47 mmol) was added to a solution of **5** (0.46 g, 1.47 mmol) in THF (8 ml) at room temperature. After being stirred for 1 h at the same temperature, Et_2O was added to the mixture and washed successively with H_2O and saturated aq. NaCl solution. The organic solution was dried over $MgSO_4$ and concentrated to afford the crude products, which was purified by silica gel column chromatography [hexane–AcOEt (4:1)] to afford **9** (0.176 g, 62%) as a colorless solid. The analytical sample was recrystallized from Et_2O–hexane to afford **9** as a colorless needle, mp 64–65°C (Found: C, 81.64; H, 6.19, requires C_9H_8O C, 81.79; H, 6.10); ν_{max} ($CHCl_3$)/cm^{-1} 3310, 3050, 2100; δ_H (500 MHz, $CDCl_3$) 2.03 (1H, t, J=6.1 Hz), 3.33 (1H, s), 4.84 (2H, d, J=6.1 Hz), 7.26 (1H, dt, J=1.2, 7.6 Hz), 7.37 (1H, dt, J=1.2, 7.6 Hz), 7.45 (1H, d, J=7.6 Hz), 7.51 (1H, d, J=7.6 Hz); m/z 132 (M^+) (Found: m/z 130.0572, requires C_9H_8O: 132.0576).

4.2.6. 2-[2-(4-Methoxyphenyl)ethynyl]benzyl alcohol (10). According to the general procedure (Section 4.2), the crude **9** which was obtained from TBAF·$3H_2O$ (0.30 g, 1.47 mmol) and **5** (0.46 g, 1.47 mmol) in THF (8 ml) as shown in Section 4.2.5, $PdCl_2(PPh_3)_2$ (0.29 g, 0.42 mmol), CuI (0.16 g, 0.83 mmol), and 4-iodoanisole (1.94 g, 8.3 mmol) in triethylamine (20 ml) were stirred for 3.5 h. The residue was purified by silica gel column chromatography using hexane–AcOEt (2:1) as an eluent to afford a solid, which was recrystallized from Et_2O to afford **10** (1.27 g, 64%) as a colorless plate, mp 102–103°C (Found: C, 80.67; H, 5.91, requires $C_{16}H_{14}O_2$ C, 80.65; H, 5.92); ν_{max} (KBr)/cm^{-1} 3350, 1250, 1050; δ_H (300 MHz, $CDCl_3$) 2.14 (1H, t, J=6.6 Hz), 3.83 (3H, s), 4.91 (2H, d, J=6.6 Hz), 6.89 (2H, d, J=8.8 Hz), 7.25–7.37 (2H, m), 7.45–7.54 (4H, m); m/z 238 (M^+) (Found: m/z 238.0969, requires $C_{16}H_{14}O_2$: 238.0994).

4.3. General procedure for TBAF promoted cyclization reaction of 2-ethynylbenzyl alcohol derivatives

TBAF (1.0 M solution in THF or TBAF·$3H_2O$) was added to a solution of the 2-ethynylbenzyl alcohol derivatives in THF at room temperature, then the mixture was refluxed. Et_2O was added to the reaction mixture and washed successively with H_2O, saturated aq. NaCl solution. The organic solution was dried over $MgSO_4$ and evaporated to afford the crude product(s), which was purified by silica gel column chromatography, if necessary.

4.3.1. 1,3-Dihydro-(1-methylene)isobenzofuran (11).[15] According to the general procedure (Section 4.3), TBAF (1.0 M solution in THF, 7.34 ml, 7.34 mmol) and **5** (1.0 g, 4.89 mmol) in THF (10 ml) was reacted for 1.5 h. The crude product was used to the next reaction without further purification, δ_H (500 MHz, $CDCl_3$) 4.36 (1H, d, J=2.4 Hz), 4.41 (1H, d, J=2.4 Hz), 5.21 (2H, s), 7.16–7.25 (3H, m), 7.41 (1H, m).

4.3.2. 1,3-Dihydro-1-methylisobenzofuran (12).[16] A mixture of the crude **11** and a catalytic amount of Pd–C in

toluene (20 ml) was stirred under hydrogen gas for 24 h. Pd–C was filtered off, and then toluene was removed at an atmospheric pressure. The residue was successively purified by silica gel column chromatography [hexane–AcOEt (9:1)] and bulb to bulb distillation to afford **12** [0.31 g, 47% (two steps)] as a colorless oil, bp 25°C/15 mmHg (lit.[16] 80°C/20 mmHg); ν_{max} (film)/cm^{-1} 1040; δ_H (500 MHz, $CDCl_3$) 1.50 (3H, d, J=6.7 Hz), 5.04 (1H, d, J=13.0 Hz), 5.12 (1H, dd, J=1.8, 13.0 Hz), 5.31 (1H, br q), 7.14–7.33 (4H, m); m/z 134 (M^+) (Found: m/z 134.0735, requires $C_9H_{10}O$: 134.0732).

4.3.3. 1-[(*Z*)-Benzylidene]isobenzofuran (13).[7b,8a,c,d,15,17] According to the general procedure (Section 4.3), **8** (59 mg, 0.28 mmol) and TBAF (1.0 M solution in THF, 0.31 ml, 0.31 mmol) was refluxed for 2 h. The crude products were purified by silica gel column chromatography using hexane–Et_2O (10:1) as an eluent to afford **13** (47 mg, 80%) as a colorless viscous oil, δ_H (300 MHz, $CDCl_3$) 5.51 (2H, s), 5.95 (1H, s), 7.14 (1H, t, J=7.4 Hz), 7.30–7.38 (5H, m), 7.55–7.59 (1H, m), 7.74 (2H, d, J=7.4 Hz); m/z 208 (M^+) (Found m/z 208.0888, requires $C_{15}H_{12}O$: 208.0926).

4.3.4. 1-[(*Z*)-4-(Methoxyphenyl)methylidene]isobenzofuran (14). According to the general procedure (Section 4.3), **10** (0.11 g, 0.46 mmol) and TBAF·3H_2O (0.13 g, 0.46 mmol) was refluxed for 4 h. The crude products was purified by silica gel column chromatography using hexane–AcOEt (10:1) as an eluent to afford **14** (0.105 g, 95%) as a colorless solid, the analytical sample was recrystallized from Et_2O to give a colorless plate, mp 98–100°C (Found: C, 80.39; H, 5.98, requires $C_{16}H_{14}O_2$, C, 80.65; H, 5.92%); δ_H (500 MHz, $CDCl_3$) 3.81 (3H, s), 5.49 (2H, s), 5.89 (1H, s), 6.88 (2H, d, J=9.2 Hz), 7.32 (3H, m), 7.52 (1H, d, J=6.7 Hz), 7.67 (2H, d, J=9.2 Hz); m/z 238 (M^+) (Found m/z 238.1011, requires $C_{16}H_{14}O_2$: 238.0993).

4.3.5. 3-Butyl-1*H*-2-benzopyran (15). TBAF (1.0 M solution in THF, 1.0 ml, 1.0 mmol) was added to a solution of **6** (99.8 mg, 0.53 mmol) in THF (2 ml) and DMF (0.5 ml) and refluxed for 60 h. H_2O (30 ml) was added to the mixture and extracted with Et_2O. The organic solution was dried over $MgSO_4$ and concentrated in vacuo to afford the crude products, which was chromatographed on silica gel using hexane as an eluent to afford **15** (10 mg, 10%) as a colorless viscous oil, δ_H (300 MHz, $CDCl_3$) 0.93 (3H, t, J=7.4 Hz), 1.38 (2H, m), 1.55 (2H, m), 2.19 (2H, t, J=7.1 Hz), 5.03 (2H, s), 5.64 (1H, s), 6.91 (1H, d, J=7.4 Hz), 6.98 (1H, d, J=7.4 Hz), 7.08 (1H, dt, J=1.4, 7.4 Hz), 7.18 (1H, dt, J=1.4, 7.4 Hz); m/z 188 (M^+) (Found m/z 188.1208, requires $C_{13}H_{16}O$: 188.1201).

4.3.6. (3,3-Dimethyl-1-butynyl)benzaldehyde (16). According to the general procedure (Section 4.3), **7** (0.10 g, 0.53 mmol) and TBAF·3H_2O (0.17 g, 0.53 mmol) in dioxane (2 ml) was stirred at 100°C for 6 d. The crude products were purified by silica gel column chromatography using hexane–AcOEt (50:1) as an eluent to afford **16** (18 mg, 20%) as a colorless viscous oil, ν_{max} (film)/cm^{-1} 1700; δ_H (300 MHz, $CDCl_3$) 1.35 (9H, s), 7.35–7.52 (3H, m), 7.89 (1H, d, J=7.7 Hz), 10.55 (1H, s); m/z 186 (M^+) (Found m/z 186.1052, requires $C_{13}H_{14}O$: 186.1044). From the later fraction, **7** (49 mg, 49%) was recovered.

4.3.7. 2-Iodobenzylazide (17).[20] 1,8-Diazabicyclo[5.4.0]-undec-7-ene (DBU) (1.93 g, 12.7 mmol) was added to a solution of 2-iodobenzyl alcohol (2.34 g, 10 mmol), $(PhO)_2P(O)N_3$ (3.3 g, 12 mmol) in toluene (20 ml) at room temperature, then being stirred for 1 h. 3N HCl (20 ml) was added to the mixture and extracted with Et_2O. The combined organic solution was successively washed with H_2O and saturated aq. NaCl solution, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography [hexane–AcOEt (19:1)] to afford **17** (2.34 g, 90%) as a colorless oil; ν_{max} (KBr)/cm^{-1} 2150; δ_H (300 MHz, $CDCl_3$) 4.46 (2H, s), 7.04 (1H, dt, J=4.4, 8.0 Hz), 7.34–7.43 (2H, m), 7.89 (1H, d, J=8.0 Hz); m/z 259 (M^+) (Found m/z 258.9606, requires $C_7H_6IN_3$: 258.9607).

4.3.8. *N*-(2-Iodobenzyl)-(4-methylphenyl)sulfonamide (19). Triphenylphosphine (2.62 g, 10 mmol) was added to a solution of 2-iodobenzylazide (**17**) (2.34 g, 9.03 mmol) in THF (40 ml) at 0°C and the mixture was stirred at room temperature. After 16 h, aq. NH_3 solution (10 ml) was added to the mixture and stirred for 3 h, and then 3N aq. NaOH solution (50 ml) was added. After being stirred for 1 h, the mixture was neutralized with 3N HCl (20 ml) and the aqueous solution was extracted with Et_2O. The organic solution was washed successively with H_2O and saturated aq. NaCl solution, dried over $MgSO_4$, and concentrated in vacuo to afford the crude amine, which was used to the next reaction without further purification.

p-Toluenesulfonyl chloride (1.33 g, 7.0 mmol) was added to a solution of the crude **18** (2.07 g) and triethylamine (5 ml) in THF (20 ml) at 0°C and being stirred at room temperature for 2 h. The reaction mixture was extracted with AcOEt. The combined organic solution was successively washed with H_2O and saturated aq. NaCl solution, and dried over $MgSO_4$. The solvent was evaporated to afford the crude products, which was purified by silica gel column chromatography using hexane–AcOEt (1:2) as the eluent to afford **19** (1.46 g, 91%) as a colorless solid. The analytical sample was recrystallized from Et_2O. Colorless needle, mp 101–103°C (Found: C, 43.34; H, 3.73; I, 32.75; N, 3.47; S, 8.21, requires $C_{14}H_{14}INO_2S$: C, 43.42; H, 3.64; I, 32.77; N, 3.62; S, 8.28); ν_{max} (film)/cm^{-1} 3280, 1330, 1155; δ_H (300 MHz, $CDCl_3$) 2.42 (3H, s), 4.18 (2H, d, J=6.6 Hz), 4.94 (1H, t, J=6.6 Hz), 6.94 (1H, dt, J=1.9, 7.4 Hz), 7.23–7.32 (4H, m), 7.73 (3H, m); m/z: 387 (M^+) (Found: m/z 386.9767, requires $C_{14}H_{14}INO_2S$: 386.9790).

4.3.9. *N*-(2-Iodobenzyl)acetamide (20). Acetic anhydride (0.82 g, 8.0 mmol) was added to a solution of the crude **18** in pyridine (15 ml) at 0°C and being stirred at room temperature for 2 h. The excess pyridine was removed in vacuo and the residue was extracted with AcOEt. The combined organic solution was successively washed with H_2O and saturated aq. NaCl solution, and dried over $MgSO_4$. The solvent was evaporated to afford **20** as a colorless solid. The analytical sample was recrystallized from Et_2O–hexane. Colorless needle, mp 133–135°C; ν_{max} ($CHCl_3$)/cm^{-1} 3447, 3009, 1670, 1514; δ_H (300 MHz, $CDCl_3$) 2.02 (3H, s), 4.46 (2H, d, J=6.1 Hz), 5.95 (1H, br), 6.98 (1H, dt, J=2.0, 7.7 Hz), 7.30–7.40 (2H, m), 7.83 (1H, d, J=7.7 Hz); m/z: 276 (M^++1) (Found: m/z 275.9874, requires $C_9H_{11}INO$: 275.9885).

4.3.10. *t*-Butyl *N*-(2-iodobenzyl)carbamate (21). Di-*t*-butyl dicarbonate (1.09 g, 5.0 mmol) was added to a solution of the crude **18** in THF (30 ml) at 0°C and being stirred at room temperature for 2 h. The reaction mixture was extracted with Et_2O. The combined organic solution was successively washed with H_2O and saturated aq. NaCl solution, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (6:1)] to afford **21** as a viscous colorless oil, δ_H (300 MHz, $CDCl_3$) 1.46 (9H, s), 4.34 (2H, br d, J=5.8 Hz), 5.01 (1H, br), 6.97 (1H, dt, J=2.2, 7.7 Hz), 7.26–7.38 (2H, m), 7.82 (1H, d, J=7.7 Hz); *m/z*: 276 (M^+-C_4H_9) (Found: *m/z* 275.9486, requires $C_8H_7INO_2$: 275.9522).

4.3.11. *N*-[2-[2-(Trimethylsilyl)ethynyl]benzyl]-(4-methylphenyl)sulfonamide (22). According to the general procedure (Section 4.2), trimethylsilylacetylene (0.19 g, 3.02 mmol), $PdCl_2(PPh_3)_2$ (53 mg, 76 μmol), CuI (29 mg, 0.15 mmol), and **19** (0.58 g, 1.51 mmol) in triethylamine (4 ml) and THF (5 ml) were stirred for 3 h. The residue was purified by silica gel column chromatography eluting with hexane–AcOEt (3:1) to afford **22** (0.47 g, 86%) as a colorless oil, ν_{max} (neat)/cm^{-1} 3280, 2150, 1330, 1160; δ_H (300 MHz, $CDCl_3$) 0.22 (9H, s), 2.39 (3H, s), 4.30 (2H, d, J=6.6 Hz), 5.06 (1H, br t), 7.17–7.24 (5H, m), 7.36 (1H, m), 7.69 (2H, d, J=8.5 Hz); *m/z*: 357 (M^+) (Found: *m/z* 357.1202, requires $C_{19}H_{23}NO_2SSi$: 357.1219).

4.3.12. *N*-[2-[2-(Trimethylsilyl)ethynyl]benzyl]acetamide (23). According to the general procedure (Section 4.2), trimethylsilylacetylene (0.28 g, 4.50 mmol), $PdCl_2(PPh_3)_2$ (79 mg, 0.11 mmol), CuI (43 mg, 0.23 mmol), and **20** (0.62 g, 2.25 mmol) in triethylamine (4 ml) and THF (5 ml) were stirred for 3 h. The residue was purified by silica gel column chromatography eluting with hexane–AcOEt (1:1) to afford **23** (0.44 g, 80%) as a colorless solid. The analytical sample was recrystallized from Et_2O–hexane. Colorless needles, mp 76°C (Found: C, 68.49; H, 7.70; N, 5.67; S, 8.21, requires $C_{14}H_{19}NOSi$: C, 68.52; H, 7.80; N, 5.71); ν_{max} (KBr)/cm^{-1} 3280, 2160, 1640, 1560; δ_H (300 MHz, $CDCl_3$) 0.23 (9H, s), 2.00 (3H, s), 4.58 (2H, br d, J=6.0 Hz), 5.96 (1H, br), 7.25–7.38 (3H, m), 7.45 (1H, m); *m/z*: 245 (M^+) (Found: *m/z* 245.1248, requires $C_{14}H_{19}NOSi$: 245.1209).

4.3.13. *t*-Butyl *N*-[2-[2-(trimethylsilyl)ethynyl]benzyl]-carbamate (24). According to the general procedure (Section 4.2), trimethylsilylacetylene (0.40 g, 6.38 mmol), $PdCl_2(PPh_3)_2$ (112 mg, 0.16 mmol), CuI (61 mg, 0.32 mmol), and **21** (0.95 g, 3.14 mmol) in triethylamine (10 ml) were stirred for 2 h. The residue was purified by silica gel column chromatography eluting with hexane–AcOEt (4:1) to afford **24** (0.84 g, 89%) as a colorless viscous oil, ν_{max} (neat)/cm^{-1} 3350, 2150, 1720, 1250, 1165; δ_H (300 MHz, $CDCl_3$) 0.27 (9H, s), 1.45 (9H, s), 4.45 (2H, br d, J=6.1 Hz), 5.12 (1H, br), 7.21 (1H, dt, J=1.4, 7.1 Hz), 7.30 (1H, dd, J=1.4, 7.1 Hz), 7.34 (1H, d, J=7.1 Hz), 7.45 (1H, dd, J=1.4, 7.1 Hz); *m/z*: 303 (M^+) (Found: *m/z* 303.1635, requires $C_{17}H_{25}NO_2Si$: 303.1654).

4.3.14. *t*-Butyl *N*-[2-(2-phenylethynyl)benzyl]carbamate (25). $PdCl_2(PPh_3)_2$ (0.119 g, 0.17 mmol) and CuI (0.063 g, 0.33 mmol) were added to a solution of **21** (1.09 g, 3.3 mmol), phenylacetylene (0.408 g, 4.0 mmol), and *i*-Pr_2NH (0.410 g, 4.0 mmol) in THF (40 ml) at 0°C. After being stirred for 12 h at room temperature, H_2O (50 ml) was added and the aqueous solution was extracted with AcOEt (×3). The organic solution was dried over $MgSO_4$ and evaporated. The crude oil was purified by silica gel column chromatography using hexane–AcOEt (10:1) as an eluent to afford **25** (0.582 g, 57%) as a viscous colorless oil, δ_H (300 MHz, $CDCl_3$) 1.45 (9H, s), 4.55 (2H, br d, J=6.0 Hz), 5.02 (1H, br), 7.23–7.41 (6H, m), 7.51–7.57 (3H, m); *m/z* 307 (M^+) (Found: *m/z* 307.1568, requires $C_{20}H_{21}NO_2$: 307.1572).

4.3.15. *N*-[2-(1-Hexynyl)benzyl]-(4-methylphenyl)sulfonamide (26). $PdCl_2(PPh_3)_2$ (91 mg, 0.13 mmol) and CuI (51 mg, 0.27 mmol) were added to a solution of **19** (1.00 g, 2.68 mmol), 1-hexyne (0.246 g, 3.0 mmol), and *i*-Pr_2NH (0.306 g, 3.0 mmol) in THF (5 ml) at 0°C. After being stirred for 5 h at room temperature, H_2O (50 ml) was added and the aqueous solution was extracted with AcOEt (×3). The organic solution was dried over $MgSO_4$ and evaporated. The crude oil was purified by silica gel column chromatography using hexane–AcOEt (2:1) as an eluent to afford **26** (0.807 g, 88%) as a viscous colorless oil, δ_H (300 MHz, $CDCl_3$) 0.94 (3H, t, J=7.1 Hz), 1.39–1.59 (4H, m), 2.36 (2H, t, J=6.9 Hz), 2.40 (3H, s), 4.27 (2H, d, J=6.3 Hz), 5.02 (1H, t, J=6.3 Hz), 7.13–7.19 (3H, m), 7.23 (2H, d, J=8.2 Hz), 7.28–7.33 (1H, m), 7.70 (2H, d, J=8.2 Hz); *m/z* 341 (M^+) (Found: *m/z* 341.1445, requires $C_{20}H_{23}NO_2S$: 341.1450).

4.3.16. *t*-Butyl *N*-[2-(1-hexynyl)benzyl]carbamate (27). $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol) and CuI (11 mg, 0.06 mmol) were added to a solution of **21** (1.00 g, 3.0 mmol), 1-hexyne (0.295 g, 3.6 mmol), and *i*-Pr_2NH (0.410 g, 4.0 mmol) in THF (3 ml) at 0°C. After being stirred for 2.5 h at room temperature, H_2O (50 ml) was added and the aqueous solution was extracted with AcOEt (×3). The organic solution was dried over $MgSO_4$ and evaporated. The crude oil was purified by silica gel column chromatography using hexane–Et_2O (20:1) as an eluent to afford **27** (0.636 g, 74%) as a viscous colorless oil, δ_H (300 MHz, $CDCl_3$) 0.96 (3H, t, J=7.4 Hz), 1.45 (9H, s), 1.47–1.66 (4H, m), 2.45 (2H, t, J=6.8 Hz), 4.43 (2H, br d, J=5.8 Hz), 5.00 (1H, br), 7.16–7.41 (4H, m); *m/z* 287 (M^+) (Found: *m/z* 287.1899, requires $C_{18}H_{25}NO_2$: 287.1885).

4.3.17. *N*-[2-(3-Hydroxypropynyl)benzyl]-(4-methylphenyl)sulfonamide (28). $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol) and CuI (7.6 mg, 0.04 mmol) were added to a solution of **19** (0.15 g, 0.40 mmol), propargyl alcohol (45 mg, 0.80 mmol) in *i*-Pr_2NH (3.0 ml) at room temperature and stirring was continued further 6 h at the same temperature. The mixture was filtered through a Celite® pad eluting with AcOEt. The organic solution was washed with saturated aq. NaCl solution, dried over $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography using $CHCl_3$ as an eluent to afford **28** (0.120 g, 95%) as a colorless solid. The analytical sample was recrystallized from Et_2O–hexane. Colorless needle, mp 118–119°C, ν_{max} ($CHCl_3$)/cm^{-1} 3510, 3368, 3026, 1329, 1159; δ_H (300 MHz, $CDCl_3$) 2.40 (3H, s), 2.61 (1H, t, J=6.3 Hz), 4.24 (2H, d, J=6.3 Hz), 4.45 (2H, d, J=

6.3 Hz), 5.16 (1H, t, J=6.3 Hz), 7.15–7.26 (5H, m), 7.34 (1H, m), 7.72 (2H, d, J=8.2 Hz); m/z 315 (M^+) (Found: m/z 315.0967, requires $C_{17}H_{17}NO_3S$: 315.0929).

4.3.18. *N*-[2-(3,3-Dimethyl-1-butynyl)benzyl]-(4-methylphenyl)sulfonamide (29). According to the general procedure (Section 4.2), 3,3-dimethyl-1-butyne (0.82 g, 10.0 mmol), $PdCl_2(PPh_3)_2$ (0.18 g, 0.25 mmol), CuI (95 mg, 0.50 mmol), and **19** (1.94 g, 5.0 mmol) in triethylamine (15 ml) and THF (5 ml) were stirred for 2.5 h. The residue was purified by silica gel column chromatography eluting with hexane–AcOEt (9:1) to afford a colorless solid, which was recrystallized from Et_2O–hexane to afford **29** (1.31 g, 77%) as colorless plates, mp 66°C (Found: C, 70.25; H, 6.81; N, 4.18; S, 9.11, requires $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79; N, 4.10; S, 9.39); ν_{max} (neat)/cm^{-1} 3250, 1330, 1160; δ_H (300 MHz, $CDCl_3$) 1.27 (9H, s), 2.39 (3H, s), 4.26 (2H, br d, J=6.7 Hz), 5.02 (1H, br t), 7.14–7.30 (6H, m), 7.69 (2H, d, J=8.2 Hz); m/z: 341 (M^+) (Found: m/z 341.1431, requires $C_{20}H_{23}NO_2S$: 341.1450).

4.3.19. *N*-[2-(2-Phenylethynyl)benzyl]-(4-methylphenyl)sulfonamide (32).[20] DBU (0.73 g, 4.56 mmol) was added to a solution of **8** (0.800 g, 3.8 mmol), $(PhO)_2P(O)N_3$ (1.25 g, 4.56 mmol) in toluene (10 ml) at room temperature, then being stirred for 12 h. 3N HCl (10 ml) was added to the mixture and extracted with Et_2O. The combined organic solution was successively washed with H_2O and saturated aq. NaCl solution, dried over $MgSO_4$, and concentrated. The residue used to the next reaction without further purifications.

Triphenylphosphine (1.10 g, 4.2 mmol) was added to a solution of the crude azide (**30**) in THF (15 ml) at 0°C and the mixture was stirred for 2 h at room temperature, then for 5 h at 40°C. Aq. NH_3 solution (5 ml) was added to the mixture and stirred for 12 h, then 3N aq. NaOH solution (15 ml) was added. After been stirred for 2 h, the aqueous solution was extracted with Et_2O. The organic solution was washed successively with H_2O and saturated aq. NaCl solution, dried over $MgSO_4$, and concentrated in vacuo to afford the crude amine, which was used to the next reaction without further purification.

p-Toluenesulfonyl chloride (0.72 g, 3.8 mmol) was added to a solution of the crude amine (**31**) in pyridine (10 ml) at 0°C and stirred at room temperature for 30 h. The reaction mixture was extracted with AcOEt, then the combined organic solution was successively washed with H_2O, aq. $CuSO_4$ solution, 3N HCl, and saturated aq. NaCl solution. The solution was dried over $MgSO_4$ and the solvent was evaporated to afford the crude products, which was purified by silica gel column chromatography using hexane–AcOEt (19:1) as the eluent to afford **32** [0.62 g, 46% (3 steps)] as a colorless solid. The analytical sample was recrystallized from Et_2O–hexane. Colorless needles, mp 170°C (Found: C, 73.05; H, 5.29; N, 3.77; S, 8.89, requires $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88; S, 8.87); ν_{max} (KBr)/cm^{-1} 3280, 1325, 1160; δ_H (300 MHz, $CDCl_3$) 2.38 (3H, s), 4.37 (2H, d, J=6.6 Hz), 4.94 (1H, t, J=6.6 Hz), 7.29 (2H, d, J=8.5 Hz), 7.23–7.47 (9H, m), 7.71 (2H, d, J=8.5 Hz); m/z: 361 (M^+) (Found: m/z 361.1156, requires $C_{22}H_{19}NO_2S$: 361.1137).

4.4. General procedure for TBAF promoted cyclization reaction of 2-ethynylbenzylamine derivatives (Scheme 4)

$TBAF{\cdot}3H_2O$ was added to a solution of the 2-ethynylbenzylamine derivatives in THF at room temperature. After being stirred at the same temperature, a catalytic amount of Pd–C was added to the mixture and stirred under H_2. Et_2O was added to the reaction mixture and washed successively with H_2O, saturated aq. NaCl solution. The organic solution was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography.

4.4.1. 1,3-Dihydro-1-methyl-2-(4-methylphenylsulfonyl)-isoindole (36). According to the general procedure (Section 4.4), $TBAF{\cdot}3H_2O$ (97 mg, 0.31 mmol) and **22** (0.11 g, 0.31 mmol) in THF (2 ml) was stirred for 9 h at room temperature, followed by being stirred under H_2 for 18.5 h. The crude mixture was purified by silica gel column chromatography using hexane–AcOEt (6:1) as an eluent to afford **36** (76 mg, 86%) as a colorless solid. The analytical sample was recrystallized from Et_2O–hexane to afford colorless prisms; mp 91°C (Found: C, 52.16; H, 7.65; N, 2.96; S, 11.25, requires $C_{16}H_{17}NO_2S$: C, 52.04; H, 7.64; N, 3.03; S, 11.16); ν_{max} (neat)/cm^{-1} 1340, 1160; δ_H (300 MHz, $CDCl_3$) 1.67 (3H, d, J=6.3 Hz), 2.37 (3H, s), 4.56 (1H, d, J=14.0 Hz), 4.73 (1H, dd, J=2.5, 14.0 Hz), 4.92 (1H, dq, J=2.5, 6.3 Hz), 7.09–7.24 (4H, m), 7.27 (2H, d, J=8.2 Hz), 7.76 (2H, d, J=8.2 Hz); m/z: 287 (M^+) (Found: m/z 287.0994, requires $C_{16}H_{17}NO_2S$: 287.0980).

4.4.2. 2-Acetyl-1,3-dihydro-1-methylisoindole (37). According to the general procedure (Section 4.4), $TBAF{\cdot}3H_2O$ (0.13 g, 0.41 mmol) and **23** (0.10 g, 0.41 mmol) in THF (2 ml) was refluxed for 8 h, followed by being stirred under H_2 for 13 h. The crude mixture was purified by silica gel column chromatography using hexane–AcOEt (2:1) as an eluent to afford **37** (65 mg, 91%) as a colorless viscous oil, ν_{max} (neat)/cm^{-1} 1650; δ_H (300 MHz, $CDCl_3$) 1.52 (3H, d, J=6.1 Hz), 2.15 (1.8H, s), 2.21 (1.2H, s), 4.63 (0.4H, d, J=16.0 Hz), 4.75 (0.6H, d, J=14.0 Hz), 4.82 (0.6H, d, J=14.0 Hz), 4.95 (0.4H, d, J=16.0 Hz), 5.12 (0.4H, q, J=5.7 Hz), 5.31 (0.6H, q, J=6.1 Hz), 7.20–7.34 (4H, m); m/z: 175 (M^+) (Found: m/z 175.1000, requires $C_{11}H_{13}NO$: 175.0997).

4.4.3. 2-*t*-Butoxycarbonyl-1,3-dihydro-1-methylisoindole (38). According to the general procedure (Section 4.4), $TBAF{\cdot}3H_2O$ (95 mg, 0.30 mmol) and **24** (0.10 g, 0.30 mmol) in THF (2 ml) was refluxed for 25 h, followed by being stirred under H_2 for 18 h. The crude mixture was purified by silica gel column chromatography using hexane–AcOEt (10:1) as an eluent to afford **38** (51 mg, 73%) as a colorless viscous oil, ν_{max} (neat)/cm^{-1} 1700, 1175, 1120; δ_H (300 MHz, $CDCl_3$) 1.47 (3H, d, J=6.6 Hz), 1.53 (9H, s), 4.59–4.78 (2H, m), 5.06 (1H, m), 7.10 (4H, m); m/z: 233 (M^+) (Found: m/z 233.1411, requires $C_{14}H_{19}NO_2$: 233.1415).

4.4.4. 2,3-Dihydro-2-[(4-methylphenyl)sulfonyl]-1-[(*Z*)-phenylmethylidene]isoindole (39)[9b] **(Table 2: entry 1).** $TBAF{\cdot}3H_2O$ (87 mg, 0.28 mmol) was added to a solution of **32** (0.10 g, 0.28 mmol) in THF (2 ml) at room temperature,

and then the mixture was refluxed for 28 h. Et_2O was added to the reaction mixture and washed successively with H_2O, saturated aq. NaCl solution. The organic solution was dried over $MgSO_4$ and evaporated to afford the residue, which was purified by silica gel column chromatography using hexane–AcOEt (9:1) as an eluent to afford **39** (32 mg, 32%) as a colorless viscous oil, δ_H (300 MHz, $CDCl_3$) 2.15 (3H, s), 4.70 (2H, s), 6.66 (1H, s), 6.90–7.19 (7H, m), 7.30 (2H, d, J=8.4 Hz), 7.45 (2H, d, J=8.2 Hz), 7.80 (2H, d, J=8.4 Hz); m/z: 361 (M^+).

4.4.5. 2-*t*-Butoxycarbonyl-2,3-dihydro-1-[(*Z*)-phenylmethylidene]isoindole (40) (Table 2: entry 2). TBAF (1.0 M THF solution, 0.11 ml, 0.11 mmol) was added to a solution of **25** (32 mg, 0.104 mmol) in THF (1 ml) at room temperature, and then the mixture was refluxed for 3 h. H_2O was added to the reaction mixture and extracted with Et_2O. The organic solution was dried over $MgSO_4$ and evaporated to afford the residue, which was purified by silica gel column chromatography using hexane–AcOEt (10:1) as an eluent to afford **40** (17.8 mg, 56%) as a colorless viscous oil, δ_H (300 MHz, $CDCl_3$) 1.19 (9H, s), 4.95 (2H, s), 6.48 (1H, s), 7.15 (1H, t, J=7.1 Hz), 7.24–7.34 (5H, m), 7.38 (2H, d, J=7.4 Hz), 7.57–7.61 (1H, m); m/z:307 (M^+) (Found: m/z 307.1579, requires $C_{20}H_{21}NO_2$: 307.1573).

4.4.6. 3-Butyl-2-[(4-methylphenyl)sulfonyl]-1,2-dihydroisoquinoline (42) and 3-butylisoquinoline (44)[18] (Table 2 entry 4). TBAF (1.0 M THF solution, 1.1 ml, 1.1 mmol) was added to a solution of **26** (0.12 g, 0.35 mmol) in dioxane (1 ml) at room temperature, then the mixture was refluxed for 12 h. H_2O was added to the reaction mixture and extracted with AcOEt. The organic solution was dried over $MgSO_4$ and evaporated to afford the residue, which was purified by silica gel column chromatography using hexane–AcOEt (4:1) as an eluent to afford **42** (65 mg, 54%) as colorless a viscous oil, δ_H (300 MHz, $CDCl_3$) 0.95 (3H, t, J=7.4 Hz), 1.36–1.44 (2H, m), 1.60–1.70 (2H, m), 2.18 (3H, s), 2.68 (2H, t, J=6.9 Hz), 4.70 (2H, s), 6.15 (1H, s), 6.63 (1H, d, J=8.0 Hz), 6.85 (2H, d, J=8.2 Hz), 6.92–7.02 (3H, m), 7.31 (2H, dt, J=1.9, 8.2 Hz); m/z: 341 (M^+). From the later fractions, **44** (24 mg, 36%) was afforded as colorless viscous oil, δ_H (300 MHz, $CDCl_3$) 0.96 (3H, t, J=7.4 Hz), 1.43 (2H, sextet, J=7.6 Hz), 1.80 (2H, quintet, J=7.6 Hz), 2.94 (2H, t, J=7.6 Hz), 7.47 (1H, s), 7.52 (1H, t, J=8.0 Hz), 7.64 (1H, t, J=8.2 Hz), 7.74 (1H, d, J=8.2 Hz), 7.93 (1H, d, J=8.0 Hz), 9.20 (1H, s); m/z:185 (M^+) (Found: m/z 185.1211, requires $C_{13}H_{15}N$: 185.1204).

4.4.7. 3-Butyl-2-[(4-methylphenyl)sulfonyl]-1,2-dihydroisoquinoline (42) (Table 2 entry 5). TBAF·$3H_2O$ (95 mg, 0.30 mmol) was added to a solution of **26** (83 mg, 0.25 mmol) in dioxane (2 ml) at room temperature, and then the mixture was refluxed for 12 h. TBAF·$3H_2O$ (25 mg, 0.08 mmol) was added to a solution, and then the mixture was further refluxed for 12 h. H_2O was added to the reaction mixture and extracted with AcOEt. The organic solution was dried over $MgSO_4$ and evaporated to afford the residue, which was purified by silica gel column chromatography using hexane–AcOEt (4:1) as an eluent to afford **42** (69 mg, 84%) as a colorless viscous oil.

4.4.8. 3-Dihydro-2-[(4-methylphenyl)sulfonyl]-1-(hydroxymethylmethylidene)isoindole (41) and 3-hydroxymetnyl-2-[(4-methylphenyl)sulfonyl]-1,2-dihydroisoquinoline (43) (Table 2: entry 7). TBAF·$3H_2O$ (107 mg, 0.29 mmol) was added to a solution of **28** (90 mg, 0.29 mmol) in THF (2 ml) at room temperature, and then the mixture was refluxed for 2.5 h. AcOEt was added to the reaction mixture and the organic solution was washed successively with H_2O and saturated aq. NaCl solution. The organic solution was dried over $MgSO_4$ and evaporated to afford the residue, which was purified by silica gel column chromatography using hexane–AcOEt (2:1) as an eluent to afford **43** (27 mg, 30%) as a colorless viscous oil, ν_{max} ($CHCl_3$)/cm^{-1} 3394, 1344, 1161; δ_H (500 MHz, $CDCl_3$) 2.17 (3H, s), 2.72 (1H, br), 4.50 (2H, s), 4.74 (2H, s), 6.38 (1H, s), 6.73 (1H, d, J=7.3 Hz), 6.87 (2H, d, J=8.3 Hz), 6.94 (1H, d, J=7.3 Hz), 6.99 (1H, dt, J=1.2, 7.3 Hz), 7.05 (1H, dt, J=1.2, 7.3 Hz), 7.34 (2H, d, J= 8.3 Hz); δ_C (125 MHz, $CDCl_3$) 21.3, 50.5, 64.2, 120.2, 124.6, 125.0, 127.0, 127.5, 127.9, 128.8, 129.3, 130.3, 134.6, 139.8, 143.6; m/z: 315 (M^+) (Found: m/z 315.0928, requires $C_{17}H_{17}NO_3S$ 315.0929). From the later fractions, **41** (60 mg, 66%) was afforded as colorless viscous oil, ν_{max} ($CHCl_3$)/cm^{-1} 3387, 1352, 1165; δ_H (300 MHz, $CDCl_3$) 2.21 (1H, br), 2.25 (3H, s), 4.57 (2H, t, J=7.7 Hz), 4.69 (2H, s), 6.10 (2H, t, J=7.7 Hz), 6.99 (1H, d, J=6.6 Hz), 7.05 (2H, d, J=8.5 Hz), 7.08–7.17 (2H, m), 7.31 (1H, d, J=6.6 Hz), 7.55 (2H, d, J=8.5 Hz); m/z: 315 (M^+) (Found: m/z 315.0912, requires $C_{17}H_{17}NO_3S$ 315.0929).

4.4.9. *N*-Butyl-*N*-[2-(3,3-dimethyl-1-butynyl)benzyl]-(4-methylphenyl)sulfonamide (45). TBAF·$3H_2O$ (90 mg, 0.29 mmol) was added to a solution of **29** (0.10 g, 0.289 mmol) in dioxane (2 ml) at room temperature, then the mixture was refluxed for 8 d. Et_2O was added to the reaction mixture and washed successively with H_2O and saturated aq. NaCl solution. The organic solution was dried over $MgSO_4$ and evaporated to afford the residue, which was purified by silica gel column chromatography using hexane–AcOEt (10:1) as an eluent to afford **45** (42 mg, 35%) as a colorless viscous oil, ν_{max} (neat)/cm^{-1} 1340, 1160; δ_H (300 MHz, $CDCl_3$) 0.74 (3H, t, J=7.3 Hz), 1.14 (2H, m), 1.25 (9H, s), 1.30 (2H, m), 2.44 (3H, s), 3.07 (2H, t, J=7.7 Hz), 4.51 (2H, s), 7.18 (1H, dt, J=1.4, 7.4 Hz), 7.24 (1H, dt, J=1.6, 7.4 Hz), 7.30 (3H, m), 7.45 (1H, d, J=7.7 Hz), 7.76 (2H, d, J=8.5 Hz); m/z(FAB):398 (M^++1). From the later fractions, **29** (63 mg, 63%) was recovered.

4.4.10. Cyclization reaction of 2-(trimethylsilylethynyl)-benzyl alcohol (5) by TBACl and AgF (Table 3: entry 15). TBACl (1.36 g, 4.89 mmol) was added to a solution of 2-(trimethylsilylethynyl)benzyl alcohol (**5**) (1.0 g, 4.89 mmol) and AgF (0.62 g, 4.89 mmol) in THF (10 ml) at room temperature, then the mixture was refluxed for 6 h. Et_2O was added to the reaction mixture and the organic solution was washed successively with H_2O and saturated aq. NaCl solution. The organic solution was dried over $MgSO_4$ and evaporated to afford the crude product, which was used to the next reaction without further purification. The ^1H NMR spectrum of the crude product showed only the presence of **11**.

A mixture of the crude **11** and a catalytic amount of Pd–C in

toluene (10 ml) was stirred under H_2 for 2 d. Pd–C was filtered off, and then toluene was removed at an atmospheric pressure. The residue was successively purified by silica gel column chromatography [hexane–AcOEt (9:1)] and bulb to bulb distillation to afford **12** [0.151 g, 23% (two steps)] as a colorless oil.

4.5. General procedure for the cyclization reaction of 2-(trimethylsilylethynyl)benzyl alcohol (5) by catalytic amount of TBAF

TBAF·$3H_2O$ was added to a solution of 2-(trimethylsilylethynyl)benzyl alcohol (**5**) in THF at room temperature, then the mixture was refluxed. Et_2O was added to the reaction mixture and the organic solution was washed successively with H_2O and saturated aq. NaCl solution. The organic solution was dried over $MgSO_4$ and evaporated to afford the crude product, which was used to the next reaction without further purification.

A mixture of the crude **11** and a catalytic amount of Pd-C in toluene was stirred under H_2. Pd–C was filtered off, and then toluene was removed at an atmospheric pressure. The residue was successively purified by silica gel column chromatography [hexane–AcOEt (9:1)] and bulb to bulb distillation to afford **12** as a colorless oil.

4.5.1. Cyclization reaction of 2-(trimethylsilylethynyl)-benzyl alcohol (5) by 50 mol% of TBAF (Table 3: entry 16). According to the general procedure (Section 4.5), TBAF·$3H_2O$ (0.77 g, 2.45 mmol), 2-(trimethylsilylethynyl)benzyl alcohol (**5**) (1.00 g, 4.89 mmol) in THF (10 ml) was refluxed for 2.5 h, and then worked up. The ^{1}H NMR spectrum of the crude product showed only the presence of **11**.

After hydrogenation and purification as described in Section 4.5, **12** [0.323 g, 49% (two steps)] was obtained as a colorless oil.

4.5.2. Cyclization reaction of 2-(trimethylsilylethynyl)-benzyl alcohol (5) by 50 mol% of TBAF (Table 3: entry 16). According to the general procedure (Section 4.5), TBAF·$3H_2O$ (147 mg, 0.47 mmol), 2-(trimethylsilylethynyl)benzyl alcohol (**5**) (0.95 g, 4.65 mmol) in THF (10 ml) was refluxed for 1.5 h, and then worked up. The ^{1}H NMR spectrum of the crude product showed only the presence of **11**.

After hydrogenation and purification as described in Section 4.5, **12** [0.321 g, 51% (two steps)] was obtained as a colorless oil.

References

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