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Synthesis of Azepines via a [6 + 1] Annulation of Ynenitriles with Reformatsky Reagents

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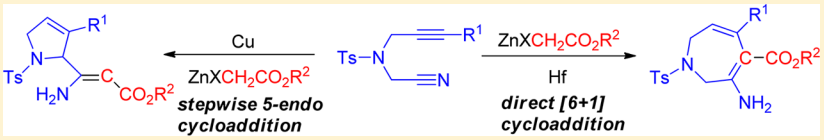
Supporting Information



ABSTRACT: A protocol for the direct synthesis of azepines using a hafnium(III)-catalyzed [6 + 1] annulation of N-tethered ynenitriles with Reformatsky reagents is reported. A broad range of 3-amino-2,7-dihydro-1*H*-azepine-4-carboxylates **4aa**−**4he** were obtained in high yields and with excellent functional group tolerance. The copper-mediated reactions of isolable Blaise intermediates (enamino esters **3**), uniquely underwent 5-endo cyclization to afford the *β*-2,5-dihydropyrrolyl *α*,*β*-unsaturated esters **5aa**−**5fc**, which exhibit anticancer activity.

The synthesis of azepines and its derivatives is a subject of continued interest because of their therapeutic uses (i.e., antiepileptic, antidepressant, Alzheimer's disease, anticancer, and Gram-positive antibacterial agents).[1] However, monocyclic azepines are comparatively rarer than benzazepines and dibenzazepines because it is difficult to construct the monocyclic seven-membered-ring systems.[2] The cycloaddition reaction is a fundamental and powerful tool for the construction of azepine derivatives. However, approaches using the cycloaddition strategy for azepine derivatives are much less abundant. The early methods are limited to more specialized substrates derived from some unique ring expansion reactions of pyrroles with dimethyl acetylenedicarboxylate.[3] Among the recently reported methods, ring-closure metathesis (RCM) may be one of the most powerful tools for the synthesis of monocyclic azepines on the basis of its substrate scope and product yields (Scheme 1).[4a−d] However, RCM can usually require large amounts of catalyst for successful conversions of *α*,*ω*-dienes and enynes to azepines and it is often difficult to remove the residual metals.[4e] Recent advances may allow for the direct formation of azepines via a metal-catalyzed [5 + 2][5] or [4 + 3][6] cycloaddition reaction of vinylaziridines with electron-deficient alkynes (EDA), reactions of iminocyclopropanes with EDA, and reactions of 4-amino ketones with arylalkynes. Despite the impressive challenge and considerable efforts in this area, particular focus has been placed on the synthesis of azepines because of their high potential to exhibit unique biological activities.

Previously, we investigated functionalization−cyclizations (FCs) of 1,6-diynes using oxygen and nitrogen nucleophiles, which led to alkoxymethyl, aryloxymethyl-,[7a] aminomethyl-,[7b] alkynylmethyl-,[7c] and deuterium-substituted furans and pyrroles;[7d,e] these have been utilized to synthesize the tanshinon anticancer derivatives.[7f] In continuing studies in this area, we explored the FC process of ynenitriles. Our basic strategy is shown at the bottom of Scheme 1.[8] By treatment of N-tethered ynenitriles

Scheme 1. Monocyclic Azepine Syntheses

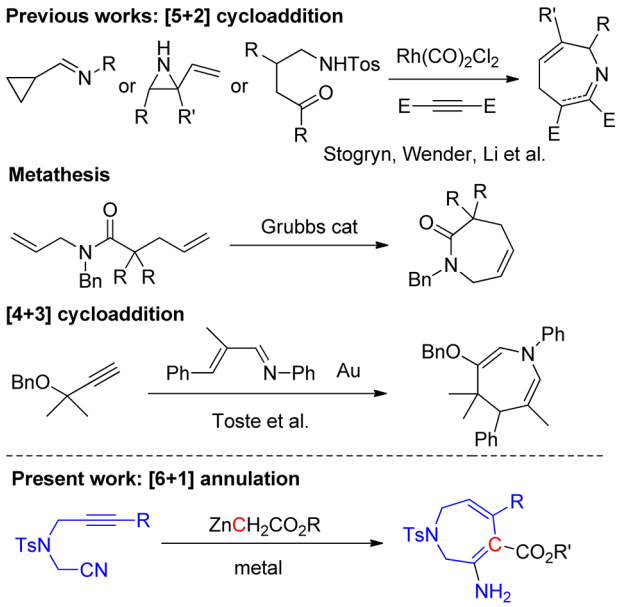


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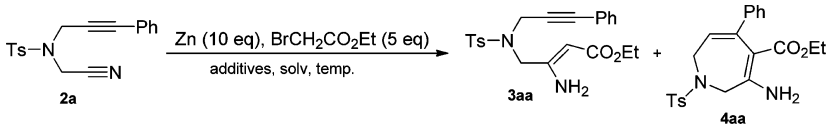
Table 1. Screening for Suitable Reaction Conditions



entry	conditions[a]	Lewis acid (amt (equiv))	yield (%) 3aa	yield (%) 4aa
1	THF, 75 °C, 0.5 h		quant	0
2	THF, 75 °C, 9 h	$Cu(OAc)_2$ (0.2)	40	60
3	THF, 75 °C, 40 h	CuBr (0.2)	31	41
4	THF, 75 °C, 36 h	$Cu(OTf)_2$ (0.2)	30	60
5	THF, 75 °C, 42 h	$Yb(OTf)_3$ (0.2)	60	38
6	THF, 75 °C, 21 h	$Hf(OTf)_4$ (0.2)	5	78
7	THF, 75 °C, 20 h	$InCl_3$ (0.2)	28	47
8	dioxane, 100 °C, 9 h	$Hf(OTf)_4$ (0.2)	1	85
9	THF, 75 °C, 39 h[b]	$Hf(OTf)_4$ (0.2)	15	57
10	THF, 75 °C, 22 h	$La(OTf)_3$ (0.2)	50	50
11	THF, 75 °C	$GaCl_3$ (0.2)	0	8[c]
12	THF, 75 °C, 20 h	$Sc(OTf)_3$ (0.2)	25	54

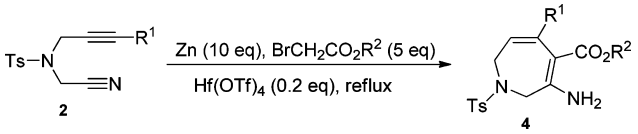
[a]Zinc was activated with chlorotrimethylsilane. Each experiment was performed using **2a** (0.16 mmol)/Zn (1.6 mmol)/$BrCH_2CO_2Et$ (0.80 mmol) in THF or dioxane (1.0 mL). [b]0.1 equiv of phenathroline was used as an additive. [c]Compound **2a** was recovered in 70% yield.

with Reformatsky reagents, the in situ generated Blaise-type intermediates can undergo a 7-endo cyclization reaction to form azepines that bear both amino and ester groups. If a protocol for monocyclic azepine synthesis from ynenitriles can be achieved by using our FC process, new functionalized azepines can be evaluated for new therapeutic uses. Herein, we report the specific formation of azepines and 2,5-dihydropyrroles from ynenitriles, the results from DFT calculations, and anticancer activities.

First, we examined the reaction of ynenitrile **2a** with Reformatsky reagent, which was generated in situ from ethyl bromoacetate/zinc in THF to afford a Blaise intermediate (i.e., *β*-enamino ester **3aa**) in excellent yield. However, the cyclized products were not obtained (Table 1, entry 1). Therefore, the reaction of **2a** in the presence of typical metal catalysts yielded azepine derivatives **4aa**. Screening of the catalysts and solvents revealed that the use of both hafnium(IV) triflate and 1,4-dioxane reduced the reaction time while retaining **3aa** (entry 8). The use of other catalysts such as $Cu(OAc)_2$, CuBr, $Yb(OTf)_3$, $InCl_3$, $La(OTf)_3$, $GaCl_3$, and $Sc(OTf)_3$ were not satisfactory for the formation of azepine **4aa** (entries 2–5, 7, 10–12). Increasing the reaction temperature significantly reduced the reaction time (entries 6 and 8). Amine additives, such as phenanthroline, were not effective in the cycloaddition (entry 9).

With the optimized reaction conditions in hand, we examined the scope of the [6 + 1] cycloaddition reaction of ynenitriles with Reformatsky reagents, and the results are shown in Table 2. In general, high yields were obtained with substrates that contained electron-rich and electron-deficient aryl, alkyl, hydrogen, and phenylsulfanyl groups. The scope of the bromo ester component of the Reformatsky reagents was also investigated. With a Reformatsky reagent generated from a methyl ester, the reaction afforded 1*H*-azepine **4ab** in good yield. However, the bulky *tert*-butyl ester led not to the desired azepine but to the adduct (i.e., Blaise intermediate **3ac**). The results indicated that the [6 + 1] cycloaddition reaction is affected by steric interaction between R^1 and R^2. Next, the scope of the ynenitrile component (i.e., R^1 group at the alkyne termini) was investigated in the cycloaddition. Substrate **2b**

Table 2. Substrate Scope for Azepine Formations



entry	R^1	R^2	conditions	product (yield (%))[a]
1	Ph	Me	dioxane, 1 h	**4ab** (80)
2		*t*-Bu	THF, 20 min	**3ac** (quantitative)
3	$MeOC_6H_4$	Et	THF, 33 h	**4ba** (78)
4		Me	THF, 0.5 h	**4bb** (68)
5		*t*-Bu	dioxane, 12 h	**3bc** (68)
6	*p*-ClC_6H_4	Et	dioxane, 22 h	**4ca** (98)
7		Me	dioxane, 2 h	**4cb** (97)
8	Et	Et	dioxane, 1 h	**4da** (65)
9		Me	THF, 1.5 h	**4db** (74)
10		*t*-Bu	dioxane, 3 h	**4dc** (53)
11	H	Me	THF, 40 min	**4ea** (37)
12		*t*-Bu	THF, 0.5 h	**4eb** (25)
13	PhS	Et	THF, 12 h	**4fa** (80)
14		Me	THF, 2 h	**4fb** (32)
15		*t*-Bu	dioxane, 2.5 h	**4fc** (66)
16		Ph	dioxane, 19 h	**4fd** (60)

[a]All products were isolated. Each reaction was performed at the scale of 0.14–1.8 mmol, and the experimental details are described in the Supporting Information. The reactions of most substrates were performed under the optimized conditions in both THF and dioxane. The better results are given.

(R^1 = *p*-$MeOC_6H_4$) reacted with ethyl and methyl bromoacetates, which resulted in azepines **4ba** and **4bb**, respectively. In addition, the reaction with a *tert*-butyl derivative also afforded the Blaise intermediate **3bc** in good yield. Regarding the similar trend in entries 6–16, the steric strain imposed by the interaction between the R^1 and R^2 groups most likely prevented the [6 + 1] azepine formation. The reactions were tolerant of ynenitriles **2c** and **2d** bearing *p*-chlorophenyl and ethyl groups (entries 6—10). Surprisingly, the reaction of ynenitrile (R^1 = Et) with the *tert*-butyl reagent exclusively

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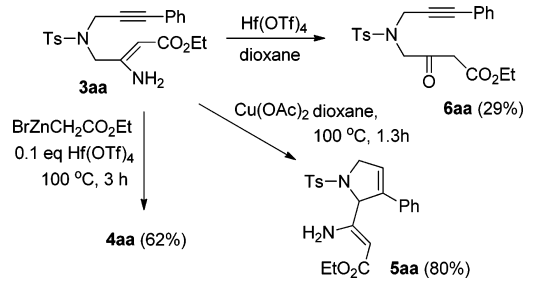
afforded azepine **4dc** (entry 10). 1*H*-Azepines **4ea** and **4eb** (R^1 = H) gave rise to low yields because they gradually decomposed due to their lability (entries 11 and 12). This transformation also tolerates substrates bearing a sulfanyl group at the alkyne termini with ethyl, methyl, and *tert*-butyl esters (entries 13−16). Fine single crystals of **4fa** were obtained, and their structural confirmation was established on the basis of X-ray crystallographic analysis, revealing that **4fa** was the 2,7-dihydro-1*H*-azepine derivative.

To gain additional insight into the mechanisms for the azepine formation, we carried out intramolecular cyclization reactions of the isolable Blaise intermediate **3aa**, which was easily prepared from the reaction of ynenitrile **2a** with a Reformatsky reagent ($Zn/BrCH_2CO_2Et$ in THF), under the selected conditions, as shown in Scheme 2. First, the reaction of **3aa** in

Scheme 2. Cyclization of Enamino Ester 3aa

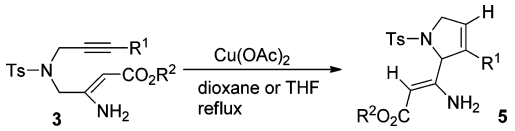


the presence of hafnium triflate in dioxane was examined. However, the product was not an azepine but hydrated keto ester **6aa** as an isolable sole product. This result indicates that the cyclization of **3aa** cannot be achieved by only activating the alkyne with hafnium triflate. In addition, the copper-mediated cyclization did not afford azepine **4aa** but 2,5-dihydropyrrole **5aa**. Analysis of the ^{1}H NMR spectrum implies a different type of ring closure under the hafnium conditions in comparison with that leading to 1*H*-azepines, such as **4aa**. Under the same conditions as the azepine formation with Reformatsky reagents generated by ethyl bromoacetate/zinc/hafnium triflate (0.1 equiv), the reaction of **3aa** successfully afforded azepine **4aa** in good yield. The result indicated that the completion of the reaction requires both hafnium triflate and a large excess of the Reformatsky reagent.

Next, we investigated the intramolecular cyclization of the isolable Blaise-type intermediates **3** to clarify the generality of the results shown in Scheme 2. Surprisingly, the copper-mediated reactions of *t*-butyl esters **3ac**−**3fc**, which did not yield azepines under the hafnium triflate catalyzed conditions, afforded 2,5-dihydropyrroles **5ac**−**5fc** in good yields (entries 2, 3, 5, 7, and 9). In addition, the reaction of ethyl esters **3aa** also afforded 2,5-dihydropyrrole **5aa** but not azepines (entries 1, 4, and 6). However, the reaction of methyl ester **3fc** gave rise to low selectivity. Both azepine **4fc** and 2,5-dihydropyrrole **5fc** were obtained in nearly the same yield.

The mechanism outlined in Scheme 3 was proposed. Because the Blaise intermediate (i.e., *β*-enaminoesters **3**) has already been isolated, from the reactions of ynenitriles with Reformatsky reagents, the first step involves the nucleophilic attack of the Reformatsky reagent on the nitrile carbon.[9] The formed imino ester **8** would react with a large excess of Reformatsky reagent to form the key intermediate **9**, which has a zinc enolate structure that is activated by hafnium metals, and **9** regioselectively undergoes carbometalation leading to 1*H*-azepine **10**

Table 3. Copper-Mediated 5-Endo Cyclization of Enamino Esters 3



entry	R^1	R^2	solv, time (h)	product (yield (%))[a]
1	Ph	Et	dioxane, 1.3	**5aa** (80)
2		*t*-Bu	dioxane, 2.5	**5ac** (77)
3	$MeOC_6H_4$	*t*-Bu	dioxane, 14	**5bc** (78)
4	Et	Et	dioxane, 2	**5da** (62)
5		*t*-Bu	dioxane, 0.5	**5dc** (76)
6	H	Et	THF, 12	**5ea** (23)
7		*t*-Bu	THF, 16	**5ec** (66)
8	PhS	Me	dioxane, 2	**5fb** (56)[b]
9		*t*-Bu	dioxane, 19	**5fc** (quantitative)

[a]All products were isolated. [b]**4fb** was also obtained in 44% yield.

(path a). The tautomerization of **10** to intermediate **11** would be accelerated by a large excess of the Reformatsky reagent. The usual protodemetalation and subsequent hydrolysis of **11** afford azepine **12** and regenerate the hafnium triflate.

In the reactions of ynenitriles (R = Ar, Et, H) with Reformatsky reagents (R′ = ethyl, methyl) shown in Table 2, the 7-endo cyclization of **9** would easily proceed due to the low steric hindrance between the R and R′ groups. A large steric strain that is imposed by the interaction between R and R′ in intermediate **9** (R′ = *t*-BuO) would prevent the 7-endo cyclization and give rise to the formation of adduct **13**. Under the copper-mediated conditions, the intramolecular cyclization of isolable **13** would produce 2,5-dihydropyrrole **16** via the enamine intermediate **14**. The different reactivities between the hafnium-catalyzed 7-endo cyclization and the copper-mediated intramolecular 5-endo cyclization appear to be due to the nature of the metal used. To gain a better understanding of this speculation, density functional theory (DFT) calculations were performed on all of the intermediates (i.e., **9**, **TS-7en-Hf**, **10**, **13**, **14**, **6ex-Hf**, **TS-6ex-Hf**, **TS-Cu-A**, **TS-Cu-B**, and **TS-Cu-C**) using Gaussian 09. As shown in Figure 1, the competing 7-endo- and 6-exo pathways were calculated using Hf(II) triflate models for simplification of the calculations. The barrier of the **TS-7en-Hf** transition state (9.0 kcal/mol) is nearly the same as that of **TS-6ex-Hf** (7.1 kcal/mol) (Figure 1). In addition, **TS-7en-Hf** would also afford both 1*H*-azepine **10** (−20.6 kcal/mol) and piperidine **6-ex-Hf** (−20.9 kcal/mol). In addition, Lee and co-workers reported that the in situ generated Blaise intermediates reacted with 1-alkynes and 1,3-enynes to afford a vinylzinc intermediate, whose deprotonation−isomerization yielded vinyl enamino esters as the product.[9b−d] In our system, the 6-exo cyclization would provide a similar vinylzinc intermediate. Therefore, the 6-exo pathway also appears to be favorable.[10] However, no 6-exo cyclized products were obtained in the cycloaddition reactions of ynenitriles with Reformatsky reagents. On the basis of the Mulliken charge of **9**, the hafnium metal coordinates with the inner carbon of the alkyne, and the exo carbon of the alkyne bearing the ethyl group would have a positive charge (Figure 2). However, the Mulliken charge of **TS-6ex-Hf** indicates that the alkyne has a negative charge. Therefore, the nucleophilic attack of zinc enamine **9** would occur at the *α*-carbon of the ethyl group to exclusively afford azepine, and the hafnium-catalyzed azepine formation was

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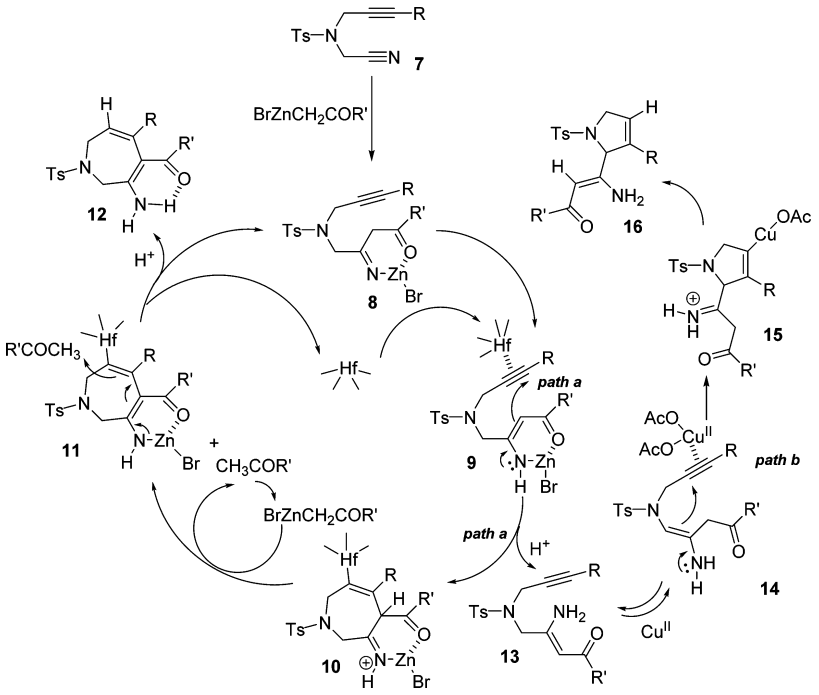
Scheme 3. Proposed Mechanism



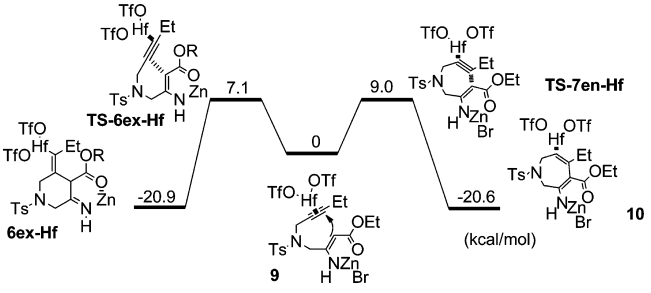


Figure 1. DFT calculation for the azepine formation.

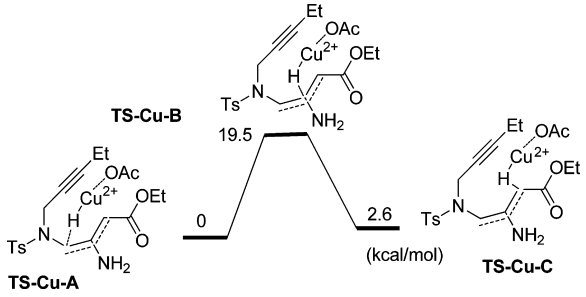


Figure 3. Isomerization of **13** to **14**.

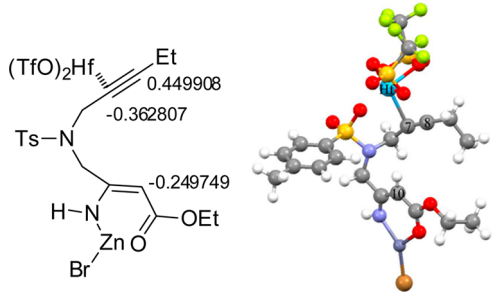


Figure 2. Mulliken charge of **9**.

the most favorable process from intermediate **9**. Next, the isomerization−cyclization of enamino ester **13** was calculated to gain insight into the formation of dihydropyrroles **16** (Figure 3). The results indicate that the relative free energy of enamine **14** is lower than that of **13** (ca. 4 kcal/mol) and that the reaction of **13** would proceed toward the dihydropyrrole formation. Therefore, the isomerization from intermediate **13** to **14** involves a copper-mediated hydride transfer step,[11] which proceeds from the carbon adjacent to the nitrogen of **TS-Cu-A** to the α-carbon to the ester group to afford **TS-Cu-C** via **TS-Cu-B**, as shown in Figure 3. Therefore, the copper-mediated 5-endo cyclization reaction of enamino esters would selectively afford the corresponding dihydropyrrole derivatives **16**.

The antiproliferative activity of several types of Michael acceptors, including α,β-unsaturated ketones and esters, against P388 and L1210 leukemias[12] have been reviewed. In the current study, the antiproliferative activity of the synthesized β-amino-β-pyrrolylenamino esters against HCT-116 cells was investigated, and the data are shown in Figure 4. To prepare

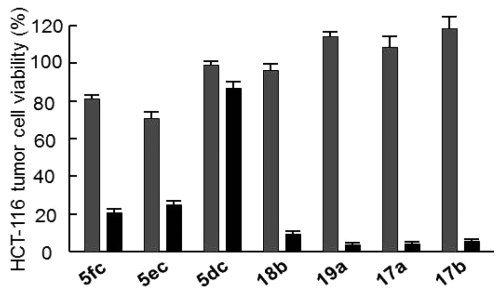


Figure 4. Antiproliferative activeties of β-amino-β-pyrrolyl enamino esters against HCT-116 cells. HCT-116 cells were treated with 10 (gray column) or 100 μM (filled column) of β-amino-β-pyrroryl enamino esters, and then their viability was assessed using the MTT method. Data shown are means ± SEM values (n = 3).

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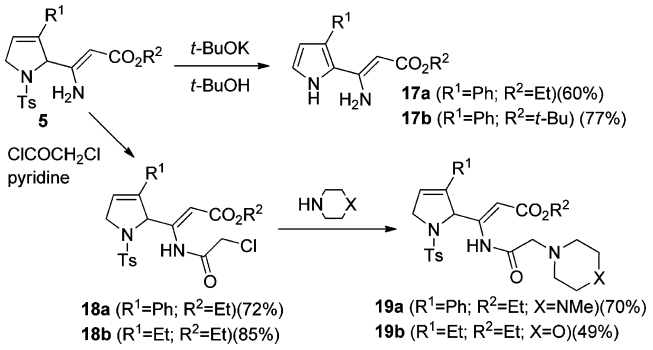
Scheme 4. Synthesis of 2,5-Dihydro-1*H*-pyrrole Analogues



these analogues for anticancer activities, the transformation of 2,5-dihydropyrroles from compound **5** was examined (Scheme 4). The reaction of **5aa** and **5ac** with *t*-BuOK in *t*-BuOH afforded 3-amino-3-pyrrolyl-α,β-unsaturated esters **17a,b** in good yields. The amino group of **5** easily underwent chloroacetylation, and the following amination provided amides **19a,b**. 2,5-Dihydropyrroles **5ec** and **5fc** slightly inhibited the tumor cell viability in 10 μM treatments, and nearly all of the tested compounds, except **5dc**, exhibited antiproliferative activity at a 100 μM treatment.

In summary, we have developed a hafnium-catalyzed [6 + 1] cycloaddition reaction for ynenitriles **2** using Reformatsky reagents, which affords 3-amino-1*H*-azepine-4-carboxylates in high yields. In addition, the copper-mediated reaction of β-enamino esters **3** underwent 5-endo cyclization to afford 2,5-dihydropyrroles with anticancer activity. The mechanistic investigations of the selective 7-endo and 5-endo cyclization reactions were performed using DFT calculations.

EXPERIMENTAL SECTION

General Information. All new compounds were fully characterized. NMR spectra were recorded on a 600 MHz spectrometer. Chemical shifts are expressed in parts per million (ppm) with respect to tetramethylsilane as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; q, quartet; IR spectra are expressed in reciprocal centimeters (cm^{-1}). EI mass spectra (MS) were obtained with a direct-insertion probe at 70 eV. All high-resolution mass determinations were obtained with an on line system. Melting points were determined on a Micro melting point apparatus and are uncorrected. The data of **4fb** and **5dc** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1016452 and CCDC 1016451, respectively.

Preparations of Ynenitriles. *N-Cyanomethyl-N-[3-phenyl-2-propyn-1-yl]-p-toluenesulfonamide (**2a**). Typical Procedure.* To a THF (12.5 mL) solution of *N*-(*p*-toluenesulfonyl)aminoacetonitrile[13] (**1**; 2.5 g, 11.9 mmol), phenylpropargyl alcohol (1.9 g, 11.9 mmol), and triphenylphosphine (3.1 g, 11.9 mmol) was added dropwise DEAD (5.4 mL, 11.9 mmol) at room temperature. The reaction mixture was stirred for 1 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with AcOEt/*n*-hexane (1/10, 1/5) as eluent. The residue was purified by column chromatography on silica gel with AcOEt/*n*-hexane (1/10, 1/5) as eluent to give the title compound **2a** (3.2 g, 82%) as a white powder: mp 95−96 °C (from CH_2Cl_2/*n*-hexane); IR (KBr, cm^{-1}) ν 2982, 2925, 2854, 2246, 1598, 1491, 1442, 1357, 1260, 1166, 1121, 1093, 1073, 969, 909, 888, 816; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (3H, s, Me), 4.37 (2H, s, CH_2), 4.38 (2H, s, CH_2), 7.22−7.35 (7H, m, ArH), 7.78 (2H, d, J = 8.2 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 35.2 (t), 38.5 (t), 79.8 (s), 87.3 (s), 113.6 (s), 121.5 (s), 127.8 (d × 2), 128.2 (d × 2), 128.9 (d), 130.0 (d × 2), 131.6 (d × 2), 134.0 (s), 144.9 (s); EIMS m/z 324 (M^+), 169 (M^+ − Ts). Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.65; H, 4.97; N, 8.64. Found: C, 66.67; H, 5.02; N, 8.43.

*N-Cyanomethyl-N-[3-(4-methoxyphenyl)-2-propyn-1-yl]- p-toluenesulfonamide (**2b**).* A triethylamine (2.5 mL) solution of *N*-cyanomethyl-*N*-(2-propyn-1-yl)-*p*-toluenesulfonamide (**2e**; 0.30 g, 1.21 mmol), 4-iodoanisole (0.28 g, 1.21 mmol), copper iodide (23 mg, 1.21×10^{-5} mmol), and bis(triphenylphosphine)palladium(II) dichloride (24 mg, 2.06×10^{-3} mmol) was stirred for 2.5 h at 50 °C. The reaction mixture was poured into water (50 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel (AcOEt/*n*-hexane (1/4) as eluent) to give the title compound **2b**[12] (0.20 g, 46%) as a pale yellow oil: IR (KBr, cm^{-1}) ν 2921, 2850, 2223, 1606, 1510, 1457, 1442, 1356, 1293, 1250, 1166, 1093, 1030, 908, 886, 834, 816, 753, 673, 576, 544, 414; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (3H, s, Me), 3.78 (3H, s, Me), 4.35 (2H, s, CH_2), 4.36 (2H, s, CH_2), 6.79 (2H, d, J = 8.2 Hz, ArH), 7.16 (2H, d, J = 8.9 Hz, ArH), 7.32 (2H, d, J = 8.2 Hz, ArH), 7.76 (2H, d, J = 8.2 Hz, ArH);[13]C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 35.0 (t), 38.6 (t), 55.2 (q), 78.4 (s), 87.2 (s), 113.4 (s), 113.7 (s), 113.8 (d × 2), 127.8 (d × 2), 129.9 (d × 2), 133.1 (d × 2), 133.9 (s), 144.8 (s), 159.9 (s); EIMS m/z 354 (M^+), 199 (M^+ − Ts); high-resolution mass (EI) calcd for $C_{19}H_{18}N_2O_3S$ 354.1038, found m/z 354.1043.

*N-Cyanomethyl-N-[3-(4-chlorophenyl)-2-propyn-1-yl]-p-toluenesulfonamide (**2c**).* A mixture of triethylamine (2.5 mL), *N*-cyanomethyl-*N*-(2-propyn-1-yl)-*p*-toluenesulfonamide (**2e**; 0.30 g, 1.21 mmol), 4-chloroiodobenzene (0.30 g, 1.21 mmol), (23 mg, 1.21×10^{-5} mmol), and bis(triphenylphosphine)palladium(II) dichloride (24 mg, 2.06×10^{-3} mmol) was stirred for 2.5 h at 50 °C. The reaction mixture was poured into water (100 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with saturated NH_4Cl solution (30 mL) and water (30 mL) and then dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel with AcOEt/*n*-hexane (1/4) as eluent to give the title compound **2c**[14] (0.33 g, 75%): mp 112−113 °C (from CH_2Cl_2/*n*-hexane) as a white powder: IR (KBr, cm^{-1}) ν 2923, 2350, 2252, 1490, 1360, 1263, 1222, 1165, 1092, 1015, 911, 885, 831, 747, 665, 583, 550; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (3H, s, Me), 3.78 (3H, s, Me), 4.35 (2H, s, CH_2), 4.36 (2H, s, CH_2), 6.79 (2H, d, J = 8.2 Hz, ArH), 7.16 (2H, d, J = 8.9 Hz, ArH), 7.32 (2H, d, J = 8.2 Hz, ArH), 7.76 (2H, d, J = 8.2 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 35.3 (t), 38.6 (t), 80.9 (q), 86.1 (s), 113.6 (s), 119.9 (s), 127.9 (d × 2), 128.6 (d × 2), 130.0 (d × 2), 132.9 (d × 2), 134.0 (s), 135.1 (s), 145.0 (s); EIMS m/z 358 (M^+ − 1), 203 (M^+ − Ts), 91 (M^+ − Ts − C_6H_4Cl). Anal. Calcd for $C_{18}H_{15}N_2O_2SCl$: C, 60.25; H, 4.21; N, 7.80. Found: C, 60.10; H, 3.86; N, 7.74.

*N-Cyanomethyl-N-(2-pentyn-1-yl)-p-toluenesulfonamide (**2d**).* To a THF (2.0 mL) solution of *N*-(*p*-toluenesulfonyl)aminoacetonitrile (**1**; 0.61 g, 2.9 mmol), 2-pentyn-1-ol (0.244 g, 2.9 mmol), and triphenylphosphine (0.76 g, 2.9 mmol) was added DEAD (1.3 mL of 2.2 M THF, 2.9 mmol) under an Ar atmosphere. The reaction mixture was stirred for 1 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/*n*-hexane 1/10) to give the title compound **2d** (0.474 g, 59%) as a yellow oil: IR (KBr, cm^{-1}) ν 2980, 2939, 2923, 2236, 1598, 1495, 1439, 1417, 1357, 1333, 1255, 1167, 1122, 1094, 1018, 908, 888, 816, 745, 661, 574, 544, 424; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.00 (3H, t, J = 7.6 Hz, Me), 2.04−2.07 (2H, m, CH_2), 2.44 (3H, s, Me), 4.10 (2H, t, J = 2.1 Hz, CH_2), 4.30 (2H, s, CH_2), 7.35 (2H, br d, J = 8.3 Hz, ArH), 7.73 (2H, br d, J = 8.2 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.1 (t), 13.3 (q), 21.5 (q), 34.8 (t), 38.1 (t), 70.2 (s), 89.6 (s), 113.6 (s), 127.8 (d × 2), 129.9 (d × 2), 134.0 (s), 144.7 (s); high-resolution mass (EI) calcd for $C_{14}H_{16}N_2O_2S$ 276.0932, found m/z 276.0950.

*N-Cyanomethyl-N-(2-propyn-1-yl)-p-toluenesulfonamide (**2e**).* To a THF (6 mL) solution of *N*-(*p*-toluenesulfonyl)aminoacetonitrile

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(1.0 g, mmol), propargyl alcohol (1.26 g, 4.8 mmol), and triphenylphosphine (0.269 g, 4.8 mmol) was added DEAD (2.2 mL, 4.8 mmol) under an Ar atmosphere. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/*n*-hexane 1/10 then 1/5) to give the title compound[15] **2e** (1.00 g, 89%) as white needles: mp 55−56 °C (from CH_2Cl_2/*n*-hexane); IR (KBr, cm^{-1}) ν 3290, 2987, 2925, 2361, 2124, 1709, 1598, 1357, 1167, 1094, 903, 886, 817, 754, 664, 577, 544, 492, 403; ^1H NMR (600 MHz, $CDCl_3$) δ 2.30 (1H, t, J = 2.1 Hz, CH), 2.45 (3H, s, Me), 4.13 (2H, s, CH_2), 4.33 (2H, s, CH_2), 7.37 (2H, d, J = 8.2 Hz, ArH), 7.73 (2H, d, J = 8.2 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 34.8 (t), 37.4 (t), 74.8 (s), 75.7 (s), 113.3 (s), 127.8 (d × 2), 130.1 (d × 2), 133.8 (s), 145.1 (s); EIMS m/z 248 (M^+).

N-Cyanomethyl-N-[3-(phenylsulfanyl)-2-propyn-1-yl]-p-toluenesulfonamide (2f). To a THF (12.5 mL) solution of *N*-(*p*-toluenesulfonyl)aminoacetonitrile (2.50 g, 11.9 mmol), 3-(phenylsulfanyl)-propargyl alcohol (1.90 g, 11.9 mmol), and triphenylphosphine (3.10 g, 11.9 mmol) was added dropwise diethyl azodicarboxylate (2.2 M, 5.40 mL, 11.9 mmol) under an Ar atmosphere. The reaction mixture was stirred for 1 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with AcOEt/*n*-hexane (1/10, then 1/5) to give the title compound **2f** (4.20 g, 100%) as colorless prisms: mp 45−47 °C (from CH_2Cl_2/*n*-hexane); IR (KBr, cm^{-1}) ν 2978, 2924, 2188, 1709, 1596, 1582, 1479, 1441, 1356, 1330, 1165, 1094, 908, 886, 815; ^1H NMR (600 MHz, $CDCl_3$) δ 2.39 (3H, s, Me), 4.32 (2H, s, CH_2), 4.39 (2H, s, CH_2), 7.29-7.34 (7H, m, ArH), 7.72 (2H, d, J=8.2 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 35.1 (t), 39.0 (t), 75.4 (s), 89.5 (s), 113.4 (s), 126.6 (d × 2), 127.0 (d), 127.7 (d × 2), 129.4 (d × 2), 130.1 (d × 2), 131.3 (s), 133.7 (s), 145.1 (s); EIMS m/z 356 (M^+), 266 (M^+ − Tol). Anal. Calcd for $C_{18}H_{16}N_2O_2S_2$: C, 60.65; H, 4.52; N, 7.86. Found: C, 60.51; H, 4.48; N, 7.83.

Screening for Suitable Reaction Conditions. Results of Table 1 and Preparation of Alkyl 4-(Prop-2-yn-1-ylamino)but-2-enoates (3). *Procedure of Entry 1 in Table 1.* *N*-Cyanomethyl-*N*-(3-phenyl-2-propyn-1-yl)-*p*-toluenesulfonamide (**3aa**; 50 mg, 0.16 mmol) was added to a THF (1 mL) suspension of ethyl bromoacetate (0.134 g, 0.80 mmol) and zinc (0.10 g, 1.60 mmol, activated by 2 drops of TMSCl) at room temperature. The reaction mixture was refluxed for 1 h and then poured into water. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was separated by preparative TLC on silica gel with AcOEt/*n*-hexane (1/5) as eluent to give ethyl 3-amino-4-[*N*-3-(phenylprop-2-yn-1-yl)-*N*-(*p*-toluenesulfonyl)amino]but-2-enoate (**3aa**; 65 mg, quantitative) as colorless prisms. The large-scale reaction of **2a** (0.50 g, 1.54 mmol) with zinc (0.50 g, 7.71 mmol) and ethyl bromoacetate (0.77 g, 4.62 mmol) in THF (8.0 mL) and the workup procedure gave a crude residue, which was precipitated from hexane. The almost pure **3aa** was quantitatively obtained as a white powder: mp 127−128 °C; IR (KBr, cm^{-1}) 3459, 2925, 2853, 1733, 1672, 1625, 1569, 1491, 1443, 1351, 1284, 1164, 1092, 1041, 903, 814, 794, 758, 662, 586, 549, 417; ^1H NMR (600 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.6 Hz, Me), 2.35 (3H, s, Me), 3.85 (2H, s, CH_2), 4.13 (2H, q, J = 7.5 Hz, CH_2), 4.33 (2H, s, CH_2), 4.62 (1H, s, olefinic H), 5.37 (2H, br s, NH), 7.08 (2H, d, J = 7.6 Hz, ArH), 7.25−7.28 (5H, m, ArH), 7.79 (2H, d, J = 8.2 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5 (q), 21.4 (q), 37.6 (t), 50.1 (t), 59.0 (t), 80.9 (s), 85.4 (q), 86.3 (s), 121.8 (s), 127.8 (d × 2), 128.1 (d × 2), 128.6 (d), 129.7 (d × 2), 131.5 (d × 2), 135.4 (s), 144.1 (s), 155.4 (s), 169.6 (s); EIMS m/z 412 (M^+), 257 (M^+ − Ts). Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.06; H, 5.86; N, 6.79. Found: C, 63.92; H, 5.89; N, 6.71.

Ethyl 3-Amino-2,7-dihydro-5-phenyl-1-(*p*-toluenesulfonyl)-1*H*-azepine-4-carboxylate (4aa), Entry 8 in Table 1. Typical Procedure. *N*-Cyanomethyl-*N*-(3-phenyl-2-propyn-1-yl)-*p*-toluenesulfonamide (**2a**; 50 mg, 0.16 mmol) was added to a dioxane (1 mL) suspension of ethyl bromoacetate (0.134 g, 0.80 mmol) and zinc (0.10 g, 1.60 mmol, activated by 2 drops of TMSCl) at room temperature. To the resulting mixture was then added hafnium(IV) triflate (24.8 mg, 0.032 mmol), and the mixture was stirred for 9 h at 100 °C. Workup and purification by preparative TLC on silica gel with AcOEt/*n*-hexane (1/5) as eluent gave the title compound **4aa** (56 mg, 85%) as a white powder, accompanied by a small amount of **2a**: mp 184−185 °C; IR (KBr, cm^{-1}) ν 3435, 2925, 2854, 1732, 1665, 1615, 1532, 1456, 1446, 1330, 1259, 1161, 1092, 915, 756, 548, 446; ^1H NMR (600 MHz, $CDCl_3$) δ 0.63 (3H, t, J = 6.9 Hz, Me), 2.40 (3H, s, Me), 3.78−4.14 (6H, m, CH_2), 5.01 (1H, s, NH), 5.81 (1H, t, J = 7.6 Hz, CH), 7.21−7.26 (5H, m, ArH), 7.28 (2H, d, J = 8.3 Hz, ArH), 7.72 (2H, d, J = 8.3 Hz, ArH), 8.26 (1H, s, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.4 (q), 21.5 (q), 44.2 (t), 50.1 (t), 59.1 (t), 96.8 (s), 117.9 (d), 126.5 (d × 2), 127.2 (d × 2), 127.3 (d), 127.9 (d × 2), 129.9 (d × 2), 135.7 (s), 141.8 (s), 143.8 (s), 147.3 (s), 155.6 (s), 168.6 (s); EIMS m/z 412 (M^+), 256 (M^+ − Ts). Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.06; H, 5.86; N, 6.79. Found: C, 63.77; H, 5.90; N, 6.69.

Methyl 3-Amino-5-phenyl-1-(*p*-toluenesulfonyl)-2,7-dihydro-1*H*-azepine-4-carboxylate (4ab), Entry 1 in Table 2. *N*-Cyanomethyl-*N*-(3-phenylprop-2-ynyl)-*p*-toluenesulfonamide (**2a**; 50 mg, 0.15 mmol) was added to a dioxane (1.0 mL) suspension of methyl bromoacetate (0.11 g, 0.75 mmol) and zinc (98 mg, 1.50 mmol, activated by 2 drops of TMSCl) at room temperature. To the resulting mixture was then added hafnium(IV) triflate (23 mg, 0.03 mmol), and this mixture was stirred for 1 h at 100 °C. Workup and purification by preparative TLC gave a crude residue, which was precipitated from hexane. The title compound **4ab** (48 mg, 80%) was obtained as a pale yellow powder: mp 170−171 °C (from CH_2Cl_2/*n*-hexane); IR (KBr, cm^{-1}) ν 3437, 3057, 3028, 2949, 2924, 1671, 1615, 1535, 1492, 1458, 1346, 1330, 1264, 1162, 1091, 1064, 905, 810, 756, 700, 681, 665, 756, 700, 681, 665, 624, 580, 548; ^1H NMR (600 MHz, $CDCl_3$) δ 2.40 (3H, s, Me), 3.31 (3H, s, OMe), 3.80 (4H, br s, CH_2 × 2), 5.12 (1H, br s, NH), 5.83 (1H, t, J = 7.5 Hz, CH), 7.21−7.27 (5H, m, ArH), 7.29 (2H, d, J = 8.3 Hz, ArH), 7.72 (2H, d, J = 8.2 Hz, ArH), 8.34 (1H, br s, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 44.1 (t), 50.0 (t), 50.5 (q), 96.2 (s), 118.2 (d), 126.2 (d × 2), 127.2 (d × 2), 127.4 (d), 128.0 (d × 2), 129.9 (d × 2), 135.7 (s), 141.3 (s), 144.1 (s), 146.8 (s), 155.6 (s), 169.0 (s); EIMS m/z 398 (M^+), 243 (M^+ − Ts). Anal. Calcd for $C_{21}H_{22}N_2O_4S$: C, 63.30; H, 5.56; N, 7.03. Found: C, 63.18; H, 5.60; N, 6.82.

***tert*-Butyl 3-Amino-4-[*N*-3-(phenylprop-2-yn-1-yl)-*N*-(*p*-toluenesulfonyl)amino]but-2-enoate (3ac), Entry 2 in Table 2.** *N*-Cyanomethyl-*N*-[3-phenyl-2-propyn-1-yl]-*p*-toluenesulfonamide (**2a**; 0.40 g, 1.23 mmol) was added to a THF (4.0 mL) suspension of *tert*-butyl bromoacetate (0.72 g, 3.70 mmol) and zinc (0.40 g, 6.70 mmol, activated by 2 drops of TMSCl) at room temperature, and the mixture was stirred for 10 min at 75 °C. Workup and precipitation from hexane gave the title compound **3ac** (0.47 g, 87%) as white needles: mp 97−98 °C (from CH_2Cl_2/*n*-hexane). A small-scale reaction of **2a** (50 mg, 0.15 mmol) with *tert*-butyl bromoacetate under similar conditions afforded **3ac** in quantitative yield, as shown in Table 2, entry 2: IR (KBr, cm^{-1}) ν 3471, 3339, 2926, 1668, 1562, 1491, 1443, 1390, 1351, 1290, 1252, 1163, 1092, 997, 901, 852, 797, 759, 718, 705, 691, 662, 585, 549; ^1H NMR (600 MHz, $CDCl_3$) δ 1.47 (9H, s, Me × 3), 2.32 (3H, s, Me), 3.82 (2H, s, CH_2), 4.32 (2H, s, CH_2), 4.56 (1H, s, olefinic H), 7.05 (2H, d, J = 8.2 Hz, ArH), 7.23−7.27 (5H, m, ArH), 7.77 (2H, d, J = 8.2 Hz, ArH), two protons of amino group were not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3 (q), 28.4 (q × 3), 37.4 (t), 50.0 (t), 78.6 (s), 81.0 (s), 86.1 (s), 87.0 (d), 121.7 (s), 127.6 (d × 2), 128.0 (d × 2), 128.4 (d), 129.6 (d × 2), 131.4 (d × 2), 135.3 (s), 143.9 (s), 154.5 (s), 169.3 (s); EIMS m/z 440 (M^+), 383 (M^+ − *t*-Bu). Anal. Calcd for $C_{24}H_{28}N_2O_4S$: C, 65.43; H, 6.41; N, 6.36. Found: C, 65.17; H, 6.54; N, 6.33.

Ethyl 3-Amino-5-(4-methoxyphenyl)-1-(*p*-toluenesulfonyl)-1*H*-azepine-4-carboxylate (4ba), Entry 3 in Table 2. *N*-Cyanomethyl-*N*-[3-(4-methoxyphenyl)prop-2-yn-1-yl]-*p*-toluenesulfonamide (**2b**; 50 mg, 0.14 mmol) was added to a dioxane (2.0 mL) suspension of ethyl bromoacetate (0.12 g, 0.71 mmol) and zinc (92 mg, 1.4 mmol, activated by 2 drops of TMSCl) at room temperature. To the resulting mixture was then added hafnium(IV) triflate (22 mg, 0.03 mmol), and the mixture was stirred for 33 h at 100 °C. Workup and purification by preparative TLC gave the title compound **4ba** (48 mg, 78%) as colorless plates: mp 171−172 °C (from CH_2Cl_2/*n*-hexane); IR (KBr, cm^{-1}) ν 3436, 3315, 2926, 2854, 2359, 2342, 1665, 1609, 1540, 1509, 1457,

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1365, 1343, 1329, 1292, 1250, 1161, 1091, 1062, 1036, 917, 831, 760, 679, 607, 548; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.70 (3H, t, J = 7.6 Hz, Me), 2.40 (3H, s, Me), 3.79 (3H, s, OMe), 3.84 (6H, br s, $CH_2 \times 3$), 5.17 (1H, br s, NH), 5.74 (1H, t, J = 7.6 Hz, CH), 6.79 (2H, d, J = 9.0 Hz, ArH), 7.14 (2H, d, J = 9.0 Hz, ArH), 7.29 (2H, d, J = 8.3 Hz, ArH), 7.72 (2H, d, J = 8.3 Hz, ArH), 8.26 (1H, br s, NH); ^{1}H NMR (600 MHz, C_5D_5N) δ 0.69 (3H, t, J = 6.9 Hz, Me), 2.06 (3H, s, Me), 3.65 (3H, s, OMe), 3.90 (2H, br s, CH_2), 4.20 (4H, br s, $CH_2 \times 2$), 5.01 (1H, br s, NH), 5.85 (1H, t, J = 7.6 Hz, CH), 6.93 (2H, d, J = 8.9 Hz, ArH), 7.35 (2H, d, J = 8.9 Hz, ArH), 7.58 (2H, s, ArH), 8.00 (2H, d, J = 6.9 Hz, ArH), 9.19 (1H, br s, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.6 (q), 21.5 (q), 44.2 (t), 50.1 (t), 55.3 (q), 59.1 (t), 96.8 (s), 113.3 (d × 2), 116.5 (d), 127.2 (d × 2), 127.5 (d × 2), 129.9 (d × 2), 134.4 (s), 135.7 (s), 143.7 (s), 146.6 (s), 155.4 (s), 159.1 (s), 168.6 (s); EIMS m/z 442 (M^+), 287 (M^+ − Ts). Anal. Calcd for $C_{23}H_{26}N_2O_5S$: C, 62.42; H, 5.92; N, 6.33. Found: C, 62.09; H, 5.96; N, 6.29.

Methyl 3-Amino-2,7-dihydro-5-(*p*-methoxyphenyl)-1-(*p*-toluenesulfonyl)-1*H*-azepine-4-carboxylate (4bb), Entry 4 in Table 2. *N*-Cyanomethyl-*N*-[3-(4-methoxyphenyl)-2-propynyl]-*p*-toluenesulfonamide (**2b**; 50 mg, 0.14 mmol) was added to a dioxane (1.0 mL) suspension of methyl bromoacetate (0.134 g, 0.80 mmol) and zinc (79 mg, 1.2 mmol, activated by 2 drops of TMSCl) at room temperature. To the resulting mixture was then added hafnium(IV) triflate (24.8 mg, 0.032 mmol), and the mixture was stirred for 40 min at 100 °C. Workup and purification by preparative TLC gave the title compound **4bb** (30 mg, 71%) as a white powder: mp 164−165 °C; IR (KBr, cm^{-1}) ν 3436, 3321, 2949, 1669, 1608, 1510, 1458, 1441, 1345, 1329, 1250, 1161, 1091, 1037, 904, 831, 760, 679, 662, 607, 548; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.40 (3H, s, Me), 3.35 (3H, s, OMe), 3.79 (7H, br s, OMe and $CH_2 \times 2$), 5.04 (1H, br s, NH), 5.77 (1H, t, J = 7.5 Hz, ArH), 6.79 (2H, d, J = 7.9 Hz, ArH), 7.15 (2H, d, J = 8.3 Hz, ArH), 7.29 (2H, d, J = 8.3 Hz, ArH), 7.71 (2H, d, J = 7.5 Hz, ArH), 8.34 (1H, br s, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 44.1 (t), 50.0 (t), 50.6 (q), 55.2 (q), 96.4 (s), 113.4 (d × 2), 116.7 (d), 126.3 (d × 2), 127.2 (d × 2), 129.9 (d × 2), 133.9 (s), 135.8 (s), 143.7 (s), 146.2 (s), 155.5 (s), 159.2 (s), 169.1 (s); EIMS m/z 428 (M^+), 337 (M^+ − Tol), 273 (M^+ − Ts). Anal. Calcd for $C_{22}H_{24}N_2O_5S$: C, 61.70; H, 5.65; N, 6.54. Found: C, 61.45; H, 5.70; N, 6.45.

Preparation of *tert*-Butyl (*Z*)-3-Amino-4-[3-(*p*-methoxyphenyl)-*N*-(*p*-toluenesulfonylprop-2-ynylamino)but-2-enoate (3bc), Entry 5 in Table 2. *N*-Cyanomethyl-*N*-[3-(4-methoxyphenyl)prop-2-yn-1-yl]-4-methylphenylsulfonamide (**7**; 3 mg, 0.21 mmol) was added to a THF (2.0 mL) suspension of *tert*-butyl bromoacetate (0.172 g, 1.03 mmol) and zinc (135 mg, 2.06 mmol, activated by 2 drops of TMSCl) at room temperature, and the mixture was stirred for 40 min at 75 °C. Workup and purification by preparative TLC gave the title compound **6f** (76 mg, 78%) as pale yellow oil; IR (KBr, cm^{-1}) ν 3464, 3342, 2974, 2927, 1668, 1623, 1567, 1510, 1457, 1350, 1292, 1250, 1163, 1092, 1033, 902, 834, 799, 765, 747, 669, 580, 548; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (9H, s, Me × 3), 2.36 (3H, s, Me), 3.79 (3H, s, OMe), 3.81 (2H, s, CH_2), 4.31 (2H, s, CH_2), 4.55 (1H, s, olefinic H), 6.77 (2H, d, J = 9.0 Hz, ArH), 7.01 (2H, d, J = 8.2 Hz, ArH), 7.27 (2H, d, J = 8.2 Hz, ArH), 7.77 (2H, d, J = 8.2 Hz, ArH), the two hydrogen of amino group were not observed in the ^{1}H NMR spectrum; ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4 (q), 28.4 (q × 3), 37.6 (t), 50.0 (t), 55.2 (q), 78.7 (s), 79.6 (s), 86.0 (s), 87.0 (d), 113.7 (d × 2), 113.8 (s), 127.7 (d × 2), 129.6 (d × 2), 132.9 (d × 2), 135.4 (s), 143.9 (s), 154.6 (s), 159.7 (s), 169.4 (s); EIMS m/z 470 (M^+), 413 (M^+ − *t*-Bu). Anal. Calcd for $C_{25}H_{30}N_2O_5S$: C, 63.81; H, 6.43; N, 5.95. Found: C, 63.63; H, 6.37; N, 5.74.

Ethyl 3-Amino-5-(4-chlorophenyl)-2,7-dihydro-1-(*p*-toluenesulfonyl)-1*H*-azepine-4-carboxylate (4ca), Entry 6 in Table 2. *N*-Cyanomethyl-*N*-[3-(4-chlorophenyl)prop-2-yn-1-yl]-*p*-toluenesulfonamide (**2c**; 50 mg, 0.14 mmol) was added to a dioxane (2.0 mL) suspension of ethyl bromoacetate (0.12 g, 0.70 mmol) and zinc (92 mg, 1.4 mmol, activated by 2 drops of TMSCl) at room temperature, and the mixture was stirred for 21.5 h. Workup and purification by preparative TLC gave the title compound **4ca** (61.1 mg, 98%) as colorless prisms: mp 183−184 °C; IR (KBr, cm^{-1}) ν 3445, 3306, 2926, 2360, 1668, 1615, 1541, 1490, 1457, 1345, 1330, 1259, 1162, 1091, 1062, 1015, 916, 817, 761, 677, 586, 549; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.70 (3H, t, J = 7.6 Hz, Me), 2.41 (3H, s, Me), 3.80 (6H, br s, CH_2), 5.15 (1H, br s, NH), 5.76 (1H, t, J = 7.6 Hz, olefinic H), 7.13 (2H, d, J = 8.3 Hz, ArH), 7.21 (2H, d, J = 8.3 Hz, ArH), 7.30 (2H, d, J = 8.3 Hz, ArH), 7.72 (2H, d, J = 8.2 Hz, ArH), 8.35 (1H, br s, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.5 (q), 21.5 (q), 44.1 (t), 50.1 (t), 59.2 (t), 96.2 (s), 118.3 (d), 127.2 (d × 2), 127.7 (d × 2), 128.0 (d × 2), 129.9 (d × 2), 133.0 (s), 135.5 (s), 140.4 (s), 143.9 (s), 146.1 (s), 155.8 (s), 168.3 (s); EIMS m/z 446 (M^+ − 1), 291 (M^+ − Ts). Anal. Calcd for $C_{22}H_{23}N_2O_4SCl$: C, 59.12; H, 5.19; N, 6.27. Found: C, 58.89; H, 5.16; N, 6.25.

Methyl 3-Amino-5-(4-chlorophenyl)-2,7-dihydro-1-(*p*-toluenesulfonyl)-1*H*-azepine-4-carboxylate (4cb), Entry 7 in Table 2. *N*-Cyanomethyl-*N*-[3-(4-chlorophenyl)prop-2-yn-1-yl]-*p*-toluenesulfonamide (**2c**; 40 mg, 0.11 mmol) was added to a dioxane (1.0 mL) suspension of methyl bromoacetate (84 mg, 0.55 mmol) and zinc (73 mg, 1.4 mmol, activated by 2 drops of TMSCl) at room temperature, and the mixture was stirred for 40 min at 100 °C. Workup and purification by preparative TLC gave the title compound **4cb** (47 mg, 97%) as colorless needles: mp 181−183 °C (from CH_2Cl_2/*n*-hexane); IR (KBr, cm^{-1}) ν 3435, 3318, 2949, 1671, 1614, 1532, 1488, 1440, 1402, 1345, 1329, 1263, 1161, 1091, 1063, 1013, 1905, 828, 762, 677, 586, 549; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.36 (3H, s, Me), 3.33 (3H, s, Me), 3.79 (4H, br s, $CH_2 \times 2$), 5.24 (1H, br s, NH), 5.79 (1H, t, J = 7.5 Hz, olefinic H), 7.14 (2H, d, J = 8.3 Hz, ArH), 7.21 (2H, d, J = 8.9 Hz, ArH), 7.29 (2H, d, J = 8.2 Hz, ArH), 7.71 (2H, d, J = 8.3 Hz, ArH), one hydrogen of amino group was not observed in the ^{1}H NMR spectrum; ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 44.0 (t), 50.0 (t), 50.6 (q), 95.8 (s), 118.6 (d), 127.2 (d × 2), 127.5 (d × 2), 128.2 (d × 2), 129.9 (d × 2), 133.2 (s), 135.6 (s), 139.9 (s), 143.9 (s), 145.8 (s), 156.0 (s), 168.7 (s); EIMS m/z 432 (M^+), 277 (M^+ − Ts). Anal. Calcd for $C_{21}H_{21}ClN_2O_4S$: C, 58.30; H, 4.89; N, 6.47. Found: C, 58.13; H, 4.91; N, 6.36.

Ethyl 3-Amino-5-ethyl-2,7-dihydro-1-(*p*-toluenesulfonyl)-1*H*-azepine-4-carboxylate (4da), Entry 8 in Table 2. *N*-Cyanomethyl-*N*-(2-pentyn-1-yl)-*p*-toluenesulfonamide (**2d**; 500 mg, 1.80 mmol) was added to a dioxane (6.0 mL) suspension of ethyl bromoacetate (0.91 g, 5.43 mmol) and zinc (0.65 g, 10.0 mmol, activated by 5 drops of TMSCl) at room temperature. To the resulting mixture was then added hafnium(IV) triflate (50.0 mg, 0.065 mmol), and the mixture was stirred for 1 h at 100 °C. Workup and purification by preparative TLC gave the title compound **4da** (433 mg, 65%) as a white powder: mp 144−145 °C; IR (KBr, cm^{-1}) ν 3328, 2923, 2360, 2342, 1600, 1339, 1257, 1162, 1090, 908, 761, 669; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.6 Hz, Me), 1.25 (3H, t, J = 6.9 Hz, Me), 2.29 (2H, q, J = 6.9 Hz, CH_2), 2.44 (3H, s, Me), 3.68 (4H, br s, CH_2), 4.12−4.14 (2H, m, CH_2), 5.40 (1H, t, J = 7.6 Hz, CH), 7.33 (2H, d, J = 7.6 Hz, ArH), 7.71 (2H, d, J = 8.3 Hz, ArH), two hydrogens were not observed in the ^{1}H NMR spectrum; ^{1}H NMR (600 MHz, C_5D_5N) δ 0.87 (3H, t, J = 7.8 Hz, Me), 1.12 (3H, t, J = 6.9 Hz, Me), 2.18 (3H, s, Me), 2.43 (2H, d, J = 7.4 Hz, CH_2), 3.99 (4H, br s, CH_2), 4.16 (2H, d, J = 6.9 Hz, CH_2), 4.60 (1H, s, NH), 5.42 (1H, t, J = 7.2 Hz, CH), 7.27 (2H, d, J = 7.8 Hz, ArH), 7.99 (2H, d, J = 8.2 Hz, ArH), 8.89 (1H, s, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.7 (q), 14.2 (q), 21.5 (q), 28.7 (t), 43.8 (t), 50.0 (t), 59.4 (t), 97.0 (s), 116.3 (d), 127.3 (d × 2), 129.8 (d × 2), 135.5 (s), 143.7 (s), 149.3 (s), 154.4 (s), 168.4 (s); EIMS m/z 364 (M^+), 209 (M^+ − Ts). Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.32; H, 6.64; N, 7.69. Found: C, 59.51; H, 6.84; N, 7.44.

Methyl 3-Amino-5-ethyl-2,7-dihydro-1-(*p*-toluenesulfonyl)-1*H*-azepine-4-carboxylate (4db), Entry 9 in Table 2. *N*-Cyanomethyl-*N*-(2-pentyn-1-yl)-4-methylphenylsulfonamide (**2d**; 50 mg, 0.18 mmol) was added to a dioxane (1.0 mL) suspension of methyl bromoacetate (0.14 g, 0.91 mmol) and zinc (0.12 g, 1.8 mmol, activated by 2 drops of TMSCl) at room temperature. To the resulting mixture was then added hafnium(IV) triflate (28 mg, 0.036 mmol), and the mixture was stirred for 1.3 h at 100 °C. Workup and purification by preparative TLC gave the title compound **4db** (47 mg, 74%) as a white powder: mp 129−130 °C; IR (KBr, cm^{-1}) ν 3443, 3322, 2964, 2872, 1670, 1615, 1529, 1458, 1439, 1347, 1328, 1252, 1186,

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1163, 1091, 991, 905, 812, 760, 708, 676, 620, 549; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 7.5 Hz, Me), 2.27 (2H, q, J = 7.5 Hz, CH_2), 2.44 (3H, s, Me), 3.66 (3H, s, OMe), 3.70 (4H, br s, $CH_2 \times 2$), 5.40 (1H, t, J = 7.6 Hz, olefinic H), 7.33 (2H, d, J = 8.3 Hz, ArH), 7.71 (2H, d, J = 8.3 Hz, ArH), two protons of amino group were not observed in the ^{1}H NMR spectrum; ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.7 (q), 21.5 (q), 28.7 (t), 43.7 (t), 50.0 (t), 50.7 (q), 96.6 (s), 116.4 (d), 127.3 (d × 2), 129.8 (d × 2), 135.4 (s), 143.7 (s), 149.1 (s), 154.5 (s), 168.8 (s); EIMS m/z 350 (M^+), 195 ($M^+ - Ts$). Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.26; H, 6.33; N, 7.99. Found: C, 58.11; H, 6.34; N, 7.94.

***tert*-Butyl 3-Amino-5-ethyl-2,7-dihydro-1-(*p*-toluenesulfonyl)-1*H*-azepine-4-carboxylate (4dc), Entry 10 in Table 2.** *N*-Cyanomethyl-*N*-(2-pentyn-1-yl)-*p*-toluenesulfonamide (**2d**; 0.38 g, 1.37 mmol) was added to a THF (2.0 mL) suspension of *tert*-butyl bromoacetate (1.33 g, 6.84 mmol) and zinc (0.89 g, 13.7 mmol, activated by 2 drops of TMSCl) at room temperature. The mixture was stirred for 2 h at 100 °C. Workup and purification by preparative TLC gave the title compound **4dc** (0.29 g, 53%) as a white powder: mp 169−170 °C (colorless prisms from CH_2Cl_2/*n*-hexane); IR (KBr, cm^{-1}) ν 3448, 3308, 3291, 2979, 2931, 2873, 2853, 1658, 1604, 1523, 1456, 1390, 1366, 1341, 1327, 1292, 1277, 1252, 1157, 1089, 1058, 1039, 947, 917, 848, 818, 807, 766, 848, 818, 807, 766, 708, 670, 618, 548; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.5 Hz, Me), 1.45 (9H, s, *t*-Bu), 1.54 (3H, s, Me), 2.28 (2H, q, J = 6.9 Hz, CH_2), 2.43 (2H, s, CH_2), 3.67 (2H, br d, J = 6.9 Hz, CH_2), 5.35 (1H, t, J = 7.5 Hz, CH), 7.32 (2H, d, J = 8.6 Hz, ArH), 7.70 (2H, d, J = 8.0 Hz, ArH), two hydrogens were not observed in the ^{1}H NMR spectrum; ^{1}H NMR (600 MHz, C_5D_5N) δ 0.89 (3H, t, J = 7.5 Hz, Me), 1.47 (9H, s, *tert*-Bu), 2.18 (3H, s, Me), 2.43 (2H, q, J = 7.3 Hz, CH_2), 3.99 (2H, br d, J = 5.6 Hz, CH_2), 4.13 (2H, br s, CH_2), 4.90 (1H, s, NH), 5.40 (1H, t, J = 7.5 Hz, CH), 7.24 (2H, d, J = 8.5 Hz, ArH), 7.95 (2H, d, J = 8.2 Hz, ArH), 8.73 (1H, s, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.6 (q), 21.5 (q), 28.4 (q × 3), 28.7 (t), 43.9 (t), 50.2 (t), 79.8 (s), 98.7 (s), 115.9 (d), 127.4 (d × 2), 129.7 (d × 2), 135.8 (s), 143.6 (s), 149.6 (s), 153.8 (s), 168.2 (s); EIMS m/z 392 (M^+), 237 ($M^+ - Ts$). Anal. Calcd for $C_{20}H_{28}N_2O_4S$: C, 61.20; H, 7.19; N, 7.14. Found: C, 61.06; H, 7.14; N, 7.23.

Methyl 3-Amino-2,7-dihydro-1-(*p*-toluenesulfonyl)-1*H*-azepine-4-carboxylate (4ea), Entry 11 in Table 2. *N*-Cyanomethyl-*N*-(2-propyn-1-yl)-*p*-toluenesulfonamide (**2e**; 100 mg, 0.40 mmol) was added to a THF (2.0 mL) suspension of methyl bromoacetate (0.18 mg, 1.20 mmol) and zinc (0.13 g, 2.0 mmol, activated by 2 drops of TMSCl) at room temperature. To the resulting mixture was then added hafnium(IV) triflate (32 mg, 0.04 mmol), and the mixture was stirred for 2 h at 75 °C. Workup and purification by preparative TLC gave the title compound **4ea** (49 mg, 37%) as a pale yellow powder: mp 174−176 °C; IR (KBr, cm^{-1}) ν 3392, 2924, 2854, 1670, 1616, 1540, 1440, 1335, 1259, 1160, 1092, 976, 901, 805, 757, 709, 668, 597, 583; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.40 (3H, s, Me), 3.64 (3H, s, OMe), 3.93 (2H, s, CH_2), 3.97 (2H, dd, J = 4.1 and 1.6 Hz, CH_2), 5.12 (1H, br s, NH), 5.25 (1H, dt, J = 11.7 and 4.1 Hz, olefinic H), 6.28 (1H, d, J = 11.7 Hz, olefinic H), 7.26 (2H, d, J = 8.2 Hz, ArH), 7.67 (2H, d, J = 8.3 Hz, ArH), 8.43 (1H, br s, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 48.7 (t), 50.9 (q), 51.9 (t), 94.8 (s), 118.3 (d), 127.3 (d × 2), 127.5 (d), 129.5 (d × 2), 135.8 (s), 143.5 (s), 156.8 (s), 168.9 (s); EIMS m/z 322 (M^+). Anal. Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.90; 5.63; 8.69. Found: C, 55.77; H, 5.61; N, 8.51.

***tert*-Butyl 3-Amino-2,7-dihydro-1-(*p*-toluenesulfonyl)-1*H*-azepine-4-carboxylate (4eb), Entry 12 in Table 2.** *N*-Cyanomethyl-*N*-(2-propyn-1-yl)-*p*-toluenesulfonamide (**2e**; 50 mg, 0.20 mmol) was added to a THF (1.0 mL) suspension of *tert*-butyl bromoacetate (0.19 g, 1.0 mmol) and zinc (0.13 g, 2.0 mmol, activated by 2 drops of TMSCl) at room temperature. To the resulting mixture was then added hafnium(IV) triflate (31 mg, 0.04 mmol), and the mixture was stirred for 0.5 h at 75 °C. Workup and purification by preparative TLC gave the title compound **4eb** (19 mg, 25%) as a pale yellow powder: mp 124−126 °C; IR (KBr, cm^{-1}) ν 3436, 2976, 2925, 2852, 1664, 1611, 1534, 1455, 1249, 1160, 1092, 967, 903, 849, 815, 753, 709, 668, 549; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.44 (9H, s, Me), 2.40 (3H, s, Me), 3.89 (2H, br s, CH_2), 3.95 (2H, dd, J = 1.4 and 4.1 Hz, CH_2), 5.20 (1H, dt, J = 4.2 and 12.3 Hz, olefinic H), 6.27 (1H, dt, J = 1.4 and 12.4 Hz, olefinic H), 7.26 (2H, d, J = 8.2 Hz, ArH), 7.67 (2H, d, J = 8.3 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 28.4 (q × 3), 48.6 (t), 52.0 (t), 79.5 (d), 96.5 (s), 117.6 (d), 127.3 (d × 2), 128.5 (d), 129.5 (d × 2), 135.8 (s), 143.4 (s), 156.0 (s), 168.3 (s); EIMS m/z 364 (M^+). Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.32; H, 6.64; N, 7.69. Found: C, 59.28; H, 6.46; N, 7.55.

Ethyl 3-Amino-2,7-dihydro-5-(phenylsulfanyl)-1-(*p*-toluenesulfonyl)-1*H*-azepine-4-carboxylate (4fa), Entry 13 in Table 2. *N*-Cyanomethyl-*N*-[3-(phenylsulfanyl)-2-propyn-1-yl]-*p*-toluenesulfonamide (**2f**; 50 mg, 0.14 mmol) was added to a THF (1 mL) suspension of ethyl bromoacetate (70 mg, 0.42 mmol) and zinc (46 mg, 0.70 mmol, activated by 2 drops of TMSCl) at room temperature. To the resulting mixture was then added copper(II) acetate hydrate (6 mg, 0.03 mmol), and the mixture was stirred for 7 h at 75 °C. After being cooled, the reaction mixture was poured into a mixture of aqueous solution of NH_4Cl (5 mL) and water (50 mL). The whole mixture was diluted with AcOEt, and the organic layer was separated. The aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The residue was purified by preparative TLC on silica gel with AcOEt-*n*-hexane (1/4) as eluent to give the title compound **4fa** (50 mg, 80%) as pale yellow prisms: mp 187−188 °C (from CH_2Cl_2/*n*-hexane); IR (KBr, cm^{-1}) ν 3431, 3315, 2980, 1660, 1613, 1528, 1338, 1259, 1162, 1090, 1060, 912, 754, 671, 547; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.29 (3H, t, J = 6.8 Hz, Me), 2.45 (3H, s, Me), 3.73 (4H, s, $CH_2 \times 2$), 4.13 (2H, q, J = 6.9 Hz, CH_2), 5.18 (1H, br s, NH), 5.46 (1H, t, J = 7.6 Hz, CH), 7.25 (5H, d, J = 4.9 Hz, ArH), 7.30 (2H, d, J = 8.3 Hz, ArH), 7.66 (2H, d, J = 8.3 Hz, ArH), 8.24 (1H, br s, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2 (q), 21.6 (q), 44.2 (t), 50.0 (t), 60.0 (t), 95.8 (s), 119.6 (d), 127.2 (d × 2), 127.8 (d), 128.9 (d × 2), 129.9 (d × 2), 133.4 (d × 2), 133.8 (s), 135.3 (s), 143.6 (s), 143.8 (s), 155.1 (s), 167.7 (s); EIMS m/z 444 (M^+), 371 ($M^+ - CO_2Et$), 335 ($M^+ - SPh$), 289 ($M^+ - Ts$). Anal. Calcd for $C_{22}H_{24}N_2O_4S_2$: C, 59.44; H, 5.44; N, 6.30. Found: C, 59.39; H, 5.36; N, 6.08.

***tert*-Butyl 3-Amino-5-(phenylsulfanyl)-1-(*p*-toluenesulfonyl)-2,7-dihydro-1*H*-azepine-4-carboxylate (4fb), Entry 14 in Table 2.** *N*-Cyanomethyl-*N*-[3-(phenylsulfanyl)-2-propyn-1-yl]-*p*-toluenesulfonamide (**2f**; 50 mg, 0.14 mmol) was added to a dioxane (1 mL) suspension of *tert*-butyl bromoacetate (137 mg, 0.70 mmol) and zinc (46 mg, 0.70 mmol, activated by 2 drops of TMSCl) at room temperature. To the resulting mixture was then added hafnium triflate (22 mg, 0.03 mmol), and the mixture was stirred for 2.5 h at 100 °C. After being cooled, the reaction mixture was poured into a mixture of aqueous solution of NH_4Cl (5 mL) and water (50 mL). The whole mixture was diluted with AcOEt, and the organic layer was separated. The aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The residue was purified by preparative TLC on silica gel with AcOEt/*n*-hexane (1/4) as eluent to give the compound **4fb** (44 mg, 66%) as a white powder: mp 168−169 °C; IR (KBr, cm^{-1}) ν 3435, 3309, 2978, 2926, 1663, 1611, 1528, 1477, 1457, 1338, 1288, 1252, 1162, 1091, 1063, 911, 816, 785, 671, 549; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.48 (9H, s, Me × 3), 2.44 (3H, s, Me), 3.66 (2H, br s, CH_2), 3.71 (2H, br s, CH_2), 5.36 (1H, t, J = 7.5 Hz, CH), 7.25−7.26 (5H, m, ArH), 7.29 (2H, d, J = 8.3 Hz, ArH), 7.65 (2H, d, J = 8.2 Hz, ArH), two hydrogens were not observed in the ^{1}H NMR spectrum; ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 28.4 (q × 3), 37.9 (t), 50.0 (t), 73.5 (s), 78.9 (s), 87.3 (d), 91.0 (s), 126.2 (d × 2), 126.7 (d), 127.6 (d × 2), 129.2 (d × 2), 129.7 (d × 2), 131.7 (s), 134.9 (s), 144.2 (s), 154.2 (s), 169.4 (s); EIMS m/z 472 (M^+), 317 ($M^+ - Ts$). Anal. Calcd for $C_{24}H_{28}N_2O_4S_2$: C, 60.99; H, 5.97; N, 5.93. Found: C, 60.67; H, 6.01; N, 6.13.

Methyl 3-Amino-5-(phenylsulfanyl)-1-(*p*-toluenesulfonyl)-2,7-dihydro-1*H*-azepine-4-carboxylate (4fc), Entry 15 in Table 2. *N*-Cyanomethyl-*N*-[3-(phenylsulfanyl)-2-propynyl]-*p*-toluenesulfonamide (**2f**; 50 mg, 0.14 mmol) was added to a THF (1 mL) suspension of methyl bromoacetate (64 mg, 0.42 mmol) and zinc (46 mg, 0.70 mmol, activated by 2 drops of TMSCl) at room temperature. To the resulting mixture was then added hafnium(IV) triflate (11 mg,

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0.014 mmol), and the mixture was stirred for 3.5 h at 75 °C. Workup and purification by preparative TLC gave the title compound **4fc** (21 mg, 32%) as colorless plates: mp 172−173 °C; IR (KBr, cm^{-1}) ν 3433, 3318, 2948, 2925, 1671, 1615, 1530, 1440, 1338, 1263, 1163, 1091, 902, 756, 673, 548; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.45 (3H, s, Me), 3.67 (3H, s, Me), 3.74 (4H, s, CH_2), 5.26 (1H, br s, NH), 5.48 (1H, t, J = 7.5 Hz, CH), 7.25 (5H, br s, ArH), 7.30 (2H, d, J = 8.2 Hz, ArH), 7.67 (2H, d, J = 8.2 Hz, ArH), 8.18 (1H, br s, NH); ^{1}H NMR (600 MHz, C_5D_5N) δ 2.22 (3H, s, Me), 3.69 (3H, s, Me), 4.04 (2H, s, CH_2), 4.23 (1H, s, NH), 4.93 (2H, s, CH_2), 5.66 (1H, t, J = 7.6 Hz, CH), 7.23 (2H, d, J = 8.3 Hz, ArH), 7.26−7.29 (3H, m, ArH), 7.46 (2H, dd, J = 1.4 and 8.2 Hz, ArH), 7.91 (2H, d, J = 8.2 Hz, ArH), 9.00 (1H, s, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 44.2 (t), 50.0 (t), 51.0 (q), 95.6 (s), 119.2 (d), 127.3 (d × 2), 128.0 (d), 128.9 (d × 2), 129.9 (d × 2), 133.4 (s), 133.7 (d × 2), 135.3 (s), 143.5 (s), 143.9 (s), 155.2 (s), 168.0 (s); EIMS m/z 430 (M^+), 275 (M^+ − Ts). Anal. Calcd for $C_{21}H_{22}N_2O_4S_2$: C, 58.59; H, 5.15; N, 6.51. Found: C, 58.28; H, 5.20; N, 6.39.

3-Amino-4-benzoyl-5-(phenylsulfanyl)-1-(*p*-toluenesulfonyl)-2,7-dihydro-1*H*-azepine (4fd), Entry 16 in Table 2. *N*-Cyanomethyl-*N*-[3-(phenylsulfanyl)prop-2-ynyl]-*p*-toluenesulfonamide (**2f**; 50 mg, 0.14 mmol) was added to a THF (1 mL) suspension of phenacyl bromide (0.14 g, 0.70 mmol) and zinc (92 mg, 1.4 mmol, activated by 2 drops of TMSCl) at room temperature. To the resulting mixture was then added copper(II) acetate (6 mg, 0.028 mmol), and the mixture was stirred for 19 h at 100 °C. Workup and purification by preparative TLC gave the title compound **4fd** (40 mg, 60%) as a white powder: mp 165−166 °C; IR (KBr, cm^{-1}) ν 3399, 3186, 3059, 2922, 2867, 1599, 1475, 1338, 1275, 1162, 1092, 1051, 1026, 973, 921, 875, 815, 750, 689, 666, 631, 614, 574, 548; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (3H, s, Me), 3.89 (4H, br s, CH_2 × 2), 5.28 (1H, t, J = 7.5 Hz, olefiic H), 6.91 (2H, d, J = 6.9 Hz, ArH), 7.20−7.22 (2H, m, ArH), 7.24−7.27 (1H, m, ArH), 7.29 (2H, d, J = 8.2 Hz, ArH), 7.33−7.37 (2H, m, ArH), 7.44−7.48 (3H, m, ArH), 7.70 (2H, d, J = 8.2 Hz, ArH), two hydrogens were not observed in the ^{1}H NMR spectrum; ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 44.6 (t), 50.4 (t), 104.0 (s), 115.8 (d), 127.3 (d × 2), 127.4 (d × 2), 127.8 (d × 2), 128.5 (d), 129.0 (d × 2), 129.9 (d × 2), 130.6 (d), 131.8 (s), 134.1 (d × 2), 135.1 (s), 141.7 (s), 143.9 (s), 146.5 (s), 157.8 (s), 193.7 (s); EIMS m/z 476 (M^+), 321 (M^+ − Ts). Anal. Calcd for $C_{26}H_{24}N_2O_3S_2$: C, 65.52; H, 5.08; N, 5.88. Found: C, 65.42; H, 4.97; N, 5.71.

Preparation of Ethyl 3-Amino-4-[3-(phenyl)-*N*-(*p*-toluensulonyl)prop-2-ynylamino]but-2-enoate (3aa). Typical Procedure. *N*-Cyanomethyl-*N*-(3-phenyl-2-propyn-1-yl)-*p*-toluenesulfonamide (**4**; 0.37 g, 1.14 mmol) in THF (1.0 mL) was added to a Reformatsky reagent (prepared from zinc (0.37 g, 5.70 mmol) and ethyl bromoacetate (0.57 g, 3.42 mmol) in THF (6.0 mL)). The reaction mixture was refluxed for 10 min. The cooled mixture was poured into water (50 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was crystallized from *n*-hexane to give the title compound (0.55 g, quantitative) as a white powder.

Formation of Ethyl 3-Oxo-4-[*N*-(3-phenylprop-2-yn-1-yl)-*N*-(*p*-toluenesulfonyl)amino]butanoate (6aa). Hafnium(IV) triflate (24.8 mg, 0.032 mmol) was added to a dioxane (1.0 mL) solution of ethyl 3-amino-4-[3-(phenyl)-*N*-(*p*-toluensulonyl)prop-2-ynylamino]-but-2-enoate (**3aa**; 50 mg, 0.16 mmol). The reaction mixture was refluxed for 3 h. The cooled reaction mixture was poured into water (50 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel with EtOAc/*n*-hexane (1/3) as eluent to the title compound **6aa** (19 mg, 29%) as a white powder. The compound **6aa** was synthesized by another route by hydrolysis with a catalytic amount of *p*-toluenesulfonic acid in 66% yield: IR (KBr, cm^{-1}) 3440, 2981, 2925, 2594, 2243, 1748, 1727, 1599, 1491, 1443, 1405, 1351, 1257, 1164, 1092, 1068, 1029, 927, 816, 759, 717, 693, 663, 586, 546; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.6 Hz, Me), 2.36 (3H, s, Me), 3.69 (2H, s, CH_2), 4.13 (2H, s, CH_2), 4.17 (2H, q, J = 7.5 Hz, CH_2), 4.38 (2H, s, CH_2), 7.11 (2H, d, J = 6.8 Hz, ArH), 7.23−7.26 (3H, m, ArH), 7.29 (2H, d, J = 8.3 Hz, ArH), 7.75 (2H, d, J = 8.3 Hz, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (q), 21.4 (q), 39.4 (t), 46.2 (t), 55.7 (t), 61.6 (t), 81.0 (s), 86.4 (s), 121.7 (s), 127.8 (d × 2), 128.1 (d × 2), 128.6 (d), 129.7 (d × 2), 131.5 (d × 2), 134.8 (s), 144.2 (s), 166.9 (s), 198.6 (s). The molecular ion peak was not observed in either the EI or TOF mass spectrum. Anal. Calcd for $C_{22}H_{23}NO_5S$: C, 63.91; H, 5.61; N, 3.39. Found: C, 64.09; H, 5.84; N, 3.37.

Synthesis of (*Z*)-Ethyl 3-Amino-3-[2,5-dihydro-1-(*p*-toluenesulfonyl)-3-phenyl-1*H*-pyrrol-2-yl]prop-2-enoate (5aa). Typical Procedure. Copper acetate (0.16 g, 0.82 mmol) was added to a dioxane (2.8 mL) solution of ethyl 3-amino-4-[3-(phenyl)-*N*-(*p*-toluensulonyl)-prop-2-ynylamino]but-2-enoate (**3aa**; 283 mg, 0.69 mmol). The cooled reaction mixture was poured into water (50 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel with EtOAc/*n*-hexane (1/3) as eluent to give the title compound **5aa** (225 mg, 80%) as a white powder: mp 64−65 °C; IR (KBr, cm^{-1}) 3457, 3332, 2980, 2925, 2869, 2869, 2361, 1669, 1625, 1561, 1496, 1446, 1342, 1164, 1094, 815, 792, 757, 671, 596, 550; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (3H, t, J = 7.5 Hz, Me), 2.39 (3H, s, Me), 4.05 (2H, dq, J = 7.6 and 1.3 Hz, CH), 4.27 (1H, dd, J = 4.8 and 15.8 Hz, CH), 4.38 (1H, dd, J = 4.8 and 15.8 Hz, CH), 4.66 (1H, s, olefinic H), 5.27 (1H, d, J = 4.8 Hz, 2-H), 6.16 (1H, br s, olefinic H), 7.26−7.30 (7H, m, ArH), 7.73 (2H, d, J = 8.2 Hz, ArH), two hydrogens were not observed in the ^{1}H NMR spectrum; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4 (q), 21.5 (q), 55.1 (t), 58.9 (t), 69.5 (d), 86.2 (d), 122.4 (d), 126.1 (d × 2), 127.3 (d × 2), 128.6 (d × 3), 129.7 (d × 2), 131.9 (s), 134.7 (s), 138.8 (s), 143.9 (s), 158.4 (s), 169.8 (s); EIMS m/z 412 (M^+), 367 (M^+ − EtO), 298 (M^+ − $H_2NC{=}CHCO_2Et$), 257 (M^+ − Ts); high-resolution mass calcd for $C_{22}H_{24}N_2O_4S$ 412.1457, found m/z 412.1456.

Hafnium-Catalyzed Reformatsky Reaction of 3aa with Ethyl Bromoacetate/Zinc. *N*-Cyanomethyl-*N*-(3-phenyl-2-propyn-1-yl)-*p*-toluensulonamide (**3aa**; 50 mg, 0.16 mmol) was added to a dioxane (1 mL) suspension of ethyl bromoacetate (0.134 g, 0.80 mmol) and zinc (0.10 g, 1.60 mmol, activated by 2 drops of TMSCl) at room temperature. To the resulting mixture was then added hafnium(IV) triflate (24.8 mg, 0.032 mmol), and the mixture was stirred for 9 h at 100 °C. Workup and purification by preparative TLC on silica gel gave the title compound **4aa** (56 mg, 85%) as a white powder.

Synthesis of 2,5-Dihydropyrroles from Alkyl 3-Aminoprop-2-ynylbutenoates (Table 3). *Preparation of Ethyl-3-Amino-4-[N-(pent-2-ynyl)-N-(p-toluenesulfonyl)amino]but-2-enoate (3da).* *N*-Cyanomethyl-*N*-[3-(*p*-chlorophenyl)-2-propyn-1-yl]-*p*-toluenesulfonamide (0.50 g, 1.81 mmol) in THF (1.0 mL) was added to a Reformatsky reagent (prepared from zinc (0.59 g, 9.05 mmol) and ethyl bromoacetate (0.91 g, 5.42 mmol) in THF (10.0 mL)). The reaction mixture was refluxed for 10 min and then poured into water (50 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was crystallized from *n*-hexane. The almost pure compound **3da** (0.76 g, quantitative) was obtained as a white powder: IR (KBr, cm^{-1}) ν 3465, 3340, 2979, 2936, 1672, 1624, 1567, 1444, 1351, 1285, 1163, 1092, 903, 815, 791, 763, 661, 576, 549, 405; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.6 Hz, CH_3), 1.26 (3H, t, J = 6.9 Hz, CH_3), 1.93 (2H, t, J = 2.0 and 7.5 Hz, CH_2), 2.43 (3H, s, Me), 3.76 (2H, s, CH_2), 4.08 (2H, br s, CH_2), 4.12 (2H, q, J = 6.9 Hz, CH_2), 4.57 (1H, s, olefinic H), 5.39 (1H, br s, NH), 7.32 (2H, d, J = 7.6 Hz, ArH), 7.75 (2H, d, J = 8.3 Hz, ArH), one hydrogen of amino group was not observed in the ^{1}H NMR spectrum; ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.0 (t), 13.3 (q), 14.4 (q), 21.5 (q), 37.2 (t), 49.7 (t), 58.8 (t), 71.1 (s), 85.0 (d), 88.3 (s), 127.8 (d × 2), 129.5 (d × 2), 135.5 (s), 143.9 (s), 155.7 (s), 169.5 (s); EIMS m/z 364 (M^+), 209 (M^+ − Ts). Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.32; H, 6.64; N, 7.69. Found: C, 59.38; H, 6.70; N, 7.50.

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***tert*-Butyl 3-Amino-4-[*N*-(pent-2-ynyl)-*N*-(*p*-toluenesulfonyl)-amino]but-2-enoate (3dc).** *N*-Cyanomethyl-*N*-[3-(*p*-chlorophenyl)-2-propyn-1-yl]-*p*-toluensulonamide (**2d**; 0.40 g, 1.45 mmol) was added to a dioxane (3.0 mL) suspension of *tert*-butyl bromoacetate (0.85 g, 4.34 mmol) and zinc (0.47 g, 7.25 mmol, activated by 2 drops of TMSCl) at room temperature, and the mixture was stirred for 10 min at 100 °C. Workup and purification by column chromatography gave the title compound **3dc** (0.60 g, quantitative) as a white powder: mp 61−65 °C (from CH_2Cl_2/*n*-hexane); FT-IR (KBr, cm^{-1}) 3468, 3340, 2978, 2926, 1712, 1669, 1625, 1561, 1362, 1351, 1291, 1254, 1162, 1150, 1093, 903, 798, 666, 659, 580, 573, 546; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.6 Hz, Me), 1.47 (9H, s, Me × 3), 1.91−1.93 (2H, m, CH_2), 2.43 (3H, s, Me), 3.73 (2H, s, CH_2), 4.08 (2H, s, CH_2), 4.50 (1H, s, olefinic H), 5.21 (1H, br s, NH), 7.31 (2H, d, J = 8.2 Hz, ArH), 7.75 (2H, d, J = 8.2 Hz, ArH), one proton of the amino group was not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.0 (t), 13.3 (q), 21.5 (q), 28.4 (q × 3), 37.2 (t), 49.7 (t), 71.2 (s), 78.7 (s), 86.8 (d), 88.1 (s), 127.8 (d × 2), 129.4 (d × 2), 135.5 (s), 143.8 (s), 154.8 (s), 169.4 (s); EIMS m/z 335 (M^+ − t-Bu), 319 (M^+ − t-BuO). Anal. Calcd for $C_{20}H_{28}N_2O_4S$: C, 61.20; H, 7.19; N, 7.14. Found: C, 60.87; H, 7.37; N, 7.10.

Ethyl 3-Amino-4-[*N*-(prop-2-ynyl)-*N*-(*p*-toluenesulfonyl)-amino]but-2-enoate (3ea). *N*-Cyanomethyl-*N*-(2-propyn-1-yl)-*p*-toluensulonamide (0.25 g, 1.00 mmol) in THF (1.0 mL) was added to a Reformatsky reagent (prepared from zinc (0.33 g, 5.00 mmol) and methyl bromoacetate in THF (3.0 mL)). The reaction mixture was heated to 50 °C. The workup procedure gave the title compound **3ea** (0.29 g, 86%) as a white powder: IR (KBr, cm^{-1}) ν 3487, 3462, 3347, 3288, 3277, 2982, 1666, 1622, 1598, 1561, 1444, 1348, 1280, 1157, 1119, 1092, 1069, 1037, 925, 902, 802, 765, 659, 579, 551, 535; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 6.8 Hz, CH_3), 2.05 (2H, m, CH_2), 2.30 (1H, t, J = 2.0 Hz, CH), 2.44 (3H, s, Me), 3.78 (2H, br s, CH_2), 4.12 (2H, q, J = 7.5 Hz, CH_2), 4.59 (1H, s, CH), 7.32 (2H, d, J = 8.2 Hz, ArH), 7.75 (2H, d, J = 7.2 Hz, ArH), two hydrogens were not observed in the ^{1}H NMR spectrum; ^{13}C NMR δ 14.1 (q), 21.5 (q), 36.4 (t), 49.7 (t), 58.9 (t), 74.5 (s), 85.4 (d), 127.7 (d × 2), 129.7 (d × 2), 130.1 (d), 135.3 (s), 144.2 (s), 155.1 (s), 169.5 (s); EIMS m/z 336 (M^+), 181 (M^+ − Ts). Anal. Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.13; H, 5.99; N, 8.33. Found: C, 56.88; H, 6.23; N, 8.32.

***tert*-Butyl 3-Amino-4-[*N*-(prop-2-ynyl)-*N*-(*p*-toluenesulfonyl)amino]but-2-enoate (3eb).** *N*-Cyanomethyl-*N*-(2-propyn-1-yl)-4-methylphenylsulfonamide (**2eb**; 0.40 g, 1.45 mmol) was added to a dioxane (3.0 mL) suspension of *tert*-butyl bromoacetate (0.85 g, 4.34 mmol) and zinc (0.47 g, 7.25 mmol, activated by 2 drops of TMSCl) at room temperature, and the mixture was stirred for 10 min at 100 °C. Workup and purification by column chromatography gave the title compound **3eb** (0.60 g, 99%) as a white powder: mp 108−110 °C; IR (KBr, cm^{-1}) ν 3466, 3339, 3287, 2975, 2925, 2854, 2360, 1668, 1624, 1563, 1364, 1349, 1333, 1291, 1254, 1162, 1093, 899, 815, 801, 761, 665, 580, 552; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (9H, s, Me × 3), 2.05 (1H, t, J = 2.7 Hz, acetylenic H), 2.44 (3H, s, Me), 3.74 (2H, s, CH_2), 4.13 (2H, d, J = 2.8 Hz, CH_2), 4.51 (1H, s, olefinic H), 7.31 (2H, d, J = 8.3 Hz, ArH), 7.74 (2H, d, J = 8.2 Hz, ArH), two protons of the amino group were not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 28.4 (q × 3), 36.4 (t), 49.7 (t), 74.4. (s), 75.9 (d), 78.8 (s), 87.2 (d), 127.7 (d × 2), 129.6 (d × 2), 135.3 (s), 144.1 (s), 154.2 (s), 169.4 (s); EIMS m/z 364 (M^+), 209 (M^+ − Ts). Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.32; H, 6.64; N, 7.69. Found: C, 58.94; H, 6.75; N, 7.53.

Preparation of Ethyl 3-Amino-4-[3-(phenylsulfanyl)-*N*-(*p*-toluenesulfonyl)prop-2-ynyl]but-2-enoate (3fa). Zinc (91 mg, 1.40 mmol) was first activated by addition of 2 drops of trimethylsilyl chloride (TMSCl) in THF (1.5 mL). To the resulting mixture were successively added ethyl bromoacetate (0.12 g, 0.70 mmol) and *N*-3-(phenylsulfanyl)-2-propyn-1-yl-*N*-(*p*-toluenesulfonyl)acetonitrile (**1**; 50 mg, 0.14 mmol), and the mixture was stirred for 10 min at 75 °C. After being cooled, the reaction mixture was poured into a mixture of saturated aqueous solution of NH_4Cl (5 mL) and water (50 mL). The whole mixture was diluted with AcOEt, and the organic layer was separated. The aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel with AcOEt/*n*-hexane (1/5) to give the title compound **3fa** (48 mg, 77%) as a yellow oil: IR (KBr, cm^{-1}) ν 3466, 3339, 2987, 2926, 2185, 1671, 1622, 1566, 1479, 1441, 1349, 1285, 1162, 1092, 1039, 900, 741, 668, 560, 549; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.27 (3H, t, J = 7.0 Hz, Me), 2.34 (3H, s, Me), 3.80 (2H, s, CH_2), 4.13 (2H, q, J = 7.2 Hz, CH_2O), 4.36 (2H, s, CH_2), 4.60 (1H, s, CH), 5.35 (1H, br s, NH_2), 7.20−7.26 (5H, m, ArH), 7.33 (2H, t, J = 7.6 Hz, ArH), 7.71 (2H, d, J = 9.2 Hz, ArH), 7.73 (1H, br s, NH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5 (q), 21.5 (q), 38.0 (t), 50.0 (t), 59.0 (t), 73.6 (s), 85.6 (d), 90.8 (s), 126.2 (d × 2), 126.8 (d), 127.6 (d × 2), 129.2 (d × 2), 129.7 (d × 2), 131.7 (s), 134.9 (s), 144.3 (s), 155.0 (s), 169.5 (s); EIMS m/z 444 (M^+), 335 (M^+ − SPh), 289 (M^+ − Ts). Anal. Calcd for $C_{22}H_{24}N_2O_4S_2$: C, 59.44; H, 5.44; N, 6.30. Found: C, 59.05; H, 5.44; N, 5.87.

Preparation of *tert*-Butyl 3-Amino-4-[3-(phenylsulfanyl)-*N*-(*p*-toluenesulfonylprop-2-ynyl)amino]but-2-enoate (3fb). According to the method used for the preparation of **3fa**, the reaction mixture of *N*-cyanomethyl-*N*-[3-(phenylsulfanyl)-2-propyn-1-yl]-*p*-toluenesulfonamide (**1**, 0.40 g, 1.12 mmol) with a Reformatsky reagent (prepared from zinc (0.73 g, 11.2 mmol) and *tert*-butyl bromoacetate (1.07 g, 5.6 mmol) in 1,4-dioxane (3.0 mL)) was stirred for 1 h at 100 °C. The workup procedure and purification by preparative TLC on silica gel with AcOEt/*n*-hexane (1/4) gave *tert*-butyl 3-amino-2,7-dihydro-5-(phenyl sulfanyl)-1-(*p*-toluenesulfonyl)-1*H*-azepine-4-carboxylate (**4fb**; 74 mg, 15%) and *tert*-butyl 3-amino-4-[3-(phenylsulfanyl)-*N*-(*p*-toluenesulfonylprop-2-ynylamino)but-2-enoate (**3fb**; 0.35 g, 66%).

Data for **3fb** are as follows: pale yellow prisms; mp 187−188 °C; IR (KBr, cm^{-1}) ν 3471, 3338, 2975, 2925, 1669, 1622, 1559, 1363, 1349, 1291, 1161, 1092, 899, 742, 667, 560, 549; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.48 (9H, s, Me × 3), 2.33 (3H, s, Me), 3.76 (2H, s, CH_2), 4.36 (2H, s, CH_2), 4.52 (1H, s, CH), 5.25 (1H, br s, NH), 7.19 (2H, d, J = 8.2 Hz, ArH), 7.22−7.26 (3H, m, ArH), 7.32−7.33 (2H, m, ArH), 7.71 (2H, d, J = 8.2 Hz, ArH), 2H due to the amino group were not observed in the ^{1}H NMR spectrum; ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 28.5 (q × 3), 37.9 (t), 50.1 (t), 73.5 (s), 78.9 (s), 87.4 (d), 91.0 (s), 126.2 (d × 2), 126.8 (d), 127.6 (d × 2), 129.2 (d × 2), 129.7 (d × 2), 131.7 (s), 135.0 (s), 144.2 (s), 154.2 (s), 169.4 (s); EIMS m/z 472 (M^+), 371 (M^+ − CO_2t-Bu), 317 (M^+ − Ts). Anal. Calcd for $C_{24}H_{28}N_2O_4S_2$: C, 60.99; H, 5.97; N, 5.93. Found: C, 60.84; H, 6.01; N, 5.71.

Preparation of Methyl 3-Amino-4-[3-(phenylsulfanyl)-*N*-(*p*-toluenesulfonylprop-2-ynyl)amino]but-2-enoate (3fc). According to the method used for the preparation of **3fa**, the reaction of *N*-cyanomethyl-*N*-[3-(phenylsulfanyl)-2-propyn-1-yl]-*p*-toluenesulfonamide (**2fc**; 50 mg, 0.14 mmol) with a Reformatsky reagent (prepared from zinc (46 mg, 0.70 mmol) and methyl bromoacetate (0.11 g, 0.70 mmol) in 1,4-dioxane (1.5 mL)) was stirred for 10 min at 75 °C. The workup procedure and purification by preparative TLC on silica gel with AcOEt/*n*-hexane (1/4) as eluent gave methyl 3-amino-4-[3-(phenylsulfanyl)-*N*-(*p*-toluenesulfonyl)prop-2-ynylamino]but-2-enoate (**3fc**; 44 mg, 73%) as a yellow oil: IR (KBr, cm^{-1}) ν 3466, 3339, 2947, 2186, 1740, 1674, 1622, 1566, 1479, 1441, 1349, 1287, 1161, 1091, 1024, 921, 889, 791, 741, 668, 561; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.34 (3H, s, Me), 3.67 (3H, s, Me), 3.80 (2H, s, CH_2), 4.36 (2H, s, CH_2), 4.61 (1H, s, CH), 5.32 (1H, br s, NH), 7.20−7.27 (5H, m, ArH), 7.33 (2H, t, J = 7.6 Hz, ArH), 7.71 (2H, d, J = 8.2 Hz, ArH), 7.73 (1H, br s, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 38.0 (t), 50.0 (t), 50.4 (q), 73.7 (s), 85.1 (d), 90.8 (s), 126.2 (d × 2), 126.8 (d), 127.6 (d × 2), 129.2 (d × 2), 129.7 (d × 2), 131.7 (s), 134.9 (s), 144.3 (s), 153.2 (s), 169.8 (s); EIMS m/z 430 (M^+), 321 (M^+ − SPh), 275 (M^+ − Ts); high-resolution mass (EI) calcd for $C_{21}H_{22}N_2O_4S_2$ 430.1021, found m/z 430.1008.

***tert*-Butyl (*Z*)-3-Amino-3-[2,5-dihydro-3-phenyl-1-(4-methylphenylsulfonyl)-1*H*-pyrrol-2-yl]prop-2-enoate (5ac), Entry 2 in Table 3.** To a dioxane (1.0 mL) solution of *tert*-butyl 3-amino-4-[*N*-(3-phenylprop-2-yn-1-yl)-*N*-(*p*-toluenesulfonyl)amino]but-2-enoate (**3ac**; 0.22 g, 0.50 mmol) was added copper acetate (0.12 g, 0.60 mmol).

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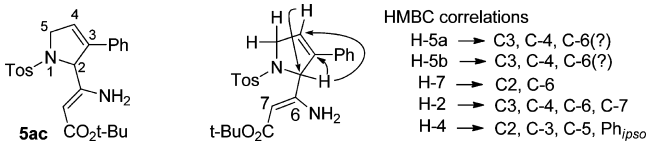
The reaction mixture was stirred for 2.5 h at 100 °C. Workup and purification by preparative TLC gave the title compound **5ac** (0.17 g, 77%) as an orange oil: IR (KBr, cm^{-1}) ν 3456, 3331, 2978, 2926, 2856, 1667, 1624, 1559, 1496, 1448, 1392, 1341, 1278, 1252, 1163, 1093, 1039, 852, 814, 795, 670, 597, 550; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.42 (9H, s, Me × 3), 2.38 (3H, s, Me), 4.27 (1H, dd, J = 2.7 and 15.8 Hz, CH), 4.40 (1H, d, J = 15.8 Hz, CH), 4.62 (1H, s, olefinic H), 5.26 (1H, d, J = 4.9 Hz, 2-H), 6.17 (1H, s, olefinic H), 7.25−7.34 (7H, m, ArH), 7.72 (2H, d, J = 8.3 Hz, ArH), two protons of the amino group were not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 28.5 (q × 3), 55.0 (t), 69.6 (d), 78.7 (s), 88.3 (s), 122.3 (d), 126.1 (d × 2), 127.3 (d × 2), 128.6 (d × 2), 129.7 (d × 2), 131.9 (s), 135.1 (s), 138.9 (s), 143.7 (s), 157.2 (s), 169.7 (s); EIMS m/z 440 (M^+), 367 (M^+ − t-BuO), 285 (M^+ − Ts); high-resolution mass (EI) calcd for $C_{24}H_{28}N_2O_4S$ 440.1769, found m/z 440.1729.

Peak Assignment of ***5ac:***



^{1}H NMR (800 MHz, $CDCl_3$) δ 1.43 (9H, s, Me × 3), 2.38 (3H, s, Me), 4.27 (1H, ddd, J = 1.6, 4.8, and 15.2 Hz, H-5a), 4.41 (1H, ddd, J = 1.6, 2.4, and 15.2 Hz, H-5b), 4.62 (1H, s, C = $CHCO_2{}^t$Bu), 5.26 (1H, ddd, J = 1.6, 1.6, 4.8 Hz, H-2), 6.17 (1H, ddd, J = 1.6, 1.6, 2.4 Hz, H-4), 7.25 (2H, d-like J = *ca.* 8.0 Hz, tosyl-H), 7.29−7.32 (5H, m, 7.72 phenyl-H), 7.73 (2H, d-like, J = ca,. 8.0 Hz, tosyl-H), two protons of the amino group were not observed; ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.5 ($CH_3C_6H_4SO_2$), 28.5 [$CO_2C(CH_3)_3$], 55.0 (C-5), 69.7 (C-2), 78.7 [$CO_2C(CH_3)_3$], 88.3 [$C(NH_2)$ = $CHCO_2{}^t$Bu], 122.4 (C-4), 126.1/128.58/128.63 (d, phenyl-C), 127.3/129.7 (d, tosyl-C), 131.9 (phenyl-C_{ipso}), 135.1/143.7 (tosyl-C_{ipso}), 138.9 (C-3), 157.2 [$C(NH_2)$ = $CHCO_2{}^t$Bu], 169.7 [$CO_2C(CH_3)_3$].

Preparation of *tert*-Butyl (*Z*)-3-Amino-4-[3-(*p*-methoxyphenyl)-*N*-(*p*-toluene-sulfonylprop-2-ynylamino)but-2-enoate (5bc), Entry 3 in Table 3. *N*-Cyanomethyl-*N*-[3-(4-methoxyphenyl) prop-2-yn-1-yl]-*p*-toluensulonamide (**3bc**; 3 mg, 0.21 mmol) was added to a THF (2.0 mL) suspension of *tert*-butyl bromoacetate (0.172 g, 1.03 mmol) and zinc (135 mg, 2.06 mmol, activated by 2 drops of TMSCl) at room temperature, and the mixture was stirred for 40 min at 75 °C. Workup and purification by preparative TLC gave the title compound **5bc** (76 mg, 78%) as a pale yellow oil: IR (KBr, cm^{-1}) 3464, 3342, 2974, 2927, 1668, 1623, 1567, 1510, 1457, 1350, 1292, 1250, 1163, 1092, 1033, 902, 834, 799, 765, 747, 669, 580, 548; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (9H, s, Me × 3), 2.36 (3H, s, Me), 3.79 (3H, s, OMe), 3.81 (2H, s, CH_2), 4.31 (2H, s, CH), 4.55 (1H, s, olefinic H), 6.77 (2H, d, J = 9.0 Hz, ArH), 7.01 (2H, d, J = 8.2 Hz, ArH), 7.27 (2H, d, J = 8.2 Hz, ArH), 7.77 (2H, d, J = 8.2 Hz, ArH), the two hydrogens of the amino group were not observed in the ^{1}H NMR spectrum; ^{13}CNMR (150 MHz, $CDCl_3$) δ 21.4 (q), 28.4 (q × 3), 37.6 (t), 50.0 (t), 55.2 (q), 78.7 (s), 79.6 (s), 86.0 (s), 87.0 (d), 113.7 (d × 2), 113.8 (s), 127.7 (d × 2), 129.6 (d × 2), 132.9 (d × 2), 135.4 (s), 143.9 (s), 154.6 (s), 159.7 (s), 169.4 (s); EIMS m/z 470 (M^+), 413 (M^+ − t-Bu). Anal. Calcd for $C_{25}H_{30}N_2O_5S$: C, 63.81; H, 6.43; N, 5.95. Found: C, 63.63; H, 6.37; N, 5.74.

Peak Assignment of ***5bc:*** ^{1}H NMR (800 MHz, $CDCl_3$) δ 1.43 (9H, s, Me × 3), 2.38 (3H, s, Me), 3.79 (3H, s, OMe), 4.25 (1H, dd, J = 1.6, 4.8, and 15.2 Hz, H-5a), 4.38 (1H, d, J = 1.6, 2.4, and 15.2 Hz, H-5b), 4.63 (1H, s, C = $CHCO_2{}^t$Bu), 5.22 (1H, d, J = 1.6, 1.6, and 4.8 Hz, H-2), 6.04 (1H, ddd, J = 1.6, 1.6, 2.4, H-4), 6.82 (2H, d, J = 8.8 Hz, PMP-H), 7.23−7.26 (4H, m, PMP-H and tosyl-H), 7.72 (2H, d, J = 8.0 Hz, tosyl-H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.5 ($CH_3C_6H_4SO_2$), 28.5 [$CO_2C(CH_3)_3$], 55.0 (C-5), 55.3 (OCH_3), 69.7 (C-2), 78.7 [$CO_2C(CH_3)_3$], 88.3 (C-7), 114.0/127.4 (d, PMP), 120.2 (C-4), 124.6/159.8 (PMP-C_{ipso}), 127.3/129.6 (tosyl-C), 135.3/143.7 (tosyl-C_{ipso}), 138.2 (C-3), 157.4 [$C(NH_2)$ = $CHCO_2{}^t$Bu], 169.7 [$CO_2C(CH_3)_3$].

Ethyl (*Z*)-3-Amino-3-[2,5-dihydro-3-(4-methoxyphenyl)-1-(*p*-toluenesulfonyl)-1*H*-pyrrol-2-yl]-2-propenoate (5da), Entry 4 in Table 3. Copper acetate (99 mg, 0.49 mmol) was added to a dioxane (1.5 mL) solution of ethyl 3-amino-4-[*N*-(*p*-toluenesulfonyl)-pent-2-ynylamino]but-2-enoate (**3da**; 150 mg, 0.41 mmol). The reaction mixture was heated at 100 °C and then poured into water (50 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel with AcOEt/*n*-hexane (1/5) as eluent to give the title compound **5da** (93 mg, 62%) as a yellow powder: IR (KBr, cm^{-1}) ν 3336, 2976, 1670, 1625, 1560, 1457, 1348, 1280, 1164, 1095, 1040, 856, 817, 791, 709, 671, 585, 549; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.5 Hz, Me), 1.28 (3H, t, J = 7.3 Hz, Me), 1.81−1.85 (1H, m, CH), 1.96−2.00 (1H, m, CH), 2.43 (3H, s, Me), 4.08−4.22 (4H, m, CH_2), 4.51 (1H, br s, olefinic H), 4.64 (1H, s, 2-H), 5.43 (1H, d, J = 1.3 Hz, olefinic H), 7.31−7.33 (2H, d, J = 8.3 Hz, ArH), 7.71−7.72 (2H, d, J = 8.2 Hz, ArH), two hydrogens due to the amino group were not observed in the ^{1}H NMR spectrum; ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3 (q), 14.5 (q), 20.8 (t), 21.5 (q), 55.2 (t), 58.9 (t), 71.6 (d), 84.9 (d), 118.7 (d), 127.6 (d × 2), 129.8 (d × 2), 133.8 (s), 142.6 (s), 144.0 (s), 159.3 (s), 169.6 (s); EIMS m/z 364 (M^+), 319 (M^+ − EtO), 250 (M^+ − $H_2NC{=}CHCO_2Et$), 209 (M^+ − Ts). high-resolution mass (EI) calcd for $C_{18}H_{24}N_2O_4S$ 364.1457, found m/z 364.1469.

***tert*-Butyl (*Z*)-3-Amino-3-[3-ethyl-2,5-dihydro-1-(*p*-toluenesulfonyl)-1*H*-pyrrol-2-yl]-2-propenoate (5dc), Entry 5 in Table 3.** To a dioxane (4.0 mL) solution of *tert*-butyl 3-amino-4-[*N*-(pent-2-yn-1-yl)-*N*-(*p*-toluenesulfonyl)amino]but-2-enoate (**3dc**; 0.37 g, 0.20 mmol) was added copper acetate (0.23 g, 1.3 mmol). The reaction mixture was stirred for 30 min at 100 °C. Workup and purification by column chromatography gave the title compound **5dc** (0.283 g, 76%) as a white powder: mp 136−137 °C; IR (KBr, cm^{-1}) ν 3457, 3335, 2977, 2928, 2876, 1667, 1625, 1558, 1457, 1393, 1365, 1352, 1287, 1252, 1164, 1094, 1056, 1016, 854, 817, 794, 671, 587, 550; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.6 Hz, Me), 1.48 (9H, s, Me × 3), 1.82−1.86 (1H, m, CH), 1.97−2.01 (1H, m, CH), 2.43 (3H, s, Me), 4.13 (1H, br d, J = 14.4 Hz, CH), 4.19 (1H, br d, J = 14.4 Hz, CH), 4.50 (1H, br s, olefinic H), 4.56 (1H, s, olefinic H), 5.42 (1H, br s, olefinic H), 7.32 (2H, d, J = 8.3 Hz, ArH), 7.71 (2H, d, J = 8.3 Hz, ArH), two hydrogens were not observed in the ^{1}H NMR spectrum; ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.4 (q), 20.8 (t), 21.5 (q), 28.6 (q × 3), 55.2 (t), 71.7 (d), 77.2 (s), 87.0 (d), 118.6 (d), 127.4 (d × 2), 129.7 (d × 2), 134.1 (s), 142.8 (s), 143.9 (s), 158.2 (s), 169.5 (s); EIMS m/z 392 (M^+). Anal. Calcd for $C_{20}H_{28}N_2O_4S$: C, 61.20; H, 7.19; N, 7.14. Found: C, 60.97; H, 7.17; N, 7.12.

Peak Assignment of ***5dc:*** ^{1}H NMR (800 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.2 Hz, CH_2CH_3), 1.80−1.87 (1H, m, $CHHCH_3$), 1.95−2.02 (1H, m, $CHHCH_3$), 2.46 (3H, s, Me), 4.14/4.18 (2H, each dm, J = 13.6 Hz, H-5a and H-5b), 4.51 (1H, br m, H-2), 4.56 (1H, s, C = $CHCO_2{}^t$Bu), 5.42 (1H, ddddd-like, J = ca. 1.6, 1.6, 1.6, 1.6, 1.6 Hz, H-4), 7.32 (2H, d, J = 8.8 Hz, tosyl-H) 7.71 (2H, d, J = 8.8 Hz, tosyl-H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.4 (CH_2CH_3), 20.9 (CH_2CH_3), 21.5 ($CH_3C_6H_4SO_2$), 28.6 [$CO_2C(CH_3)_3$], 55.2 (C-5), 71.7 (C-2), 78.7 [$CO_2C(CH_3)_3$], 87.1 [$C(NH_2){=}CHCO_2{}^t$Bu], 118.6 (C-4), 127.6/129.7 (d, tosyl-C), 134.1/143.9 (tosyl-C_{ipso}), 142.8 (C-3), 158.2 [$C(NH_2)$ = $CHCO_2{}^t$Bu], 169.5 [$CO_2C(CH_3)_3$].

(*Z*)-Ethyl 3-Amino-3-[2,5-dihydro-1-(*p*-toluenesulfonyl)-1*H*-pyrrol-2-yl]prop-2-enoate (5ea), Entry 6 in Table 3. Copper acetate (15 mg, 0.07 mmol) was added to a THF (1.0 mL) solution of ethyl 3-amino-4-[*N*-(*p*-toluensulonyl)prop-2-ynylamino]but-2-enoate (50 mg, 0.15 mmol). The reaction mixture was heated at 75 °C for 3 h. The cooled mixture was poured into water (50 mL). The workup procedure gave the title compound **5ea** (11.5 mg, 23%) as a yellow powder: mp 114−116 °C; IR (KBr, cm^{-1}) ν 3482, 3357, 3089, 2986, 2923, 2858, 2361, 1681, 1624, 1563, 1448, 1343, 1275, 1246, 1163, 1109, 1093, 1063, 1041, 849, 817, 796, 709, 673, 593, 551; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.27 (3H, t, J = 6.8 Hz, Me), 2.43 (3H, s, Me), 4.12 (2H, dq, J = 1.4 and 6.8 Hz, OCH_2), 4.19−4.23 (2H, m, CH), 4.59 (1H, s, CH), 4.83−4.85 (1H, m, olefinic H), 5.55−5.57 (1H, m, 2-H), 5.76−5.78 (1H, m, olefinic H), 7.33 (2H, d, J = 7.6 Hz, ArH), 7.72 (2H, d, J = 8.2 Hz, ArH), two hydrogens were not observed in the ^{1}H NMR spectrum; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5 (q), 21.6

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(q), 55.9 (t), 58.9 (t), 69.2 (d), 83.0 (d), 126.8 (d), 127.7 (d × 2), 128.0 (d), 129.9 (d × 2), 135.5 (s), 144.3 (s), 160.0 (s), 169.8 (s); EIMS *m*/*z* 336 (M^+), 291 (M^+ − EtO), 222 (M^+ − H_2NC═$CHCO_2Et$), 181 (M^+-Ts); high-resolution mass (EI) calcd for $C_{16}H_{20}N_2O_4S$ 336.1143, found *m*/*z* 336.1167.

***tert*-Butyl (*Z*)-3-Amino-3-[2,5-dihydro-1-(*p*-toluenesulfonyl)-1*H*-pyrrol-2-yl]prop-2-enoate (5ec), Entry 7 in Table 3.** To an ether (1.0 mL) solution of *tert*-butyl 3-amino-4-[*N*-(prop-2-yn-1-yl)-*N*-(*p*-toluenesulfonyl)amino]but-2-enoate (**3ec**; 22 mg, 0.05 mmol) was added copper acetate (8.0 mg, 0.05 mmol). The reaction mixture was stirred for 16 h at 75 °C. The workup procedure gave the title compound **5ec** (12 mg, 66%): IR (KBr, cm^{-1}) ν 3448, 2977, 2925, 1665, 1622, 1559, 1456, 1392, 1349, 1288, 1253, 1165, 1060, 849, 817, 758, 708, 668, 596, 550; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.48 (9H, s, Me × 3), 2.43 (3H, s, Me), 4.20 (2H, br s, CH_2), 4.52 (2H, s, CH), 4.81 (1H, s, CH), 5.56 (1H, br s, NH), 5.76 (1H, br s, olefinic H), 7.33 (2H, d, *J* = 8.2 Hz, ArH), 7.72 (2H, d, *J* = 8.2 Hz, ArH), one hydrogen due to the amino group was not observed in the ^{1}H NMR spectrum; ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 28.5 (q × 3), 55.9 (t), 69.3 (d), 78.7 (s), 84.9 (d), 126.7 (d), 127.7 (d × 2), 128.2 (d), 129.9 (d × 2), 133.7 (s), 144.2 (s), 159.1 (s), 169.7 (s); high-resolution mass (EI) calcd for $C_{18}H_{24}N_2O_4S$ 364.1456, found *m*/*z* 364.1448.

Methyl (*Z*)-3-Amino-3-[2,5-dihydro-3-phenylsulfanyl-1-(*p*-toluenesulfonyl)-1*H*-pyrrol-2-yl]prop-2-enoate (5fb), Entry 8 in Table 3. To a dioxane (1.0 mL) solution of methyl 3-amino-4-[*N*-(3-phenylsulfanylprop-2-yn-1-yl)-*N*-(*p*-toluenesulfonyl)amino]but-2-enoate (**3fb**; 50 mg, 0.12 mmol) was added copper acetate (1.4 mg, 0.01 mmol). The reaction mixture was stirred for 2 h at 100 °C. The workup procedure gave the title compound **5fb** (28 mg, 56%) as a pale yellow oil and **4fb** (22 mg, 44%).

Data for **5fb** are as follows: IR (KBr, cm^{-1}) ν 3445, 2924, 2854, 1671, 1624, 1560, 1456, 1282, 1189, 1168, 1092, 791, 758, 670, 599; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.47 (3H, s, Me), 3.68 (3H, s, Me), 4.20 (2H, br s, CH_2), 4.69 (2H, s, CH_2), 5.43 (1H, d, *J* = 1.4 Hz, CH), 7.26−7.32 (5H, m, ArH), 7.33 (2H, d, *J* = 8.2 Hz, ArH), 7.68 (2H, d, *J* = 8.3 Hz, ArH), two hydrogens of the amino group were not observed in the ^{1}H NMR spectrum; ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 50.4 (q), 55.5 (t), 70.4 (d), 85.2 (d), 123.4 (d), 127.7 (d × 2), 128.7 (d), 129.4 (d × 2), 129.9 (d × 2), 130.7 (s), 133.1 (d × 2), 135.6 (s), 144.3 (s), 158.0 (s), 169.9 (s); EIMS *m*/*z* 430 (M^+), 321 (M^+ − SPh), 275 (M^+ − Ts); high-resolution mass (EI) calcd for $C_{21}H_{22}N_2O_4S_2$ 430.1021, found *m*/*z* 430.1008.

***tert*-Butyl (*Z*)-3-Amino-3-[2,5-dihydro-3-phenylsulfanyl-1-(*p*-toluenesulfonyl)-1*H*-pyrrol-2-yl]prop-2-enoate (5fc), Entry 9 in Table 3.** To a THF (2.0 mL) solution of *tert*-butyl (*Z*)-3-amino-4-[*N*-(3-phenylsulfanylprop-2-yn-1-yl)-*N*-(*p*-toluenesulfonyl)amino]but-2-enoate (**3fc**; 50 mg, 0.11 mmol) was added copper triflate (4 mg, 0.01 mmol). The reaction mixture was stirred for 19 h at 75 °C. The reaction mixture was poured into water (50 mL) and diluted with AcOEt. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel with AcOEt/*n*-hexane (1/4) to give the title compound **5fc** (50 mg, quantitative) as an orange oil: IR (KBr, cm^{-1}) ν 3450, 3336, 2975, 2925, 1667, 1625, 1559, 1349, 1289, 1164, 1149, 1092, 1052, 752, 669, 598, 550, 428; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.48 (9H, s, Me × 3), 2.46 (3H, s, Me), 4.20 (2H, d, *J* = 2.7 Hz, CH_2), 4.54 (1H, s, CH), 4.62 (1H, br s, NH), 5.43 (1H, d, *J* = 2.1 Hz, CH), 7.26−7.33 (8H, m, ArH), 7.68 (2H, d, *J* = 8.3 Hz, ArH), one hydrogen due to the amino group was not observed in the ^{1}H NMR spectrum; ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 28.5 (q × 3), 55.4 (t), 70.6 (d), 78.7 (s), 87.3 (d), 123.3 (d), 127.7 (d × 2), 128.6 (d), 129.3 (d × 2), 129.8 (d × 2), 130.9 (s), 133.1 (d × 2), 133.6 (s), 135.7 (s), 144.1 (s), 156.7 (s), 169.4 (s); EIMS *m*/*z* 472 (M^+), 395 (M^+ − Ph), 317 (M^+ − Tol). Anal. Calcd for $C_{24}H_{28}N_2O_4S_2$: C, 60.99; H, 5.97, 5.93. Found: C, 60.77; H, 5.89; N, 5.83.

Synthesis of 2,5-Dihydro-1*H*-pyrrole Derivatives. *Detosylation of 2,5-Dihydro-1H-pyrroles, Scheme 2. (Z)-Ethyl 3-Amino-3-(3-phenyl-1H-pyrrol-2-yl)prop-2-enoate (**17a**).* Potassium *tert*-butoxide (63 mg, 0.56 mmol) was added to a *tert*-butyl alcohol (1.0 mL) solution of (*Z*)-ethyl 3-amino-3-[2,5-dihydro-3-phenyl-1-(*p*-toluenesulfonyl)pyrrol-2-yl]prop-2-enoate (**5aa**; 46 mg, 0.11 mmol) at room temperature. The reaction mixture was heated at 30 °C for 20 min and then poured into water (50 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel with AcOEt/*n*-hexane as eluent to give the title compound **17a** (15 mg, 52%) as a colorless oil: IR (KBr, cm^{-1}) ν 3491, 3329, 2979, 1645, 1644, 1600, 1568, 1530, 1503, 1446, 1402, 1382, 1361, 1305, 1214, 1177, 1102, 1035, 897, 790, 772, 750, 700, 620, 606; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.29 (3H, t, *J* = 7.5 Hz, CH_3), 4.15 (2H, q, *J* = 6.9 Hz, CH_2), 4.84 (1H, s, CH), 6.28 (1H, br s, NH), 6.33 (1H, t, *J* = 2.7 Hz, CH), 6.85 (1H, t, *J* = 2.7 Hz, CH), 7.28 (1H, t, *J* = 7.6 Hz, ArH), 7.37 (2H, t, *J* = 6.9 Hz, ArH), 7.46 (2H, dd, *J* = 6.8 and 1.4 Hz, ArH), 8.51 (1H, s, NH), one hydrogen of the amino group was not observed in the ^{1}H NMR spectrum; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6 (q), 58.8 (t), 81.3 (d), 112.0 (d), 119.7 (d), 123.3 (s), 125.6 (s), 126.9 (d), 128.5 (d × 2), 128.8 (d × 2), 134.9 (s), 153.0 (s), 170.5 (s); EIMS *m*/*z* 256 (M^+); high-resolution mass (EI) calcd for $C_{15}H_{16}N_2O_2$ 256.1212, found *m*/*z* 256.1185.

*(Z)-Ethyl 3-Amino-3-[2,5-dihydro-3-phenylpyrrol-2-yl]prop-2-enoate (**17b**).* Potassium *tert*-butoxide (64 mg, 0.57 mmol) was added to a *tert*-butyl alcohol (0.5 mL) solution of (*Z*)-ethyl 3-amino-3-[2,5-dihydro-3-phenyl-1-(*p*-toluenesulfonyl)pyrrol-2-yl]prop-2-enoate (**5ac**; 50 mg, 0.12 mmol) at room temperature. The reaction mixture was heated at 30 °C for 20 min, and then the workup procedure gave the compound **17b** (25 mg, 77%) as a colorless oil: IR (KBr, cm^{-1}) ν 3492, 3398, 3326, 2976, 2927, 2854, 2360, 2342, 1733, 1656, 1612, 1601, 1567, 1530, 1504, 1448, 1392, 1366, 1319, 1218, 1146, 1101, 790, 755, 700, 419; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.51 (9H, s, *t*-Bu), 4.78 (1H, s, CH), 6.09 (1H, br s, NH), 6.32 (1H, t, *J* = 2.8 Hz, CH), 6.83 (1H, t, *J* = 2.8 Hz, CH), 7.28 (1H, t, *J* = 7.6 Hz, CH), 7.37 (2H, t, *J* = 7.5 Hz, ArH), 7.47 (2H, d, *J* = 7.6 Hz, ArH), 8.45 (1H, s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.6 (q × 3), 78.6 (s), 83.1 (d), 111.9 (d), 119.3 (d), 123.6 (s), 125.2 (s), 126.8 (d), 128.5 (d × 2), 128.8 (d × 2), 135.0 (s), 152.4 (s), 170.4 (s); EIMS *m*/*z* 284 (M^+); high-resolution mass calcd for $C_{17}H_{20}N_2O_2$ 284.1525, found *m*/*z* 284.1553.

Chloroacetylation of 5aa. *(Z)-Ethyl 3-[(2-Chloroacetyl)amino]-3-[2,5-dihydro-3-phenyl-1-(p-toluenesulfonyl)pyrrol-2-yl]-propenoate (**18a**). Typical Procedure.* To a DME (0.50 mL) solution of ethyl 3-amino-3-[2,5-dihydro-3-phenyl-1-(*p*-toluenesulfonyl)pyrrol-2-yl]propenoate (**5aa**; 50 mg, 0.12 mmol) were added pyridine (48 mg, 0.61 mmol) and chloroacetyl chloride (41 mg, 0.36 mmol) at 0 °C. The reaction mixture was stirred for 10 min and poured into water (50 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel with AcOEt/*n*-hexane (1/5) as eluent to give the title compound **18a** (43 mg, 72%) as a yellow powder: mp 50−51 °C; IR (KBr, cm^{-1}) ν 2982, 2866, 1700, 1674, 1636, 1597, 1498, 1447, 1402, 1348, 1286, 1270, 1257, 1215, 1163, 1093, 1046, 918, 849, 817, 755, 696, 67, 594, 548; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t, *J* = 6.9 Hz, CH_3), 2.37 (3H, s, CH_3), 4.07−4.32 (6H, m, CH_2), 4.41 (1H, dd, *J* = 5.0 and 3.7 Hz, CH), 5.40 (1H, br s, CH), 6.04 (1H, br s, CH), 7.22−7.35 (7H, m, ArH), 7.83 (2H, d, *J* = 8.2 Hz, ArH), 11.66 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 21.5 (q), 43.4 (t), 55.3 (t), 60.6 (t), 61.9 (d), 101.1 (d), 121.6 (d), 126.6 (d × 2), 127.7 (d × 2), 128.5 (d), 128.7 (d × 2), 129.9 (d × 2), 131.7 (s), 133.6 (s), 140.8 (s), 143.9 (s), 156.3 (s), 166.3 (s), 168.5 (s); EIMS *m*/*z* 489 (small M^+), 412 (M^+ − Ph). Anal. Calcd for $C_{24}H_{25}N_2O_5SCl$: C, 58.95; H, 5.15; N, 5.73. Found: C, 58.69; H, 5.17; N, 5.32.

Chloroacetylation of 5da. To a DME (0.50 mL) solution of ethyl 3-amino-3-[2,5-dihydro-3-ethyl-1-(*p*-toluenesulfonyl)-pyrrol-2-yl]-propenoate (**5da**; 50 mg, 0.14 mmol) were added pyridine (54 mg, 0.69 mmol) and chloroacetyl chloride (46 mg, 0.41 mmol) at 0 °C. The reaction mixture was stirred for 10 min. The workup procedure gave compound **18b** (52 mg, 85%) as a brown powder: mp 153−154 °C; IR (KBr, cm^{-1}) ν 2977, 2938, 1703, 1975, 1638, 1597, 1403,

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1349, 1300, 1274, 1256, 1217, 1136, 1095, 1046, 849, 816, 708, 669, 593, 546; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.3 Hz, CH_3), 1.23 (3H, t, J = 7.3 Hz, CH_3), 1.81−1.85 (2H, m, CH_2), 2.35 (3H, s, CH_3), 4.04 (1H, br d, J = 5.0 Hz, CH), 4.07−4.18 (5H, m, CH), 5.22 (1H, d, J = 1.8 Hz, CH), 5.52 (1H, s, CH), 6.31 (1H, br s, CH), 7.26 (2H, d, J = 7.8 Hz, ArH), 7.67 (2H, d, J = 8.3 Hz, ArH), 11.84 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1 (q), 14.1 (q), 20.5 (t), 21.5 (t), 43.2 (t), 54.9 (t), 60.5 (t), 64.8 (t), 100.0 (d), 117.6 (d), 127.8 (d × 2), 129.8 (d × 2), 133.3 (s), 143.8 (s), 144.5 (s), 157.8 (s), 165.6 (s), 168.9 (s); EIMS m/z 440 (M^+), 395 (M^+ − OEt), 367 (M^+ − CO_2Et), 285 (M^+ − Ts); high-resolution mass (EI) calcd for $C_{20}H_{25}N_2O_5SCl$ 440.1111, found m/z 440.1106.

Reaction of 18a with *N*-Methylpiperazine. *N*-Methylpiperazine (30 mg, 0.06 mmol) was added to a 1,2-dichloroethane (0.50 mL) solution of (*Z*)-ethyl 3-(2-chloroacetylamino)-3-[2,5-dihydro-3-phenyl-1-(*p*-toluenesulfonyl)pyrrol-2-yl]prop-2-enoate (**18a**; 30 mg, 0.06 mmol) at room temperature. The reaction mixture was stirred for 6 h and poured into water (50 mL). The organic layer was separated, and the aqueous layer was extracted with chloroform. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel with $CHCl_3$/MeOH (20/1) as eluent to give (*Z*)- and (*E*)-ethyl 3-[2-(*N*-methylpiperazin-1-yl)acetyl]amino-3-[2,5-dihydro-3-phenyl-1-(*p*-toluenesulfonyl)pyrrol-2-yl]prop-2-enoate (**19a**; 24 mg, 70%, *Z*:*E* = 86:14) as a pale yellow powder: mp 70−71 °C; IR (KBr, cm^{-1}) ν 2925, 2851, 2798, 1698, 1682, 1625, 1495, 1462, 1350, 1295, 1285, 1252, 1229, 1207, 1165, 1139, 1095, 1050, 917, 827, 759, 737, 698, 668, 594, 551; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.25 (t, J = 6.5 Hz, *Z*-CH_3), 1.35 (t, J = 6.9 Hz, *E*-Me), 2.31 (s, *E*-Me), 2.32 (s, *Z*-CH_3), 2.39 (s, *Z*-CH_3), 2.42 (s, *E*-Me), 2.56 (br s, *Z*- and *E*-CH_2 × 2), 2.88 (d, J = 16.5 Hz, *E*-CH_2), 3.02 (d, J = 17.2 Hz, *E*-CH), 3.16 (d, J = 16.5 Hz, *Z*-CH), 3.27 (d, J = 16.5 Hz, *Z*-CH_2), 4.03−4.09 (m, *Z*-CH), 4.15−4.23 (m, *Z*- and *E*-CH_2), 4.40−4.43 (m, *Z*-CH), 5.32 (s, *Z*-CH), 5.99 (d, J = 1.4 Hz, *Z*-CH), 6.07 (br s, *E*-olefinic H), 7.23−7.27 (m, *Z*- and *E*-ArH), 7.32 (d, J = 8.3 Hz, *Z*- and *E*-ArH), 7.37 (d, J = 6.8 Hz, *Z*- and *E*-ArH), 7.53 (d, J = 5.5 Hz, *Z*- and *E*-ArH), 7.86 (d, J = 8.3 Hz, *Z*- and *E*-ArH), 9.18 (br s, *E*-NH), 11.98 (s, *Z*-NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2 (q), 21.5 (q), 46.0 (q), 53.2 (t × 2), 54.7 (t × 2), 55.7 (t), 59.9 (t), 61.9 (d), 62.5 (t), 99.6 (d), 121.1 (d), 126.8 (d × 2), 127.8 (d × 2), 128.3 (d), 128.6 (d × 2), 129.3 (d × 2), 132.0 (s), 133.5 (s), 141.4 (s), 143.7 (s), 156.5 (s), 167.7 (s), 171.2 (s); EIMS m/z 552 (M^+), 507 (t × OEt), 397 (t × Ts); high-resolution mass (EI) calcd for $C_{29}H_{36}N_4O_5S$ 552.2406, found m/z 552.2425.

Reaction of 18b with Morpholine. Morpholine (79 mg, 0.91 mmol) was added to a 1,2-dichloroethane (1.0 mL) solution of (*Z*)-ethyl 3-(2-chloroacetylamino)-3-[2,5-dihydro-3-ethyl-1-(*p*-toluenesulfonyl)pyrrol-2-yl]prop-2-enoate (**18b**; 40 mg, 0.09 mmol) at room temperature. The reaction mixture was stirred for 9 h. The work-up procedure gave the compound **19b** (22 mg, 49%) as a white powder and the *E* isomer (6 mg, 13%): mp 148−150 °C; IR (KBr, cm^{-1}) ν 2970, 2934, 2862, 2818, 1705, 1681, 1627, 1493, 1350, 1298, 1250, 123, 1200, 1164, 1116, 1095, 1050, 1016, 907, 868, 848, 817, 755, 708, 669, 595, 548; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.6 Hz, CH_3), 1.31 (3H, t, J = 6.9 Hz, CH_3), 1.86−1.93 (2H, m, CH_2), 2.42 (3H, s, CH_3), 2.50 (2H, br s, CH_2), 2.67 (2H, br s, CH_2), 3.17 (2H, ABq, J = 16.5 Hz, CH_2), 3.86 (4H, t, J = 4.8 Hz, CH_2 × 2), 3.98 (1H, d, J = 14.5 Hz, CH), 4.16−4.26 (3H, m, CH_3), 5.27 (1H, s, CH), 5.49 (1H, s, CH), 6.84 (1H, s, CH), 7.34 (2H, d, J = 8.3 Hz, ArH), 7.76 (2H, d, J = 83 Hz, ArH), 12.23 (1H, s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2 (q), 14.2 (q), 20.5 (q), 21.5 (q), 53.6 (t × 2), 54.9 (t), 60.0 (t), 62.8 (t), 64.7 (d), 66.6 (t × 2), 98.8 (d), 117.3 (d), 127.8 (d × 2), 129.7 (d × 2), 133.4 (s), 143.6 (s), 144.8 (s), 157.7 (s), 168.2 (s), 170.3 (s); EIMS m/z 491 (M^+), 446 (t × OEt), 336 (t × Ts); high-resolution mass (EI) calcd for $C_{24}H_{33}N_3O_6S$ 491.2090, found m/z 491.2086.

Data for the *E* isomer are as follows: yellow oil; IR (KBr, cm^{-1}) ν 2970, 2854, 1698, 1633, 1598, 1498, 1351, 1295, 1254, 1166, 1138, 1094, 1049, 1295, 1254, 1166, 1138, 1094, 1049, 1015, 869, 817, 759, 709, 667, 602, 567, 550; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.6 Hz, Me), 1.32 (3H, t, J = 6.9 Hz, Me), 1.84−1.91 (2H, m, CH_2), 2.44 (2H, s, Me), 2.50 (2H, br s, CH_2), 2.65 (2H, s, CH_2), 3.09 (2H, s, CH_2), 3.73 (2H, br s, CH_2), 3.82−3.85 (2H, m, CH_2), 4.03 (1H, br d, J = 14 Hz, NH), 4.18−4.21 (2H, m, CH_2), 4.39 (1H, br d, J = 11 Hz, NH), 5.40 (1H, br s, CH), 6.63 (1H, br d, CH), 7.21 (1H, s, ArH), 7.27 (1H, s, ArH), 7.37 (2H, d, J = 8.2 Hz, ArH), 7.76 (2H, d, J = 8.3 Hz, ArH), 9.57 (1H, br s, NH); EIMS m/z 491 (M^+), 446 (M^+ − OEt), 336 (M^+ − Ts).

X-ray Crystallographic Analysis. Data of azepine **4fa** and 2,5-dihydro-1*H*-pyrrole **5dc** were taken on a Rigaku RAXIS RAPID imaging plate area detector with graphite-monochromated Mo Kα radiation (λ = 0.71075 Å). The structures of **4fa** and **5dc** were solved by direct methods with SIR97. Full-matrix least-squares refinement was employed with anisotropic thermal parameters for all non-hydrogen atoms. All calculations were performed using the Crystal Structure (version 3.8, Rigaku/MSC) crystallographic software package. ORTEP drawings of compounds **4fa** and **5dc** are shown in Figures 1 and 2, respectively. The data of **4fb** and **5dc** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1016452 and CCDC 1016451, respectively.

*Crystal data for azepine **4fa**:* orthorhombic, space group *Pbca*, a = 8.07(5) Å, b = 16.28(8) Å, 32.78(16) Å, V = 4304(4) Å^3, z = 4, μ(Mo Kα) = 2.789 cm^{-1}, F(000) = 1872, D_c = 1.372 g/cm^3, crystal dimensions 0.20 × 0.25 × 0.08 mm. A total of 38784 reflections (4935 unique) were collected at a temperature of 23 °C to a maximum 2θ value of 55°. Final R and R_w values were 0.095 and 0.188, respectively. The maximum and minimum peaks in the difference map were 0.89 and −0.44 e Å^{-3}, respectively.

*Crystal data for 2,5-dihydro-1H-pyrrole derivative **5dc**:* monoclinic, space group $P2_1/c$, a = 12.94(6) Å, b = 8.30(6) Å, c = 19.86(10) Å, β = 107.49(14)°, V = 2034(2) Å^3, Z = 4, μ(Mo Kα) = 1.86 cm^{-1}, F(000) = 840, D_c = 1..282 g/cm^3, crystal dimensions 0.30 × 0.25 × 0.10 mm. A total of 19542 reflections (4643 unique) were collected were collected at a temperature of −150 °C to a maximum 2θ value of 55°. Final R and R_w values were 0.058 and 0.085, respectively. The maximum and minimum peaks in the difference map were 0.75 and −0.74 e Å^{-3}, respectively.

DFT Calculations. We performed geometry optimization calculations for all compounds (**9**, **TS-7en-Hf**, **10**, **13**, **14**, **6ex-Hf**, **TS-6ex-Hf**, **Ts-Cu-A**, **Ts-Cu-B**, **Ts-Cu-C**) by the DFT method at the B3LYP[16] level. Hay and Wadt's 18-valence-electron ECPs[17] were employed for Hf with LANL2DZ basis sets. The following basis sets were also used for the respective atoms: 6-311+G for Cu[18,19] and 6-31G(d,p)[20−22] for C, N, O, and H atoms, respectively. Frequency calculations were also preformed to confirm whether the optimized structures were energy minimum or transition state structures on the potential energy surface. The solvation effect was also included in the recalculation of **TS-7en-Hf** using the polarized continuum model (PCM) and a dielectric constant ε = 2.2099 to model the dioxane solvent environment. However, the result is almost the same as that described above. Therefore, we performed the following calculation without any solvent effects.

All electronic structure calculations were performed with the Gaussian 09, Revision D.01 package[23] on the Fujitu CX400 system at the Nagoya University Information Technology Center.

Cell Viability Assay. For testing the antitumor activities, HCT-116 human colon tumor cells, which were purchased from the American Type Culture Collection (VA, USA), were used. The cells were maintained in McCoy's 5A medium with L-glutamine and 10% heat inactivated (55 °C for 30 min) fetal bovine serum (FBS) at 37 °C under an atmosphere of 5% CO_2. The HCT-116 tumor cell viability assay, by MTT method, was carried out following the method described by Mosmann.[24] Briefly, cells were placed in 96-well flat-bottomed tissue culture plates with 6.0 × 10^3 cells per well in 100 μL of culture medium. This was followed by incubation at 37 °C under an atmosphere of 5% CO_2 for 24 h to allow cell attachment onto the wells. The cells were treated with the indicated concentrations of test agents in culture medium without FBS. Following a further 24 h incubation, 10 μL of MTT (5 mg/mL in PBS buffer) was added per well and the plate was incubated for 4 h to allow metabolism of MTT by cellular mitochondrial dehydrogenases. The excess MTT was aspirated, and the formazan crystals that formed were dissolved by the

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addition of 100 μL of DMSO. The absorbance of purple formazan was read at 570 nm using a microplate reader. The results following test agent exposure were calculated as a percentage relative to untreated controls. The data were expressed as means ± SE, with n = 3 or higher in one of at least three similar experiments.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01397.

Crystallographic data for **4fb** (CIF)
Crystallographic data for **5dc** (CIF)
^{1}H and ^{13}C NMR spectral data for all new compounds and X-ray, computational, and bioassay data (PDF)

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Notes

The authors declare no competing financial interest.

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