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Direct Synthesis of Fused Indoles by Gold-Catalyzed Cascade Cyclization of Diynes

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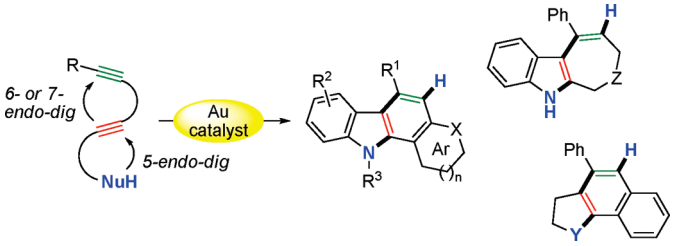

A direct, concise, and atom-economical synthetic method for the generation of fused indoles, using a gold-catalyzed cascade cyclization of diynes, has been developed. The reaction gave various fused indoles, such as aryl-annulated[*a*]carbazoles, dihydrobenzo[*g*]indoles, and azepino- or oxepinoindole derivatives in good to excellent yields, through an intramolecular cascade 5-*endo-dig* hydroamination followed by a 6- or 7-*endo-dig* cycloisomerization, without producing theoretical byproduct. Three of the resulting indoles exhibited potent antifungal activities against *T. mentagrophytes* and *T. rubrum*, demonstrating the practical application of the described cascade reaction for drug discovery.

Introduction

The indole moiety is a vital structural unit found in a large array of natural products and pharmaceuticals.[1] Aryl- and heteroaryl-annulated[*a*]carbazoles are particularly noted for their diverse biological activities.[2−6] While synthetic methodologies have been developed to generate these compounds, most include stepwise introduction or construction of the pyrrole and benzene rings.[7] The development of a direct, concise, and atom-economical synthetic route to this class of compounds, producing minimum waste/byproduct, would therefore be of considerable interest for drug discovery and process chemistry.

In recent years, cascade reactions have been recognized as an efficient approach to target molecules by minimizing the number of steps and separation processes and the amount of time, labor, and waste involved.[8] Gold catalysis is an important and powerful tool for the promotion of cascade reactions because it can promote several types of nucleophilic reaction through the electrophilic activation of carbon−carbon multiple bonds.[9] To develop a more atom-economical and direct synthetic method to aryl-annulated-[*a*]carbazoles **2**, we designed a cycloisomerization cascade

(1) For recent reviews, see: Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.
(2) For antituberculosis activity, see: Choi, T. A.; Czerwonka, R.; Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Franzblau, S. G.; Knölker, H.-J. *ChemMedChem* **2006**, *1*, 812–815.
(3) For antitumor activity, see: (a) Lescot, E.; Muzard, G.; Markovits, J.; Belleney, J.; Roques, B. P.; Le Pecq, J.-B. *J. Med. Chem.* **1986**, *29*, 1731–1737. (b) Cavazos, C. M.; Keir, S. T.; Yoshinari, T.; Bigner, D. D.; Friedman, H. S. *Cancer Chemother. Pharmacol.* **2001**, *48*, 250–254.
(4) For antifungal activity, see: Thevissen, K.; Marchand, A.; Chaltin, P.; Meert, E. M.K.; Cammue, B. P.A. *Curr. Med. Chem.* **2009**, *16*, 2205–2211.
(5) For checkpoint kinase 1 inhibitory activity, see: Conchon, E.; Anizon, F.; Aboab, B.; Prudhomme, M. *J. Med. Chem.* **2007**, *50*, 4669–4680.
(6) For thrombopoietin receptor agonistic action, see: Alper, P. B.; Marsilje, T. H.; Mutnick, D.; Lu, W.; Chatterjee, A.; Roberts, M. J.; He, Y.; Karanewsky, D. S.; Chow, D.; Lao, J.; Gerken, A.; Tuntland, T.; Liu, B.; Chang, J.; Gordon, P.; Seidel, H. M.; Tian, S.-S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5255–5258.
(7) For recent reviews, see: (a) Kirsch, G. H. *Curr. Org. Chem.* **2001**, *5*, 507–518. (b) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303–4427.
(8) For recent reviews on cascade reactions, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (d) Kirsch, S. F. *Synthesis* **2008**, 3183–3204. (e) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993–3009.

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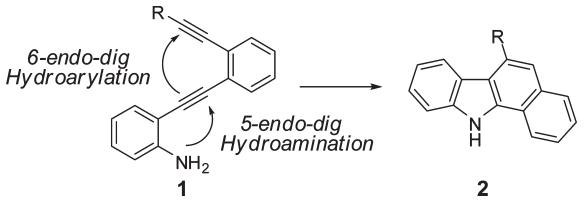
SCHEME 1. Synthesis of Aryl-Annulated[*a*]Carbazoles: Our Strategy



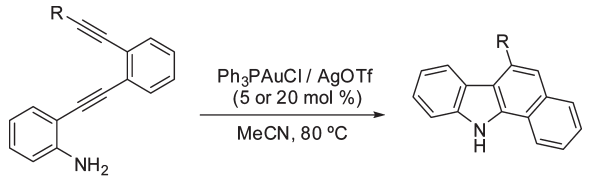
strategy on the basis of gold-catalyzed 5-*endo-dig* hydroamination[10] and subsequent 6-*endo-dig* hydroarylation[11] of diyne **1** (Scheme 1). We now report full details of our study on the synthesis of aryl-annulated[*a*]carbazoles based on this strategy.[12] Synthesis of other heterocyclic indoles, such as dihydrobenzoindole, oxepinoindole, and cycloheptaindole derivatives and the antifungal activities of these indole derivatives are also presented.

Results and Discussion

Synthesis of Aryl-Annulated[*a*]Carbazoles Using Various Aniline-Substituted Diethynylarenes. Our preliminary investigation revealed that 5 mol % of $Ph_3PAuCl/AgOTf$ in MeCN at 80 °C produced carbazoles in good yields from diyne derivatives bearing an *n*-propyl, cyclohexyl, phenyl, and electron-deficient aryl group (*p*-$F_3CC_6H_4$, *p*-NCC_6H_4, or *p*-ClC_6H_4) at the alkyne terminus (Table 1, entries 1−6). On the other hand, the reaction of **1g** or **1h** bearing an electron-rich aryl group (*p*-MeC_6H_4 or *p*-$MeOC_6H_4$) as the R substituent under identical conditions gave the corresponding carbazoles **2g** and **2h** in relatively low yields (42% and 29%, respectively, entries 7 and 8). The yields of **2g** and **2h** were only moderately improved by increasing the loading of $Ph_3PAuCl/AgOTf$ to 20 mol % (65% and 45%, respectively). The lower reactivity of these substrates can be attributed to the predominant coordination of the electron-rich aryl-substituted alkyne to the active cationic gold complex, which hinders the first cyclization step.

We further optimized the reaction conditions for diyne **1g** using highly alkynophilic gold−phosphine catalysts (**A**−**C**)

TABLE 1. Reaction of Various Aniline Derivatives under Unoptimized Conditions[a]



entry	1	R	time[b] (h)	2	yield[b] (%)
1	**1a**	*n*-Pr	0.75	**2a**	87
2	**1b**	*c*-Hex	0.75	**2b**	82
3	**1c**	Ph	1.5	**2c**	80
4	**1d**	*p*-$F_3CC_6H_4$	0.5	**2d**	84
5	**1e**	*p*-NCC_6H_4	1.0	**2e**	78
6	**1f**	*p*-ClC_6H_4	0.75	**2f**	81
7	**1g**	*p*-MeC_6H_4	3.5 (0.83)	**2g**	42 (65)
8	**1h**	*p*-$MeOC_6H_4$	4.0 (1.5)	**2h**	29 (45)

[a]Unless stated otherwise, all reactions were carried out with Ph_3PAuCl (5 mol %) and AgOTf (5 mol %) in MeCN at 80 °C. [b]Reaction times and yields in parentheses indicate those with 20 mol % of the catalysts.

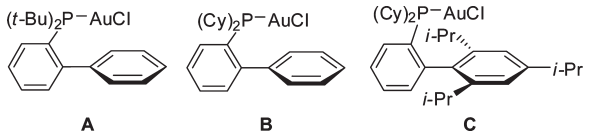


FIGURE 1. Screened gold−phosphine catalysts.

(Figure 1).[13] We postulated that the bulky biarylphosphine ligands might effectively promote dissociation of the gold catalyst from the substrate, which would improve the chance of activation of the appropriate alkyne for hydroamination.[14−16] Pleasingly, reactions carried out with 5 mol % of catalysts **A**−**C** exhibited significantly increased turnover of **1g** to give **2g**, with good yields obtained (Table 2, 71−83%, entries 2−4).

Using the optimized conditions described in entry 4 (catalyst **C**, Table 2), the cascade cyclization was extended to other types of substituted anilines. The results are summarized in Table 3. In contrast to the low yield obtained for the reaction of aniline **1h** having a methoxy group with 5 mol % of $Ph_3PAuCl/AgOTf$ (29% yield, entry 8, Table 1), the cascade cyclization of **1h** with 5 mol % of **C**/AgOTf proceeded cleanly to give **2h** in 83% yield (entry 2). When using precursors **1i**−**k**, which bear a *meta*-substituted phenyl group at R^1, the corresponding products **2i**−**k** were afforded in good to excellent yields (76−98%, entries 3−5). It should be noted that an *o*-cyano group at R^1 significantly decreased

(9) For recent reviews on gold catalysis: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (d) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (e) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221.

(10) For alkyne hydroamination to give indoles, see: (a) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610–618. (b) Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265–2273. (c) Miyazaki, Y.; Kobayashi, S. *J. Comb. Chem.* **2008**, *10*, 355–357. (d) Praveen, C.; Sagayaraj, Y. W.; Perumal, P. T. *Tetrahedron Lett.* **2009**, *50*, 644–647. Quite recently, a Pd(II)-catalyzed oxidative halocyclization cascade using highly related substrates to give benzo[*a*]carbazoles appeared: (e) Chen, C.-C.; Chin, L.-Y.; Yang, S.-C.; Wu, M.-J. *Org. Lett.* **2010**, *12*, 5652–5655.

(11) For gold-catalyzed electrophilic activation of alkynes toward intramolecular nucleophilic attack at the C-3 position of indoles, see: (a) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105–1109. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358–1373. (c) Sanz, R.; Miguel, D.; Rodríguez, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7354–7357. (d) England, D. B.; Padwa, A. *Org. Lett.* **2008**, *10*, 3631–3634. (e) Lu, Y.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009**, *351*, 1517–1522. (f) Verniest, G.; England, D.; Kimpe, N. D.; Padwa, A. *Tetrahedron* **2010**, *66*, 1496–1502. (g) Liu, Y.; Xu, W.; Wang, X. *Org. Lett.* **2010**, *12*, 1448–1451. (h) Li, G.; Liu, Y. *J. Org. Chem.* **2010**, *75*, 3526–3528.

(12) A portion of this study (Table 1, entry 1 in Table 2 and Scheme 2) has already been reported in a preliminary communication: Hirano, K.; Inaba, Y.; Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Adv. Synth. Catal.* **2010**, *352*, 368–372.

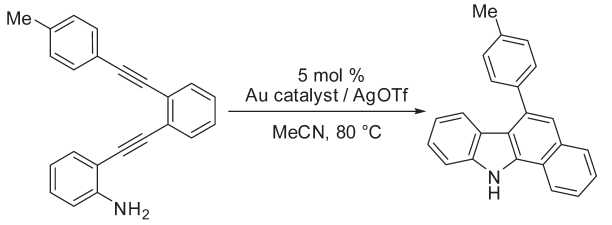
(13) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179.

(14) For a recent review on ligand effects of gold catalysis, see: Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378.

(15) For the impact of the bulky biarylphosphine ligands on gold catalysis, see: Benitez, D.; Tkatchouk, E.; Gonzalez, A. Z.; Goddard, W. A., III; Toste, F. D. *Org. Lett.* **2009**, *11*, 4798–4801.

(16) While this reference does not refer to a gold-catalyzed reaction, it discusses the origin of improved reactivity in a Pd-catalyzed C−N bond formation reaction by bulky and electron-rich monophosphinobiaryl ligands; see: Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978–13980.

TABLE 2. Investigation of Gold Catalysts Bearing Bulky Biarylphosphine Ligands[a]

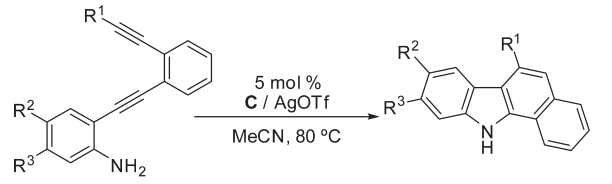


1g **2g**

entry	Au catalyst	time (min)	yield (%)
1	Ph_3PAuCl	50	42
2	**A**	45	71
3	**B**	45	80
4	**C**	45	83

[a]All reactions were carried out with Au catalyst (5 mol %) and AgOTf (5 mol %) in MeCN at 80 °C.

TABLE 3. Reaction of Various Aniline Derivatives[a]



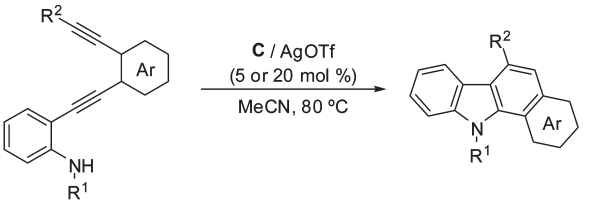
1g–t **2g–t**

entry	**1**	R^1	R^2	R^3	**2**	time (min)	yield (%)
1	**1g**	*p*-MeC_6H_4	H	H	**2g**	45	83
2	**1h**	*p*-$MeOC_6H_4$	H	H	**2h**	30	83
3	**1i**	*m*-$CF_3C_6H_4$	H	H	**2i**	40	98
4	**1j**	*m*-NCC_6H_4	H	H	**2j**	30	79
5	**1k**	*m*-MeC_6H_4	H	H	**2k**	30	76
6	**1l**	*o*-NCC_6H_4	H	H	**2l**	250	10
7	**1m**	*o*-MeC_6H_4	H	H	**2m**	40	82
8	**1n**	3-thienyl	H	H	**2n**	40	74
9	**1o**	*c*-pentyl	H	H	**2o**	40	90
10	**1p**	Ph	CO_2Me	H	**2p**	120	68
11	**1q**	Ph	Me	H	**2q**	30	83
12	**1r**	Ph	H	Cl	**2r**	40	92
13	**1s**	*c*-Hex	H	Cl	**2s**	90	96
14	**1t**	*c*-Hex	H	CF_3	**2t**	90	87

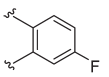
[a]All reactions were carried out with **C** (5 mol %) and AgOTf (5 mol %) in MeCN at 80 °C.

the yield (10%, entry 6), while the effect of *p*-cyanophenyl group was less important (Table 1, entry 5). This is presumably because of a coordination effect of the *o*-cyano group, which would promote an undesired interaction between the R^1 group substituted triple bond and the catalyst before hydroamination.[17] This explanation is supported by the high yield obtained with **1m**, which bears an R^1 *o*-tolyl group (82%, entry 7), showing that any steric hindrance of the reaction by *o*-substituents on R^1 is relatively unimportant. Diynes **1n** and **1o** bearing a thienyl and cyclopentyl group as R^1, respectively, were good substrates for the cascade cyclization (entries 8 and 9). We also examined the effect of substituents R^2 and R^3 on the aniline moiety (entries 10−14).

TABLE 4. Effect of a Nitrogen Substituent and Various Arene Tethers[a]



1u–y **2u–y**

entry	**1**	R^1	R^2	Ar	**2**	time (h)[b]	yield (%)[b]
1	**1u**	Boc	Ph		**2u**	2	89
2	**1v**	Me	Ph		**2v**	0.67	92
3	**1w**	H	*c*-Hex		**2w**	0.83	84
4	**1x**	H	Ph		**2x**	24 (24)	15 (37)
5	**1y**	H	Ph		**2y**	1.3	98

[a]Unless otherwise stated, all reactions were carried out with **C** (5 mol %) and AgOTf (5 mol %) in MeCN at 80 °C. [b]Reaction times and yields in parentheses indicate those with 20 mol % of the catalysts.

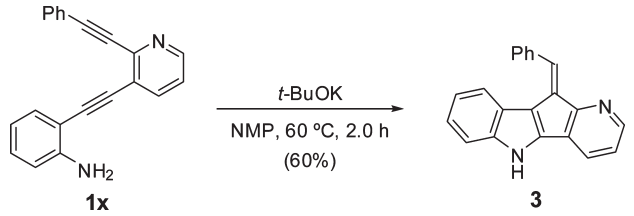
Substitution with a methoxycarbonyl group at the *para*-position decreased the reactivity of **1p**, and **2p** was only obtained in a moderate yield (68%, entry 10) with prolonged reaction time. This is presumed to be due to the decreased nucleophilicity of the amino group in the first step as well as the indole 3-position in the second step. Reaction of **1q**, containing a *p*-methyl group, led to **2q** in good yield (83%, entry 11).[18] Diynes **1r** and **1s**, which bear chlorine substituents, afforded carbazoles **2r** and **2s** in excellent yields (92% and 96%, entries 12 and 13), independent of the R^1 substituent. A trifluoromethyl group R^3 substituent was also tolerated (entry 14). From these results, the reaction using catalyst **C**, with bulky biaryl phosphine ligand, is applicable to various substrate types and affords the corresponding carbazoles in good yields, reducing the importance of substrate electronic effects to reaction outcome.

Next, we investigated nitrogen substitution and other arene tethers between the two alkynes (Table 4). *tert*-Butyl carbamate **1u** satisfactorily underwent cascade cyclization in the presence of gold catalyst **C** to give **2u** in a yield of 89% (entry 1). The reaction of **1v**, which has a methyl group as R^1 substituent, also reacted cleanly to afford **2v** in excellent yield (92%, entry 2). Anilines **1w** and **1y**, which have fluorinated phenyl or furan groups tethering the alkyne moieties, provided the desired carbazoles **2w** and **2y** in 84% and 98% yields, respectively (entries 3 and 5). However, diyne **1x**, containing a pyridine moiety, proved to be a poor substrate,

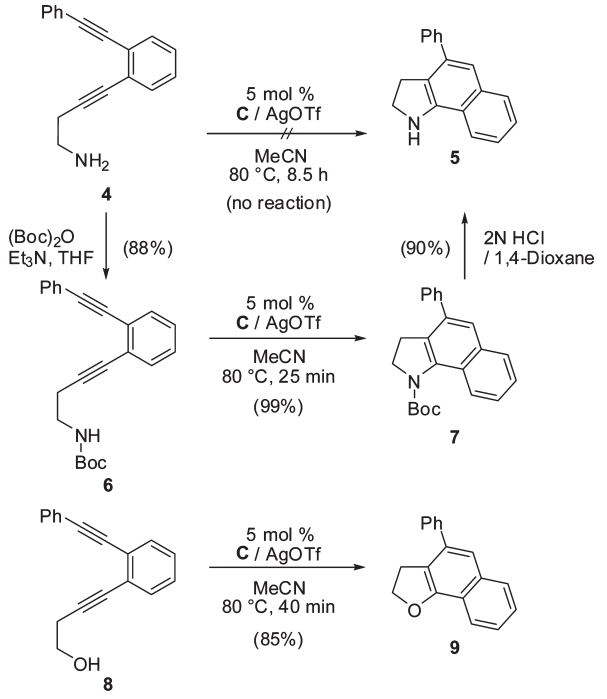
(17) For example, *N*-heterocyclic carbene gold(I) activates a nitrile group, see: Ramón, R. S.; Marion, N.; Nolan, S. P. *Chem.—Eur. J.* **2009**, *15*, 8695–8697.

(18) It is noteworthy that the reaction of **1p** or **1q** under the previous conditions (5 mol % of Ph_3PAuCl/AgOTf) gave the corresponding carbazoles **2p** or **2q** in only low yields (35% and 29%, respectively); see ref 12.

SCHEME 2. Base-Promoted Cascade Cyclization of 1x



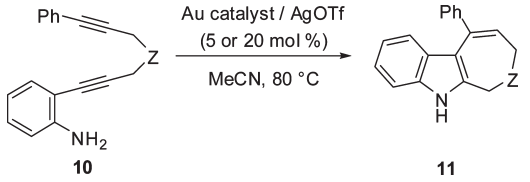
SCHEME 3. Synthesis of Dihydrobenzoindole and Dihydronaphthofuran



resulting in a low yield of **2x** (15%, entry 4). The yield of **2x** was improved slightly (37%) by the use of increased catalyst loading (20 mol %, entry 4). Interestingly, the base-promoted cyclization of **1x** using *t*-BuOK in NMP showed a dramatic change in cyclization mode, resulting in the formation of product **3** in 60% yield, as the single *E*-isomer,[19] through a cascade 5-*endo*-*dig*/5-*exo*-*dig* cyclization (Scheme 2).[20,21]

Synthesis of Dihydrobenzoindole and Dihydronaphthofuran. We examined the reactivity of nucleophilic groups other than anilines (Scheme 3). Unfortunately, the alkyl amine-derived diyne **4** did not give dihydrobenzoindole **5**. We speculated that unfavorable interactions of the amino group with the gold catalyst may be responsible for this result, and therefore tested the Boc-protected amine derivative **6**, which reacted cleanly to afford compound **7** in high yield (99%). The Boc group of **7** was easily removed by treatment with 2 N HCl/1,4-dioxane to afford dihydrobenzoindole **5** in 90% yield.[22,23] Similarly, the cyclization of alcohol **8** gave dihydronaphthofuran **9** in 85% yield.[23,24] These results show that *tert*-butyl carbamates and alcohols can also be used as the nucleophile in this cascade cyclization. Synthesis of dihydrobenzo[*g*]indole derivative such as **5** seems to be especially important in drug discovery, in terms of improvement of physiological properties of aryl-annulated[*a*]carbazoles (e.g., water solubility, lipophilicity) by removing one benzene ring from these molecules.[25]

TABLE 5. Synthesis of Seven-Membered Ring Analogues[a]



entry	diyne	Z	Au catalyst (mol %)	time (h)	product	yield (%)
1	**10a**	NTs	**C** (5)	2.5	**11a**	38
2	**10a**	NTs	**A** (5)	1.5	**11a**	42
3	**10a**	NTs	**A** (20)	1	**11a**	66
4	**10b**	O	**C** (5)	4	**11b**	49
5	**10c**	$C(CO_2Me)_2$	**C** (5)	2.5	**11c**	63

[a]All reactions were carried out with Au catalyst (5 or 20 mol %) and AgOTf (5 or 20 mol %) in MeCN at 80 °C.

Synthesis of Azepino- or Oxepino[3,4-*b*]indole and Cyclohepta[*b*]indole Derivatives. Indole-fused seven-membered ring derivatives are attractive drug templates,[26] and we envisioned their synthesis by establishing seven-membered ring formation as the second step of the cascade cyclization (Table 5). Three diyne derivatives, sulfonamide **10a**, ether **10b**, and diester **10c** were prepared and subjected to the standard conditions for the cascade cyclization. Treatment of **10a** with 5 mol % of the gold catalyst **C**/AgOTf resulted in azepinoindole **11a** in 38% yield (entry 1). This result shows that intramolecular nucleophilic attack at the C-3 position of the indole intermediate underwent 7-*endo*-*dig* cyclization as we expected.[27] The reaction was also performed by using 5 mol % (entry 2) and 20 mol % (entry 3) of the gold

(19) NOE analysis indicates that **3** has an *E*-configuration; see ref 12.

(20) For related base-mediated reactions, see: (a) Wu, M.-J.; Lee, C.-Y.; Lin, C.-F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4077–4079. (b) Lee, C.-Y.; Lin, C.-F.; Lee, J.-L.; Chiu, C.-C.; Lu, W.-D.; Wu, M.-J. *J. Org. Chem.* **2004**, *69*, 2106–2110.

(21) In 2004, Wu reported base-promoted cascade cyclization of aniline-substituted (*Z*)-endiyne derivatives to form carbazoles. However, our detailed reinvestigation of the reactions has shown that these reactions generate pyrido[1,2-*a*]indole derivatives, not carbazoles; see ref 12.

(22) For representative syntheses of dihydrobenzoindole derivatives, see: (a) Kappe, C. O.; Cochran, J. E.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 9285–9288. (b) Padwa, A.; Kappe, C. O.; Cochran, J. E.; Snyder, J. P. *J. Org. Chem.* **1997**, *62*, 2786–2797. (c) Ghoral, B. K.; Herndon, J. W. *Organometallics* **2003**, *22*, 3951–3957. (d) Kise, N.; Isemoto, S.; Sakurai, T. *Org. Lett.* **2009**, *11*, 4902–4905.

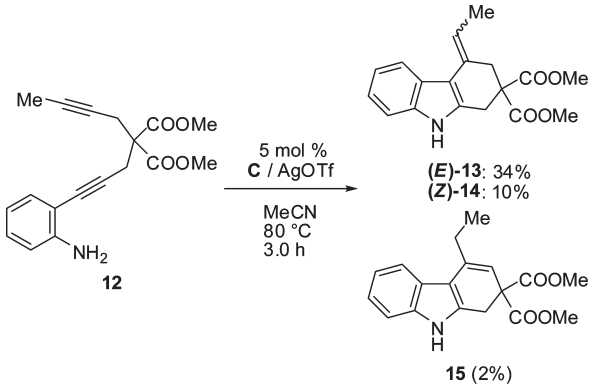
(23) For the synthesis of dihydrobenzoindole and dihydronaphthofuran derivatives, see: Taduri, B. P.; Odedra, A.; Lung, C.-Y.; Liu, R.-S. *Synthesis* **2007**, 2050–2054.

(24) For the representative synthesis of a dihydronaphthofuran derivative, see: Duperrouzel, P.; Lee-Ruff, E. *Can. J. Chem.* **1980**, *58*, 51–54.

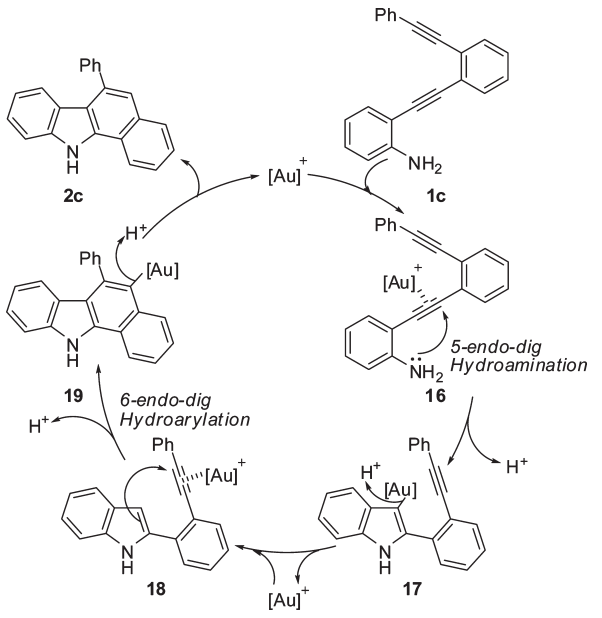
(25) Ritchie, T. J.; Macdonald, S. J. F. *Drug Discov. Today* **2009**, *14*, 1011–1020.

(26) (a) Putey, A.; Joucla, L.; Picot, L.; Besson, T.; Joseph, B. *Tetrahedron* **2007**, *63*, 867–879. (b) Singh, U. S.; Shankar, R.; Yadav, G. P.; Kharkwal, G.; Dwivedi, A.; Keshri, G.; Singh, M. M.; Moulik, P. R.; Hajela, K. *Eur. J. Med. Chem.* **2008**, *43*, 2149–2158. (c) Keller, L.; Beaumont, S.; Liu, J.-M.; Thoret, S.; Bignon, J. S.; Wdzieczak-Bakala, J.; Dauban, P.; Dodd, R. H. *J. Med. Chem.* **2008**, *51*, 3414–3421. (d) Feytens, D.; Vlaeminck, M. D.; Cescato, R.; Tourwé, D.; Reubi, J. C. *J. Med. Chem.* **2009**, *52*, 95–104. (e) Putey, A.; Popowycz, F.; Do, Q.-T.; Bernard, P.; Talapatra, S. K.; Kozielski, F.; Galmarini, C. M.; Joseph, B. *J. Med. Chem.* **2009**, *52*, 5916–5925. (f) Yeung, B. K. S.; Zou, B.; Rottmann, M.; Lakshminarayana, S. B.; Ang, S. H.; Leong, S. Y.; Tan, J.; Wong, J.; Keller-Maerki, S.; Fischli, C.; Goh, A.; Schmitt, E. K.; Krastel, P.; Francotte, E.; Kuhen, K.; Plouffe, D.; Henson, K.; Wagner, T.; Winzeler, E. A.; Petersen, F.; Brun, R.; Dartois, V.; Diagana, T. T.; Keller, T. H. *J. Med. Chem.* **2010**, *53*, 5155–5164.

SCHEME 4. Effect of Methyl Substituent at the Alkyne Terminus



SCHEME 5. Plausible Reaction Mechanism



catalyst **A**/AgOTf to give **11a** in 42% and 66% yields, respectively. The gold-catalyzed cyclization of diynes **10b** and **10c** with 5 mol % of **C**/AgOTf gave oxepinoindole **11b** (49%, entry 4) and cycloheptaindole **11c** (63%, entry 5), respectively, through the same cyclization cascade. While azepinoindole synthesis has been previously reported by us,[28] the syntheses of 3,10-dihydro-1*H*-oxepino[3,4-*b*]indole and 6,8-dihydrocyclohepta[*b*]indole derivative are unprecedented.

In contrast to the diester **10c**, which bears a phenyl group at the alkyne terminus, the cyclization of **12**, bearing a methyl group, favors 6-*exo-dig* cyclization in the second step,[29] providing *E*-olefin **13** (34%),[30] *Z*-olefin **14** (10%), and *endo*-olefin **15** (2%, Scheme 4).[31] Thus, the phenyl group at the alkyne terminus of **10** plays a crucial role in promoting 7-*endo-dig* cyclization in the second step, and we postulated that this may be due to activation of the neighboring carbon by the phenyl group.

Mechanism of the Cascade Cyclization. A plausible mechanism for the cascade cyclization is shown in Scheme 5. First, activation of the alkyne between two arenes of **1c** by the cationic gold complex (as depicted in **16**) promotes 5-*endo-dig* cyclization to form indolylgold intermediate **17**. This is followed by proto-deauration to give the first cyclization product **18**; further activation of the second alkyne by the gold catalyst to form **18** would lead to 6-*endo-dig* cyclization at the C-3 position of the indole and subsequent rearomatization to give arylgold intermediate **19**. Finally, proto-deauration of **19** would produce fused carbazole **2c** to regenerate the active catalyst. This mechanism, including the second cyclization after proto-deauration of the vinyl gold intermediate **17**, is supported by the reaction of plausible intermediate **20**: treatment of **20** under the standard reaction conditions quantitatively proceeded to afford the desired carbazole **2c** (Scheme 6).[32]

Antifungal Activities of Indoles. The synthesized indoles were evaluated for antifungal activity against *Trichophyton mentagrophytes* and *Trichophyton rubrum* (Table 6). Among

SCHEME 6. Cyclization of Plausible Intermediate 20

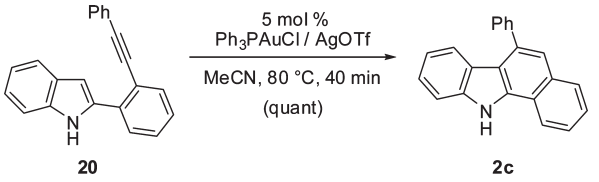
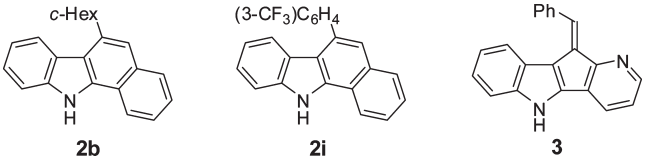


TABLE 6. Antifungal Activities of Indoles



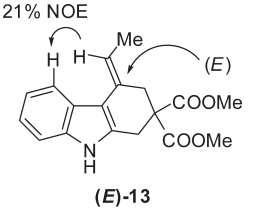
	MIC (μM)		
compd	*T. mentagrophytes* (SM-110)	*T. rubrum* (KD-1137)	LD_{50} (μM)
2b	3.13	25	5.14
2i	3.13	> 100	4.53
3	< 0.05	0.20	8.17

(27) For gold-catalyzed electrophilic activation of alkynes toward intramolecular nucleophilic attack at the C-3 position of indoles in a 7-*endo-dig* manner, see refs 11a and 11b.

(28) For the synthesis of an azepinoindole derivative based on copper-mediated multicomponent coupling and cyclization, see: (a) Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2295–2298. (b) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 7052–7058.

(29) For gold-catalyzed electrophilic activation of alkynes toward intramolecular nucleophilic attack at the C-3 position of indoles in a 6-*exo-dig* manner, see ref 11a,11b,11d,11f,11g.

(30) NOE analysis indicates that (*E*)-**13** has an *E*-configuration.



(31) The yields of (*E*)-**13**, (*Z*)-**14**, and **15** were determined by NMR.

them, carbazoles **2b** and **2i** showed good activity against *T. mentagrophytes* (minimal inhibitory concentration (MIC) = 3.13 μM in both cases). Compound **2b** demonstrated modest antifungal activity against *T. rubrum* with an MIC of 25 μM, while compound **2i** showed no activity at 100 μM. Indole **3**, fused with cyclopenta[*b*]pyridine, exhibited highly potent antifungal activities against *T. mentagrophytes* and *T. rubrum* (MIC < 0.05 and 0.20 μM, respectively). The three potent compounds were tested for in vitro toxicity against human embryonic lung (HEL) cells, and showed low cytotoxicity (50% lethal dose (LD_{50}) = 4.53−8.17 μM, Table 6). Particularly, selectivity index of indole **3** was high against both *T. mentagrophytes* (> 163-fold for MIC) and *T. rubrum* (41-fold for MIC). The unprecedented antifungal activities of fused indoles will be useful in future structure−activity relationships toward the development of this class of indole derivatives as antifungal therapeutics.

Conclusions

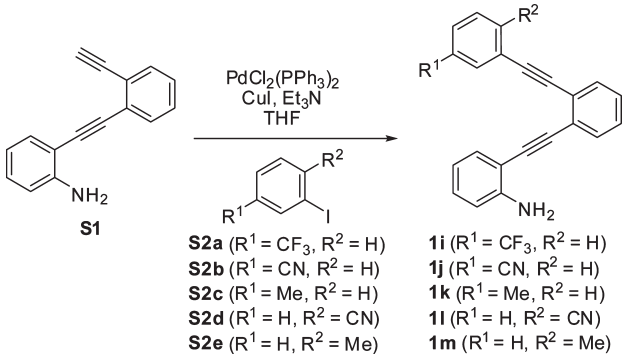
We have developed an atom-economical, new synthesis of aryl-annulated[*a*]carbazoles via gold-catalyzed 5-*endo-dig* hydroamination followed by 6-*endo-dig* hydroarylation of diynes. The electronic influence of diyne substituents in the cascade cyclization can be circumvented by using a gold catalyst with bulky biaryl phosphine ligands. Consequently, reaction with 5 mol % of catalyst gives not only aryl-annulated[*a*]carbazoles but also various other fused indoles such as dihydrobenzo[*g*]indole, azepino- or oxepinoindole, and cycloheptaindole derivatives. Three of the resulting indoles exhibited good to excellent antifungal activities against *T. mentagrophytes* and *T. rubrum*, demonstrating the practical application of the described cascade reaction for drug discovery, including the development of antifungal agents. Further optimization studies of these antifungal compounds are now underway.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 400 or 500 MHz. ^{13}C NMR spectra were recorded at 100 or 125 MHz. Internal references were used for $CDCl_3$, C_6D_6, and DMSO-d_6 in ^{1}H and ^{13}C NMR spectra. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δTMS = 0), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (J/Hz) and number of protons. ^{1}H NMR assignments were confirmed by ^{1}H−^{1}H COSY (PFG) and difference NOE analyses if necessary. Melting points were measured by a hot stage melting point apparatus and are uncorrected. For column chromatography, silica gel (45−75 μm) and amino silica gel (100−200 mesh) were employed. The compounds **1a**−**h**,**p**,**q**,**x**, **2a**−**h**,**p**,**q**,**x**, and **3** are known. Characterization data and NMR spectra for these compounds were already reported in our preliminary communication.[12]

The compounds **S5**,[33] **S6**,[33] **S8**,[34] **S10**,[12] **S17**,[35−37] **S20**,[37] **S21**,[38] **S24**,[39] and **S25**[40] were synthesized according to the literature procedures. The gold catalyst **B** was synthesized according to the literature procedures.[13] Other reagents are commercially available, which were used without further purification.

Preparation of Starting Materials



Synthesis of 2-[(2-Ethynylphenyl)ethynyl]aniline (S1). S1 was prepared according to the procedure in a preliminary communication.[12] Characterization data for **S1** are as follows: pale yellow solid; IR (neat) 3454 (NH), 3361 (NH), 2210 (C≡C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 1H, C≡CH), 4.50 (br s, 2H, NH_2), 6.73−6.69 (m, 2H, Ar), 7.17−7.13 (m, 1H, Ar), 7.30−7.26 (m, 1H, Ar), 7.34 (td, J = 7.6, 1.3 Hz, 1H, Ar), 7.38 (dd, J = 7.6, 1.5 Hz, 1H, Ar), 7.54 (dd, J = 6.2, 1.6 Hz, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.0, 83.3, 90.7, 93.3, 107.6, 114.3, 117.9, 123.9, 126.7, 127.8, 128.8, 130.2, 131.5, 132.2, 132.8, 148.4; HRMS (FAB) calcd for $C_{16}H_{11}N$ [M^+] 217.0891, found 217.0894.

Synthesis of 2-[(2-{[3-(Trifluoromethyl)phenyl]ethynyl}phenyl)-ethynyl]aniline (1i). A mixture of **S1** (0.10 g, 0.46 mmol), CuI (2.2 mg, 0.012 mmol), $PdCl_2(PPh_3)_2$ (8.1 mg, 0.012 mmol), Et_3N (0.32 mL, 2.3 mmol), and *m*-iodobenzotrifluoride (**S2a**) (66 μL, 0.46 mmol) in THF (1.0 mL) was stirred at room temperature for 6 h under argon. Concentration under reduced pressure followed by purification through a pad of silica gel with *n*-hexane/EtOAc (5:1) afforded **1i** (0.12 g, 70% yield) as a brown solid, which was recrystallized from *n*-hexane to give pure **1i** as brown crystals: mp 87−88 °C; IR (neat) 3478 (NH), 3378 (NH), 2205 (C≡C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (br s, 2H, NH_2), 6.69−6.73 (m, 2H, Ar), 7.15 (ddd, J = 7.7, 7.7, 1.5 Hz, 1H, Ar), 7.30−7.41 (m, 3H, Ar), 7.48 (dd, J = 7.7 Hz, 1H, Ar), 7.58−7.61 (m, 3H, Ar), 7.74 (d, J = 7.7 Hz, 1H, Ar), 7.86 (s, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 90.2, 90.7, 91.5, 93.4, 107.4, 114.2, 117.8, 123.7 (q, J = 273.1 Hz), 124.0, 124.4, 125.0 (q, J = 3.6 Hz), 126.1, 127.8, 128.6, 128.7 (q, J = 3.6 Hz), 128.9, 130.1, 131.0 (q, J = 32.4 Hz), 131.6, 132.0, 132.1, 134.9, 148.0. Anal. Calcd for $C_{23}H_{14}F_3N$: C, 76.45; H, 3.91; N, 3.88. Found: C, 76.65; H, 4.17; N, 3.91.

3-({2-[(2-Aminophenyl)ethynyl]phenyl}ethynyl)benzonitrile (1j). By a procedure identical to that described for the preparation of **1i**, **S1** (0.10 g, 0.46 mmol) was converted into **1j** (0.14 g, 96% yield) as a brown solid using 3-iodobenzonitrile (**S2b**) (0.11 g, 0.46 mmol): IR (neat) 3474 (NH), 3378 (NH), 2232 (C≡C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (br s, 2H, NH_2), 6.71−6.75 (m, 2H, Ar), 7.14−7.19 (m, 1H, Ar), 7.31−7.40 (m, 3H, Ar), 7.47 (dd, J = 7.8, 7.8 Hz, 1H, Ar), 7.59−7.61 (m, 3H, Ar), 7.78 (dt, J = 7.8, 1.7 Hz, 1H, Ar), 7.86−7.87 (m, 1H, Ar); ^{13}C NMR (125

(32) At present, we cannot rule out an alternative mechanism where the intermediate **17** attacks the alkyne moiety directly before protonation. For a related paper describing the formation of an arylgold(III) intermediate in an S_N2-type mechanism, see: Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596–13597.

(33) Schmittel, M.; Strittmatter, M. *Tetrahedron* **1998**, *54*, 13751–13760.

(34) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652–7662.

(35) Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378–9379.

(36) Kang, S.-K.; Baik, T.-G.; Kulak, A. N.; Ha, Y.-H.; Lim, Y.; Park, J. *J. Am. Chem. Soc.* **2000**, *122*, 11529–11530.

(37) Chang, H.-T.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2007**, *9*, 505–508.

(38) Flynn, B. L.; Funke, F. J.; Silveira, C. C.; de Meijere, A. *Synlett* **1995**, 1007–1010.

(39) García-Rubín, S.; Varela, J. A.; Castedo, L.; Saá, C. *Chem.—Eur. J.* **2008**, *14*, 9772–9778.

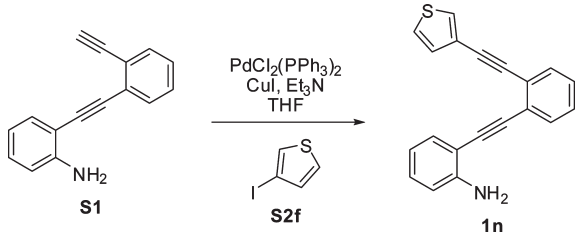
(40) Shen, Z.; Lu, X. *Adv. Synth. Catal.* **2009**, *351*, 3107–3112.

MHz, $CDCl_3$) δ 90.6, 90.7, 91.0, 93.3, 107.4, 112.9, 114.3, 117.9, 117.9, 124.1, 124.6, 126.1, 127.9, 128.8, 129.3, 130.2, 131.6, 131.6, 132.0, 132.1, 135.1, 135.8, 148.0; HRMS (FAB) calcd for $C_{23}H_{14}N_2$ [M^+] 318.1157, found 318.1158.

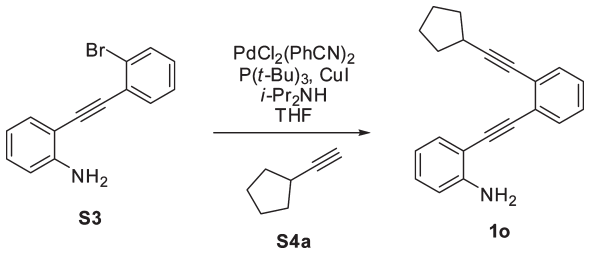
2-{[2-(*m*-Tolylethynyl)phenyl]ethynyl}aniline (1k). By a procedure identical to that described for the preparation of **1i**, **S1** (0.10 g, 0.46 mmol) was converted into **1k** (0.11 g, 76% yield) as a brown oil using 1-iodo-3-methylbenzene (**S2c**) (59 μL, 0.46 mmol): IR (neat) 3479 (NH), 3378 (NH), 2205 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3), 4.36 (br s, 2H, NH_2), 6.67−6.71 (m, 2H, Ar), 7.13 (ddd, J = 8.5, 7.0, 1.2 Hz, 1H, Ar), 7.16−7.18 (m, 1H, Ar), 7.23−7.26 (m, 1H, Ar), 7.28−7.35 (m, 2H, Ar), 7.36−7.41 (m, 3H, Ar), 7.57 (ddd, J = 7.1, 7.1, 1.6 Hz, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 88.5, 90.4, 93.3, 93.7, 107.6, 114.0, 117.6, 122.8, 125.2, 125.9, 127.7, 128.1, 128.2, 128.9, 129.5, 129.9, 131.4, 132.0, 132.0, 132.5, 138.0, 148.2; HRMS (FAB) calcd for $C_{23}H_{16}N$ [$M - H]^-$ 306.1283, found 306.1289.

2-({2-[(2-Aminophenyl)ethynyl]phenyl}ethynyl)benzonitrile (1l). By a procedure identical to that described for the preparation of **1i**, **S1** (0.11 g, 0.50 mmol) was converted into **1l** (0.15 g, 92% yield) as a brown solid using 2-iodobenzonitrile (**S2d**) (0.10 g, 0.44 mmol), which was recrystallized from *n*-hexane−EtOAc to give pure **1l** as pale brown crystals: mp 93−94 °C; IR (neat) 3475 (NH), 3370 (NH), 2228 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.38 (br s, 2H, NH_2), 6.69−6.73 (m, 2H, Ar), 7.13−7.17 (m, 1H, Ar), 7.32−7.45 (m, 4H, Ar), 7.54−7.60 (m, 2H, Ar), 7.67−7.72 (m, 3H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 89.1, 90.7, 93.2, 95.0, 107.6, 114.2, 115.4, 117.5, 117.8, 123.9, 125.9, 126.9, 127.9, 128.5, 129.1, 130.0, 131.6, 132.1, 132.4, 132.6, 132.7, 132.9, 148.1. Anal. Calcd for $C_{23}H_{14}N_2$: C, 86.77; H, 4.43; N, 8.80. Found: C, 86.80; H, 4.72; N, 8.74.

2-{[2-(*o*-Tolylethynyl)phenyl]ethynyl}aniline (1m). By a procedure identical to that described for the preparation of **1i**, **S1** (83 mg, 0.38 mmol) was converted into **1m** (30 mg, 25% yield) as a brown oil using 1-iodo-2-methylbenzene (**S2e**) (49 μL, 0.38 mmol): IR (neat) 3478 (NH), 3378 (NH), 2208 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H, CH_3), 4.32 (br s, 2H, NH_2), 6.64 (dd, J = 8.7, 0.6 Hz, 1H, Ar), 6.68 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, Ar), 7.09−7.14 (m, 1H, Ar), 7.14−7.19 (m, 1H, Ar), 7.21−7.27 (m, 2H, Ar), 7.28−7.34 (m, 2H, Ar), 7.36−7.38 (m, 1H, Ar), 7.52 (d, J = 7.8 Hz, 1H, Ar), 7.55−7.60 (m, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.9, 90.3, 92.1, 92.5, 93.7, 107.5, 114.0, 117.5, 122.7, 125.4, 125.5, 125.7, 127.8, 128.0, 128.6, 129.5, 129.9, 131.6, 132.0, 132.1, 132.1, 140.6, 148.2; HRMS (FAB) calcd for $C_{23}H_{16}N$ [$M - H]^-$ 306.1283, found 306.1279.

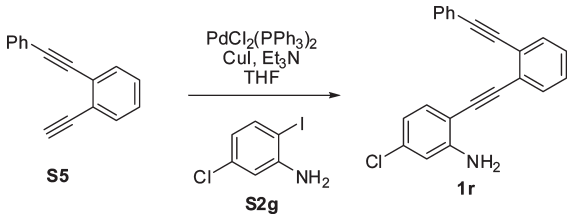


Synthesis of 2-{[2-(Thiophene-3-ylethynyl)phenyl]ethynyl}aniline (1n). To a solution of **S1** (88 mg, 0.41 mmol) in THF (1.3 mL) were successively added Et_3N (0.27 mL, 1.9 mmol), CuI (3.7 mg, 0.019 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.019 mmol), and 3-iodothiophene (**S2f**) (39 μL, 0.39 mmol) at room temperature under argon. The mixture was stirred for 50 h and quenched by addition of saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to afford **1n** (68 mg, 59% yield) as a pale brown solid: IR (neat) 3474 (NH), 3372 (NH), 2206 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (br s, 2H, NH_2), 6.68−6.72 (m, 2H, Ar), 7.13 (ddd, J = 7.8, 7.8, 1.5 Hz, 1H, Ar), 7.23−7.26 (m, 1H, Ar), 7.28−7.35 (m, 3H, Ar), 7.39 (dd, J = 7.8, 1.5 Hz, 1H, Ar), 7.55−7.59 (m, 3H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 88.2, 88.3, 90.4, 93.7, 107.6, 114.1, 117.6, 122.0, 125.0, 125.4, 125.8, 127.7, 128.1, 129.3, 129.9, 130.1, 131.4, 132.0, 132.0, 148.2; HRMS (FAB) calcd for $C_{20}H_{13}NS$ [M^+] 299.0769, found 299.0765.



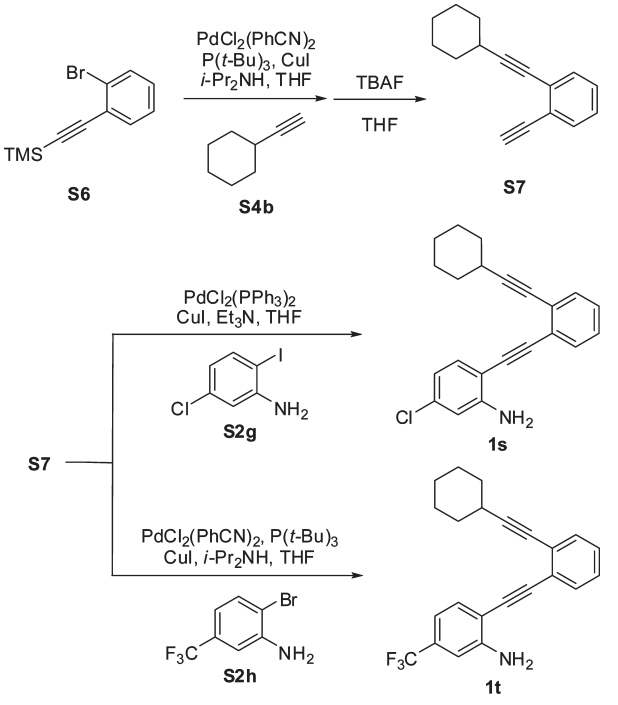
Synthesis of 2-[(2-Bromophenyl)ethynyl]aniline (S3). S3 was prepared according to the procedure in our preliminary communication.[12] Characterization data for **S3** are as follows: colorless solid; IR (neat) 3406 (NH), 3308 (NH), 2210 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.48 (br s, 2H, NH_2), 6.69−6.74 (m, 2H, Ar), 7.13−7.19 (m, 2H, Ar), 7.30 (ddd, J = 7.6, 7.6, 0.9 Hz, 1H, Ar), 7.39 (dd, J = 7.6, 1.2 Hz, 1H, Ar), 7.56 (dd, J = 7.6, 1.6 Hz, 1H, Ar), 7.62 (dd, J = 8.0, 0.7 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 91.2, 93.4, 107.4, 114.4, 117.9, 125.1, 125.7, 127.3, 129.3, 130.3, 132.2, 132.4, 133.0, 148.5; HRMS (FAB) calcd for $C_{14}H_{10}BrN$ [M^+] 270.9997, found 270.9987.

Synthesis of 2-{[2-(Cyclopentylethynyl)phenyl]ethynyl}aniline (1o). To a solution of **S3** (0.27 g, 0.99 mmol) in THF (1.7 mL) were successively added diisopropylamine (0.69 mL, 4.9 mmol), CuI (11 mg, 0.059 mmol), $PdCl_2(PhCN)_2$ (23 mg, 0.059 mmol), $P(t\text{-}Bu)_3$ (29 μL, 0.12 mmol), and ethynylcyclopentane (**S4a**) (0.13 mL, 1.0 mmol) at room temperature under argon. The mixture was stirred at room temperature for 16 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (5:1) to afford **1o** (0.14 g, 50% yield) as a brown solid, which was recrystallized from *n*-hexane to give pure **1o** as brown crystals: mp 62−63 °C; IR (neat) 3474 (NH), 3372 (NH), 2208 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57−1.64 (m, 2H, *c*-pentyl), 1.71−1.80 (m, 4H, *c*-pentyl), 1.97−2.05 (m, 2H, *c*-pentyl), 2.84−2.92 (m, 1H, *c*-pentyl), 4.47 (br s, 2H, NH_2), 6.69−6.73 (m, 2H, Ar), 7.12−7.16 (m, 1H, Ar), 7.21−7.27 (m, 4H, Ar), 7.37 (dd, J = 7.7, 1.6 Hz, 1H, Ar), 7.42−7.44 (m, 1H, Ar), 7.47−7.51 (m, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.2 (2C), 31.1, 34.2 (2C), 79.6, 89.7, 94.1, 99.0, 108.0, 114.2, 117.8, 125.6, 126.2, 127.4, 127.8, 129.9, 131.5, 132.1, 132.3, 148.1. Anal. Calcd for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.27; H, 6.70; N, 4.82.



Synthesis of 5-Chloro-2-{[2-(phenylethynyl)phenyl]ethynyl}aniline (1r). To a solution of 5-chloro-2-iodoaniline (**S2g**) (0.14 g, 0.55 mmol) in THF (0.42 mL) were successively added Et_3N

(0.38 mL, 2.8 mmol), CuI (2.6 mg, 0.014 mmol), $PdCl_2(PPh_3)_2$ (9.7 mg, 0.014 mmol), and 1-ethynyl-2-(2-phenylethynyl)-benzene (**S5**) (0.11 g, 0.55 mmol) in THF (0.50 mL) at room temperature under argon. The mixture was stirred at room temperature for 21 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on amino silica gel with *n*-hexane/EtOAc (6:1) to afford **1r** (70 mg, 39% yield) as a brown solid: IR (neat) 3460 (NH), 3363 (NH), 2200 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.43 (br s, 2H, NH_2), 6.65−6.67 (m, 2H, Ar), 7.28−7.39 (m, 6H, Ar), 7.54−7.60 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.7, 89.4, 93.1, 94.4, 106.0, 113.7, 117.8, 122.8, 125.0, 125.5, 127.9, 128.2, 128.4 (2C), 128.7, 131.4, 131.8 (2C), 132.1, 132.8, 135.5, 149.0; HRMS (FAB) calcd for $C_{22}H_{13}ClN$ $[M - H]^-$ 326.0737, found 326.0739.



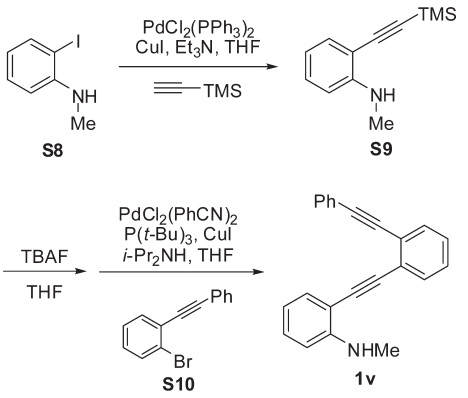
Synthesis of 1-(Cyclohexylethynyl)-2-ethynylbenzene (S7). To a solution of 2-(2-bromophenyl)ethynyltrimethylsilane (**S6**) (0.86 g, 3.4 mmol) in THF (6.8 mL) were successively added diisopropylamine (2.4 mL, 17 mmol), CuI (39 mg, 0.21 mmol), $PdCl_2(PhCN)_2$ (79 mg, 0.21 mmol), P(*t*-Bu)$_3$ (99 μL, 0.41 mmol), and cyclohexylacetylene (**S4b**) (0.48 mL, 3.8 mmol) at room temperature under argon. The mixture was stirred at room temperature for 2 h and concentrated in vacuo. To the residue were added THF (6.5 mL) and TBAF (1 M solution in THF; 3.5 mL, 3.5 mmol). The mixture was stirred at room temperature for 2.5 h and quenched by addition of saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (20:1) to afford **S7** (0.53 g, 75% yield in two steps) as a brown oil: IR (neat) 3289 (C≡*CH*), 2224 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34−1.44 (m, 3H, Cy), 1.50−1.64 (m, 3H, Cy), 1.76−1.91 (m, 4H, Cy), 2.65−2.71 (m, 1H, Cy), 3.27 (s, 1H, C≡CH), 7.18−7.29 (m, 2H, Ar), 7.39−7.41 (m, 1H, Ar), 7.47 (dd, J = 7.7, 1.3 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6 (2C), 26.0, 29.7, 32.5 (2C), 79.1, 80.4, 82.5, 99.0, 124.5, 127.0, 127.2, 128.4, 131.7, 132.4; HRMS (FAB) calcd for $C_{16}H_{16}$ $[M^+]$ 208.1252, found 208.1251.

Synthesis of 5-Chloro-2-{[2-(cyclohexylethynyl)phenyl]ethynyl}-aniline (1s). To a solution of **S2g** (0.12 g, 0.48 mmol) in THF (0.30 mL) were successively added Et_3N (0.34 mL, 2.4 mmol), CuI (4.6 mg, 0.024 mmol), $PdCl_2(PPh_3)_2$ (17 mg, 0.024 mmol), and **S7** (0.11 g, 0.55 mmol) in THF (0.50 mL) at room temperature under argon. The mixture was stirred at room temperature for 16 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on amino silica gel with *n*-hexane/EtOAc (5:1) to afford **1s** (0.11 g, 71% yield) as a colorless solid, which was recrystallized from *n*-hexane to give pure **1s** as colorless crystals: mp 90−91 °C; IR (neat) 3481 (NH), 3376 (NH), 2205 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30−1.40 (m, 2H, Cy), 1.52−1.60 (m, 4H, Cy), 1.73−1.81 (m, 2H, Cy), 1.86−1.92 (m, 2H, Cy), 2.60−2.67 (m, 1H, Cy), 4.53 (br s, 2H, NH_2), 6.68 (dd, J = 8.2, 1.6 Hz, 1H, Ar), 6.73 (d, J = 2.0 Hz, 1H, Ar), 7.23−7.29 (m, 3H, Ar), 7.43−7.51 (m, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.9 (2C), 26.0, 30.1, 32.8 (2C), 80.1, 88.6, 94.8, 98.9, 106.6, 113.9, 118.0, 125.2, 126.2, 127.5, 128.0, 131.5, 132.4, 133.0, 135.5, 149.0. Anal. Calcd for $C_{22}H_{20}ClN$: C, 79.15; H, 6.04; N, 4.20. Found: C, 79.14; H, 5.99; N, 4.25.

Synthesis of 2-{[2-(Cyclohexylethynyl)phenyl]ethynyl}-5-(trifluoromethyl)aniline (1t). To a solution of 2-bromo-5-(trifluoromethyl)aniline (**S2h**) (76 μg, 0.54 mmol) in THF (0.54 mL) were successively added diisopropylamine (0.38 mL, 2.7 mmol), CuI (6.2 mg, 0.032 mmol), $PdCl_2(PhCN)_2$ (12 mg, 0.032 mmol), P(*t*-Bu)$_3$ (16 μL, 0.065 mmol), and **S7** (0.13 mL, 1.0 mmol) in THF (0.60 mL) at room temperature under argon. The mixture was stirred at room temperature for 22 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (8:1) to afford **1t** (0.14 g, 50% yield) as a brown solid: IR (neat) 3481 (NH), 3382 (NH), 2294 (C≡C), 2221 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31−1.40 (m, 3H, Cy), 1.54−1.58 (m, 3H, Cy), 1.74−1.81 (m, 2H, Cy), 1.87−1.92 (m, 2H, Cy), 2.61−2.67 (m, 1H, Cy), 4.65 (br s, 2H, NH_2), 6.92−6.96 (m, 2H, Ar), 7.26−7.29 (m, 2H, Ar), 7.43−7.53 (m, 3H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0 (2C), 26.0, 30.1, 32.9 (2C), 80.0, 88.2, 95.9, 99.1, 110.6, 110.6, 111.2, 114.1, 114.2, 124.9, 126.4, 127.5, 128.4, 131.7, 132.4, 132.5, 148.1; HRMS (FAB) calcd for $C_{23}H_{20}F_3N$ $[M^+]$ 367.1548, found 367.1553.

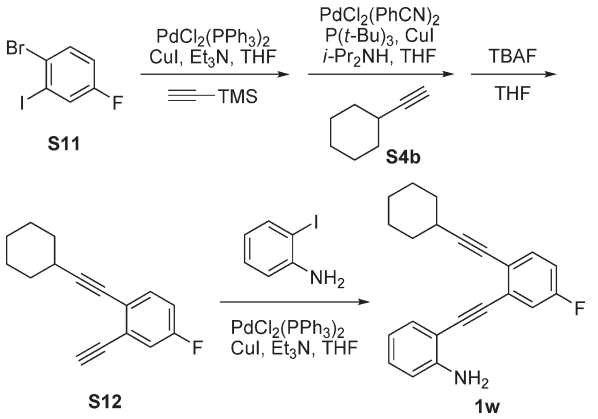
Synthesis of *tert*-Butyl 2-{[2-(Phenylethynyl)phenyl]ethynyl}-phenylcarbamate (1u). A mixture of **1c** (0.21 g, 0.73 mmol) and $(Boc)_2O$ (0.24 g, 1.1 mmol) in THF (2.0 mL) was refluxed under stirring for 18 h under argon. Concentration under reduced pressure followed by purification through a pad of silica gel with *n*-hexane/EtOAc (10:1) afforded **1u** (0.28 g, 97% yield) as a colorless solid: IR (neat) 3387 (NH), 2294 (C≡C), 2256 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 [s, 9H, $C(CH_3)_3$], 7.00 (td, J = 7.6, 1.0 Hz, 1H, Ar), 7.31−7.38 (m, 6H, Ar), 7.49−7.54 (m, 3H, Ar), 7.57−7.62 (m, 2H, Ar), 8.24 (d, J = 8.5 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 80.7, 85.3, 88.2, 88.7, 94.1, 94.9, 111.0, 117.6, 122.1, 123.2, 125.1, 126.0, 128.2, 128.5 (2C), 128.6, 128.6, 130.0, 131.8, 131.8, 132.0 (2C), 132.1, 139.9, 146.9, 152.5;

HRMS (FAB) calcd for $C_{27}H_{23}NO_2$ [M^+] 393.1729, found 393.1728.



Synthesis of *N*-Methyl-2-[(trimethylsilyl)ethynyl]aniline (S9). To a solution of 2-iodo-*N*-methylaniline (**S8**) (0.88 g, 3.8 mmol) in THF (7.5 mL) were successively added Et_3N (2.6 mL, 19 mmol), CuI (18 mg, 0.095 mmol), $PdCl_2(PPh_3)_2$ (67 mg, 0.095 mmol), and trimethylsilylacetylene (0.55 mL, 4.0 mmol) at room temperature under argon. The mixture was stirred at room temperature for 16 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (10:1) to afford **S9** (0.77 g, 100% yield) as a pale yellow oil: IR (neat) 3422 (NH), 2143 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.27 [s, 9H, $Si(CH_3)_3$], 2.91 (s, 3H, NCH_3), 4.64 (s, 1H, NH), 6.57 (d, J = 8.5 Hz, 1H, Ar), 6.59−6.62 (m, 1H, Ar), 7.22 (ddd, J = 8.6, 7.0, 1.3 Hz, 1H, Ar), 7.30 (dd, J = 7.6, 1.2 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.0 (3C), 30.1, 99.8, 101.9, 106.9, 108.6, 115.8, 130.0, 132.1, 150.0; HRMS (FAB) calcd for $C_{12}H_{17}NSi$ [M^+] 203.1130, found 203.1126.

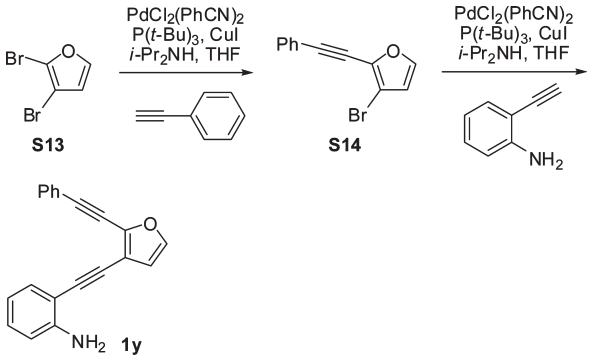
Synthesis of *N*-Methyl-2-{[2-(phenylethynyl)phenyl]ethynyl}-aniline (1v). A mixture of **S9** (0.73 g, 3.6 mmol) and TBAF (1 M solution in THF; 4.3 mL, 4.3 mmol) in THF (1.8 mL) was stirred at room temperature for 17 h, quenched by addition of saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (50:1) to afford 2-ethynyl-*N*-methylaniline (0.47 g). To a solution of 1-bromo-2-(2-phenylethynyl)benzene (**S10**) (0.27 g, 1.1 mmol) in THF (1.0 mL) were successively added diisopropylamine (0.74 mL, 5.3 mmol), CuI (12 mg, 0.064 mmol), $PdCl_2(PhCN)_2$ (24 mg, 0.064 mmol), $P(t\text{-}Bu)_3$ (31 μL, 0.13 mmol), and 2-ethynyl-*N*-methylaniline (0.15 g, 1.1 mmol) in THF (0.80 mL) at room temperature under argon. The mixture was stirred at room temperature for 46 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/Et_2O (50:1) to afford **1v** (0.13 g, 40% yield in two steps) as a pale yellow solid: IR (neat) cm^{-1} 3409 (NH), 2205 (C≡C); ^1H NMR (400 MHz, $CDCl_3$) δ 2.51 (d, J = 5.1 Hz, 3H, NCH_3), 4.97 (d, J = 3.9 Hz, 1H, NH), 6.54 (d, J = 8.3 Hz, 1H, Ar), 6.64 (ddd, J = 7.5, 7.5, 1.1 Hz, 1H, Ar), 7.20−7.37 (m, 6H, Ar), 7.40 (dd, J = 7.5, 1.5 Hz, 1H, Ar), 7.55−7.59 (m, 4H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.1, 88.8, 90.8, 93.2, 94.0, 107.1, 108.9, 116.0, 122.9, 125.0, 126.1, 127.8, 128.3, 128.5 (2C), 128.7, 130.4, 131.5, 131.9, 132.1 (2C), 132.2, 150.1; HRMS (FAB) calcd for $C_{23}H_{16}N$ [$M - H]^-$ 306.1283, found 306.1280.



Synthesis of 1-(Cyclohexylethynyl)-2-ethynyl-4-fluorobenzene (S12). To a solution of 1-bromo-4-fluoro-2-iodobenzene (**S11**) (0.22 mL, 1.7 mmol) in THF (3.0 mL) were successively added Et_3N (1.2 mL, 8.3 mmol), CuI (16 mg, 0.083 mmol), $PdCl_2(PPh_3)_2$ (58 mg, 0.083 mmol), and trimethylsilylacetylene (0.24 mL, 1.7 mmol) at room temperature under argon. The mixture was stirred at room temperature for 16 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane to afford [(2-bromo-5-fluorophenyl)ethynyl]trimethylsilane (0.43 g, 95% yield) as a pale yellow oil. To a solution of this compound (0.22 g, 0.81 mmol) in THF (1.3 mL) were successively added diisopropylamine (0.56 mL, 4.0 mmol), CuI (9.2 mg, 0.048 mmol), $PdCl_2(PhCN)_2$ (19 mg, 0.048 mmol), $P(t\text{-}Bu)_3$ (23 μL, 0.097 mmol), and **S4b** (0.11 mL, 0.89 mmol) at room temperature under argon. The mixture was stirred at room temperature for 17 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (40:1) to afford {[2-(cyclohexylethynyl)-5-fluorophenyl]ethynyl}-trimethylsilane (0.25 g, 100% yield) as a brown oil. A mixture of this compound (0.25 g, 0.81 mmol) and TBAF (1 M solution in THF; 0.89 mL, 0.89 mmol) in THF (4.0 mL) was stirred at room temperature for 2 h and quenched by addition of saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (40:1) to afford **S12** (0.12 g, 61% yield in three steps) as a brown oil: IR (neat) 3304 (C≡*CH*), 2227 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34−1.41 (m, 3H, Cy), 1.50−1.62 (m, 3H, Cy), 1.76−1.89 (m, 4H, Cy), 2.63−2.69 (m, 1H, Cy), 3.30 (s, 1H, C≡CH), 6.97 (ddd, J = 8.4, 8.4, 2.7 Hz, 1H, Ar), 7.16 (dd, J = 9.0, 2.7 Hz, 1H, Ar), 7.37 (dd, J = 8.4, 5.7 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7 (2C), 26.0, 29.7, 32.5 (2C), 78.1, 81.5 (2C), 98.6, 116.1 (d, J = 21.6 Hz), 119.1 (d, J = 24.0 Hz), 123.5, 126.3 (d, J = 9.6 Hz), 133.4 (d, J = 8.4 Hz), 161.1 (d, J = 248.3 Hz); HRMS (FAB) calcd for $C_{16}H_{15}F$ [M^+] 226.1158, found 226.1163.

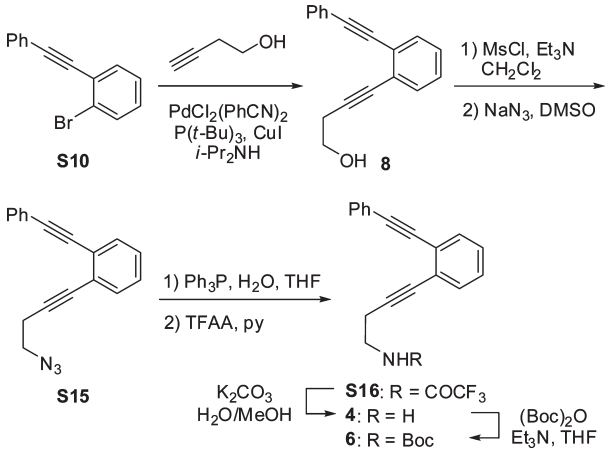
Synthesis of 2-{[2-(Cyclohexylethynyl)-5-fluorophenyl]ethynyl}-aniline (1w). To a solution of **S12** (0.10 g, 0.45 mmol) in Et_3N (4.0 mL) were successively added CuI (8.6 mg, 0.045 mmol), $PdCl_2(PPh_3)_2$ (16 mg, 0.023 mmol), and 2-iodoaniline (99 mg,

0.45 mmol) at room temperature under argon. The mixture was stirred at room temperature for 2.5 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (5:1) to afford **1w** (81 mg, 56% yield) as a brown oil: IR (neat) 3480 (NH), 3377 (NH), 2203 (C≡C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30−1.38 (m, 3H, Cy), 1.51−1.59 (m, 3H, Cy), 1.73−1.79 (m, 2H, Cy), 1.87−1.89 (m, 2H, Cy), 2.60−2.65 (m, 1H, Cy), 4.45 (s, 2H, NH_2), 6.69−6.73 (m, 2H, Ar), 6.94 (ddd, J = 8.4, 8.4, 2.5 Hz, 1H, Ar), 7.15 (dd, J = 8.4, 8.4 Hz, 1H, Ar), 7.18 (dd, J = 9.2, 2.3 Hz, 1H, Ar), 7.36 (d, J = 7.4 Hz, 1H, Ar), 7.40 (dd, J = 8.4, 5.7 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8 (2C), 25.9, 29.9, 32.7 (2C), 79.0, 90.6, 92.9, 98.2, 107.3, 114.2, 115.3 (d, J = 21.6 Hz), 117.7, 118.0 (d, J = 24.0 Hz), 122.3 (d, J = 2.4 Hz), 127.3 (d, J = 10.8 Hz), 130.1, 132.1, 133.9 (d, J = 9.6 Hz), 148.1, 161.3 (d, J = 248.3 Hz); HRMS (FAB) calcd for $C_{22}H_{20}FN$ [M^+] 317.1580, found 317.1572.



Synthesis of 3-Bromo-2-(phenylethynyl)furan (S14). To a solution of 2,3-dibromofuran (**S13**) (1.0 g, 4.6 mmol) in THF (9.3 mL) were successively added diisopropylamine (3.2 mL, 23 mmol), CuI (53 mg, 0.28 mmol), $PdCl_2(PhCN)_2$ (0.11 g, 0.28 mmol), P(*t*-Bu)$_3$ (0.14 mL, 0.56 mmol), and phenylacetylene (0.56 mL, 5.1 mmol) at room temperature under argon. The mixture was stirred at room temperature for 15 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (20:1) to give **S14** (0.45 g, 39% yield) as a colorless oil: IR (neat) cm^{-1}: 2217 (C≡C); ^1H NMR (500 MHz, $CDCl_3$) δ 6.51 (d, J = 2.3 Hz, 1H, Ar), 7.35−7.37 (m, 4H, Ar), 7.54−7.57 (m, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.5, 97.1, 105.8, 114.7, 121.9, 128.4 (2C), 129.0, 131.6 (2C), 136.5, 143.7; HRMS (FAB) calcd for $C_{12}H_7BrO$ [M^+] 245.9680; found 245.9680.

Synthesis of 2-{[2-(Phenylethynyl)furan-3-yl]ethynyl}aniline (1y). To a solution of **S14** (0.41 g, 1.7 mmol) in THF (1.6 mL) were successively added diisopropylamine (1.2 mL, 8.4 mmol), CuI (19 mg, 0.10 mmol), $PdCl_2(PhCN)_2$ (38 mg, 0.10 mmol), P(*t*-Bu)$_3$ (49 μL, 0.20 mmol), and 2-ethynylaniline (0.27 mL, 2.3 mmol) in THF (1.2 mL) at room temperature under argon. The mixture was stirred at room temperature for 14 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on amino silica gel with *n*-hexane/EtOAc (5:1) to afford **1y** (0.16 g, 34% yield) as a pale brown solid, which was recrystallized from *n*-hexane to give pure **1y** as pale brown crystals: mp 68−69 °C; IR (neat) 3479 (NH), 3382 (NH), 2203 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (s, 2H, NH_2), 6.55 (dd, J = 2.0, 0.5 Hz, 1H, Ar), 6.69−6.73 (m, 2H, Ar), 7.14 (td, J = 7.7, 1.4 Hz, 1H, Ar), 7.35−7.39 (m, 5H, Ar), 7.54−7.58 (m, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.8, 86.1, 91.6, 97.6, 107.7, 113.1, 113.2, 114.4, 118.0, 122.1, 128.6 (2C), 129.1, 130.0, 131.8 (2C), 131.9, 140.0, 143.5, 148.0. Anal. Calcd for $C_{20}H_{13}NO$: C, 84.78; H, 4.62; N, 4.94. Found: C, 85.04; H, 4.59; N, 4.95.



Synthesis of 4-[2-(Phenylethynyl)phenyl]but-3-yn-1-ol (8). To a solution of **S10** (0.52 g, 2.0 mmol) in THF (3.4 mL) were successively added diisopropylamine (1.4 mL, 10 mmol), CuI (23 mg, 0.12 mmol), $PdCl_2(PhCN)_2$ (47 mg, 0.12 mmol), P(*t*-Bu)$_3$ (59 μL, 0.24 mmol), and 3-butyn-1-ol (0.17 mL, 2.1 mmol) at room temperature under argon. The mixture was stirred at room temperature for 14 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to afford **8** (0.36 g, 72% yield) as a pale brown oil: IR (neat) 3359 (OH), 2217 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.07 (t, J = 5.9 Hz, 1H, OH), 2.77 (t, J = 6.1 Hz, 2H, CH_2CH_2OH), 3.82 (td, J = 5.7, 5.7 Hz, 2H, CH_2CH_2OH), 7.25−7.28 (m, 2H, Ar), 7.34−7.39 (m, 3H, Ar), 7.43−7.46 (m, 1H, Ar), 7.51−7.59 (m, 3H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1, 61.0, 81.5, 88.3, 90.8, 93.1, 123.0, 125.6, 125.8, 127.7, 128.0, 128.4 (2C), 128.5, 131.6 (2C), 131.7, 131.9; HRMS (FAB) calcd for $C_{18}H_{14}O$ [M^+] 246.1045, found 246.1046.

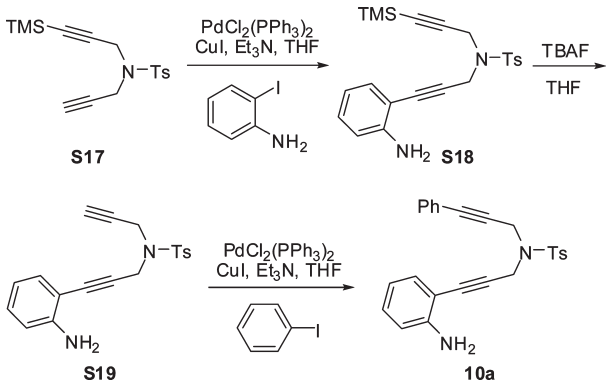
Synthesis of 1-(4-Azidobut-1-ynyl)-2-(phenylethynyl)benzene (S15). To a solution of **8** (0.26 g, 1.1 mmol) in CH_2Cl_2 (5.5 mL) were successively added Et_3N (0.18 mL, 1.3 mmol) and MsCl (87 μL, 1.1 mmol) at 0 °C for 1.5 h under argon. The mixture was stirred at room temperature for 24 h. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. To the residue were added DMSO (2.5 mL) and NaN_3 (0.11 g, 1.6 mmol). The mixture was stirred at room temperature for 18 h and quenched by addition of saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (10:1) to give **S15** (0.18 g, 62% yield in two steps) as a pale yellow oil: IR (neat) 2217 (C≡C), 2102 (N_3) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.80

(t, J = 7.0 Hz, 2H, CH_2CH$_2$N$_3$), 3.50 (t, J = 7.0 Hz, 2H, CH$_2$CH_2N$_3$), 7.23−7.30 (m, 2H, Ar), 7.34−7.38 (m, 3H, Ar), 7.44−7.46 (m, 1H, Ar), 7.50−7.57 (m, 3H, Ar); ^{13}C NMR (125 MHz, CDCl$_3$) δ 20.7, 50.0, 81.3, 88.2, 90.0, 93.1, 123.3, 125.6, 125.8, 127.8, 127.9, 128.4 (2C), 128.4, 131.6 (2C), 131.8, 131.9; HRMS (FAB) calcd for $C_{18}H_{13}N_3$ [M$^+$] 271.1109, found 271.1104.

Synthesis of 2,2,2-Trifluoro-*N*-{4-[2-(phenylethynyl)phenyl]-but-3-ynyl}acetamide (S16). To a solution of **S15** (0.34 g, 1.2 mmol) in THF (2.0 mL) were successively added PPh$_3$ (0.33 g, 1.2 mmol) in THF (1.0 mL) and H$_2$O (45 μL, 2.5 mmol) at room temperature. The mixture was stirred at room temperature for 23 h and concentrated in vacuo. To the residue were added pyridine (5.0 mL) and TFAA (0.19 mL, 1.4 mmol). The mixture was stirred at room temperature for 12 h and quenched by addition of H$_2$O and brine, dried over Na$_2$SO$_4$, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to afford **S16** (0.22 g, 53% yield in two steps) as a colorless solid, which was recrystallized from *n*-hexane/EtOAc to give pure **S16** as colorless crystals: mp 80−81 °C; IR (neat) 3323 (NH), 2217 (C≡C), 1697 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.76−2.81 (m, 2H, C≡CCH_2CH$_2$), 3.58−3.64 (m, 2H, C≡CCH$_2$-CH_2), 6.70 (br s, 1H, NH), 7.24−7.27 (m, 1H, Ar), 7.28−7.31 (m, 1H, Ar), 7.34−7.37 (m, 3H, Ar), 7.41−7.45 (m, 1H, Ar), 7.49−7.55 (m, 3H, Ar); ^{13}C NMR (125 MHz, CDCl$_3$) δ 20.1, 38.6, 81.9, 88.1, 89.5, 93.0, 115.5 (q, J = 286.7 Hz), 122.9, 125.2, 125.8, 128.0, 128.1, 128.5 (2C), 128.6, 131.5 (2C), 131.8, 131.9, 162.0 (q, J = 34.4 Hz). Anal. Calcd for $C_{20}H_{14}F_3NO$: C, 70.38; H, 4.13; N, 4.10. Found C, 70.54; H, 4.12; N, 4.08.

Synthesis of 4-[2-(Phenylethynyl)phenyl]but-3-yn-1-amine (4). To a solution of **S16** (0.13 g, 0.38 mmol) in MeOH (3.4 mL) were successively added K$_2$CO$_3$ (0.26 g, 1.9 mmol) and H$_2$O (0.21 mL) at room temperature for 12 h. The reaction mixture was filtrated, and concentrated in vacuo. The residue was purified by column chromatography on amino silica gel with *n*-hexane/EtOAc (1:2) to give **4** (89 mg, 97% yield) as a pale yellow oil: IR (neat) 3359 (NH), 3287 (NH), 2216 (C≡C) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.64 (t, J = 6.2 Hz, 2H, CH_2CH$_2$NH$_2$), 2.94 (t, J = 6.2 Hz, 2H, CH$_2$CH_2NH$_2$), 7.25−7.29 (m, 2H, Ar), 7.33−7.38 (m, 3H, Ar), 7.42−7.46 (m, 1H, Ar), 7.51−7.56 (m, 3H, Ar); ^{13}C NMR (CDCl$_3$) δ 24.8, 41.2, 80.9, 88.4, 92.3, 92.9, 123.2, 125.7, 126.0, 127.5, 128.0, 128.4 (2C), 128.4, 131.6 (2C), 131.8, 131.8; HRMS (FAB) calcd for $C_{18}H_{16}N$ [M + H]$^+$ 246.1283, found 246.1279.

Synthesis of *tert*-Butyl 4-(2-(Phenylethynyl)phenyl)but-3-ynylcarbamate (6). To a solution of **4** (78 mg, 0.32 mmol) in THF (0.50 mL) were successively added Et$_3$N (44 μL, 0.32 mmol) and (Boc)$_2$O (0.10 g, 0.47 mmol) in THF (1.0 mL) at room temperature under argon. The mixture was stirred at room temperature for 23 h and quenched by addition of H$_2$O at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na$_2$SO$_4$, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to afford **6** (96 mg, 88% yield) as a colorless solid: IR (neat) 3358 (NH), 2294 (C≡C), 2217 (C≡C), 1698 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.40 [s, 9H, (CH$_3$)$_3$], 2.69 (t, J = 6.3 Hz, 2H, C≡CCH_2CH$_2$), 3.39 (td, J = 5.9, 5.9 Hz, 2H, C≡CCH$_2$CH_2), 4.94−5.02 (br m, 1H, NH), 7.24−7.29 (m, 2H, Ar), 7.34−7.37 (m, 3H, Ar), 7.43−7.45 (m, 1H, Ar), 7.51−7.56 (m, 3H, Ar); ^{13}C NMR (125 MHz, CDCl$_3$) δ 21.2, 28.3 (3C), 39.5, 79.3, 80.8, 88.3, 91.6, 93.0, 123.2, 125.8, 125.8, 127.7, 128.0, 128.4 (2C), 128.4, 131.6 (2C), 131.8, 131.9, 155.7; HRMS (FAB) calcd for $C_{23}H_{23}NO_2$ [M$^+$] 345.1729, found 345.1719.

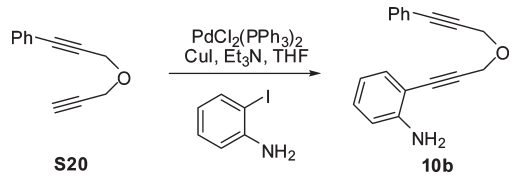


Synthesis of *N*-[3-(2-Aminophenyl)prop-2-ynyl]-4-methyl-*N*-[3-(trimethylsilyl)prop-2-ynyl]benzenesulfonamide (S18). To a solution of 4-methyl-*N*-prop-2-ynyl-*N*-(3-trimethylsilylprop-2-ynyl)benzenesulfonamide (**S17**) (0.28 g, 0.86 mmol) in THF (2.7 mL) were successively added Et$_3$N (0.57 mL, 4.1 mmol), CuI (4.7 mg, 0.025 mmol), PdCl$_2$(PPh$_3$)$_2$ (17 mg, 0.025 mmol), and 2-iodoaniline (0.18 g, 0.82 mmol) at room temperature under argon. The mixture was stirred at room temperature for 16 h and quenched by addition of saturated aqueous NH$_4$Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na$_2$SO$_4$, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (5:1) to afford **S18** (0.17 g, 50% yield) as a brown solid: IR (neat) 3482 (NH), 3382 (NH), 2175 (C≡C), 1349 (S=O), 1160 (S=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.06 [s, 9H, Si(CH$_3$)$_3$], 2.38 (s, 3H, C$_6$H$_4$CH_3), 4.10 (br s, 2H, NH$_2$), 4.23 (s, 2H, CH$_2$), 4.40 (s, 2H, CH$_2$), 6.60−6.65 (m, 2H, Ar), 7.05 (dd, J = 7.7, 1.6 Hz, 1H, Ar), 7.08−7.12 (m, 1H, Ar), 7.28 (d, J = 8.5 Hz, 2H, Ar), 7.75 (d, J = 8.3 Hz, 2H, Ar); ^{13}C NMR (100 MHz, CDCl$_3$) δ 0.0 (3C), 21.8, 37.7, 37.8, 82.9, 87.2, 91.6, 98.1, 107.1, 114.6, 117.9, 128.3 (2C), 130.0 (2C), 130.3, 132.6, 135.6, 144.2, 148.6; HRMS (FAB) calcd for $C_{22}H_{27}N_2O_2SSi$ [M + H]$^+$ 411.1563, found 411.1557.

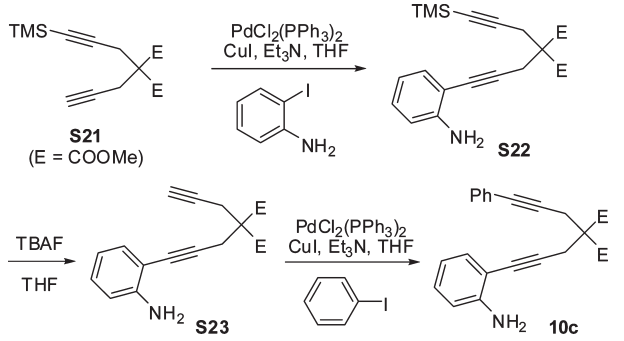
Synthesis of *N*-[3-(2-Aminophenyl)prop-2-ynyl]-4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide (S19). A mixture of **S18** (0.15 g, 0.36 mmol) and TBAF (1 M solution in THF; 0.39 mL, 0.39 mmol) in THF (1.8 mL) was stirred at room temperature for 40 min and quenched by addition of saturated aqueous NH$_4$Cl and brine, dried over Na$_2$SO$_4$, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to give **S19** (0.17 g, 50% yield) as a brown solid: IR (neat) 3478 (NH), 3380 (NH), 3285 (C≡C*H*), 2216 (C≡C), 1348 (S=O), 1160 (S=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.19 (t, J = 2.3 Hz, 1H, C≡CH), 2.38 (s, 3H, C$_6$H$_4$CH_3), 4.07 (br s, 2H, NH$_2$), 4.21 (d, J = 2.3 Hz, 2H, CH$_2$), 4.44 (s, 2H, CH$_2$), 6.60−6.65 (m, 2H, Ar), 7.01 (d, J = 7.6 Hz, 1H, Ar), 7.07−7.12 (m, 1H, Ar), 7.26−7.30 (m, 2H, Ar), 7.76 (d, J = 8.3 Hz, 2H, Ar); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.5, 36.5, 37.4, 74.0, 82.8, 86.6, 100.6, 106.6, 114.2, 117.6, 127.9 (2C), 129.6 (2C), 130.0, 132.3, 135.2, 144.0, 148.2; HRMS (FAB) calcd for $C_{19}H_{18}N_2O_2S$ [M$^+$] 338.1089, found 338.1095.

Synthesis of *N*-[3-(2-Aminophenyl)prop-2-ynyl]-4-methyl-*N*-(3-phenylprop-2-ynyl)benzenesulfonamide (10a). To a solution of **S19** (76 mg, 0.22 mmol) in Et$_3$N (2.2 mL) were successively added CuI (4.2 mg, 0.022 mmol), PdCl$_2$(PPh$_3$)$_2$ (7.8 mg, 0.011 mmol), and iodobenzene (25 μL, 0.22 mmol) at room temperature under argon. The mixture was stirred at room temperature for 14 h and quenched by addition of saturated aqueous NH$_4$Cl

at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to afford **10a** (70 mg, 75% yield) as a brown solid: IR (neat) 3474 (NH), 3382 (NH), 2212 (C≡C), 1349 (S=O), 1161 (S=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H, $C_6H_4CH_3$), 4.09 (br s, 2H, NH_2), 4.45 (s, 2H, CH_2), 4.47 (s, 2H, CH_2), 6.59−6.64 (m, 2H, Ar), 7.05 (dd, J = 7.7, 1.3 Hz, 1H, Ar), 7.09 (td, J = 7.7, 1.5 Hz, 1H, Ar), 7.18−7.32 (m, 7H, Ar), 7.78−7.81 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 37.5, 37.7, 81.7, 82.7, 85.9, 87.0, 106.7, 114.2, 117.6, 122.1, 127.9 (2C), 128.2 (2C), 128.5, 129.6 (2C), 130.0, 131.6 (2C), 132.3, 135.3, 143.9, 148.2; HRMS (FAB) calcd for $C_{25}H_{22}N_2O_2S$ [M^+] 414.1402, found 414.1404.



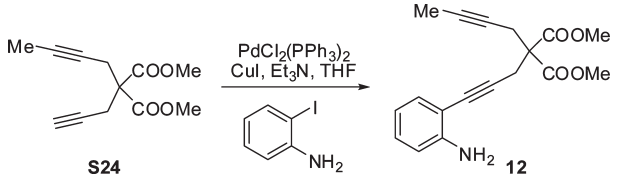
Synthesis of 2-[3-(3-Phenylprop-2-ynyloxy)prop-1-ynyl]aniline (10b). To a solution of 2-iodoaniline (0.40 g, 1.8 mmol) in THF (2.0 mL) were successively added Et_3N (1.3 mL, 9.2 mmol), CuI (8.7 mg, 0.046 mmol), $PdCl_2(PPh_3)_2$ (32 mg, 0.046 mmol), and [3-(prop-2-ynyloxy)prop-1-ynyl]benzene (**S20**) (0.33 g, 1.9 mmol) in THF (1.0 mL) at room temperature under argon. The mixture was stirred at room temperature for 4 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to give **10b** (0.18 g, 37% yield) as a brown oil: IR (neat) 3475 (NH), 3380 (NH), 2246 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (s, 2H, NH_2), 4.55 (s, 2H, CH_2), 4.60 (s, 2H, CH_2), 6.66−6.69 (m, 2H, Ar), 7.11−7.15 (m, 1H, Ar), 7.28−7.34 (m, 4H, Ar), 7.45−7.47 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.3, 57.5, 83.6, 84.3, 86.8, 89.6, 107.0, 114.3, 117.8, 122.4, 128.3 (2C), 128.5, 130.0, 131.8 (2C), 132.5, 148.2; HRMS (FAB) calcd for $C_{18}H_{15}NO$ [M^+] 261.1154, found 261.1158.



Synthesis of Dimethyl 2-[3-(2-Aminophenyl)prop-2-ynyl]-2-[3-(trimethylsilyl)prop-2-ynyl]malonate (S22). To a solution of 2-iodoaniline (0.22 g, 1.0 mmol) in THF (2.0 mL) were successively added Et_3N (0.71 mL, 5.1 mmol), CuI (9.7 mg, 0.051 mmol), $PdCl_2(PPh_3)_2$ (36 mg, 0.051 mmol), and dimethyl 2-(prop-2-ynyl)-2-[3-(trimethylsilyl)prop-2-ynyl]malonate (**S21**) (0.30 g, 1.1 mmol) in THF (2.0 mL) at room temperature under argon. The mixture was stirred at room temperature for 14 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to afford **S22** (0.23 g, 62% yield) as a pale brown solid: IR (neat) 3477 (NH), 3383 (NH), 2179 (C≡C), 1737 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.14 [s, 9H, $Si(CH_3)_3$], 3.06 (s, 2H, CH_2), 3.24 (s, 2H, CH_2), 3.77 (s, 6H, 2 × CO_2CH_3), 4.21 (br s, 2H, NH_2), 6.61−6.66 (m, 2H, Ar), 7.06−7.10 (m, 1H, Ar), 7.21 (dd, J = 7.8, 1.5 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.0 (3C), 24.2, 24.4, 53.1 (2C), 57.2, 80.6, 88.8, 89.0, 100.8, 107.7, 114.2, 117.6, 129.5, 132.2, 148.2, 169.6 (2C); HRMS (FAB) calcd for $C_{20}H_{24}NO_4Si$ [$M - H]^-$ 370.1475, found 370.1485.

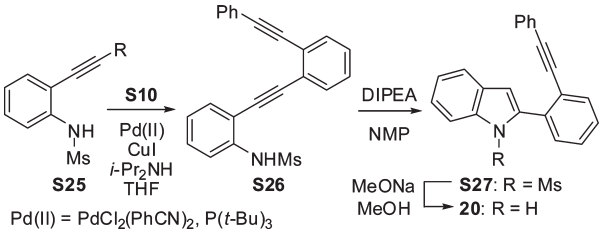
Synthesis of Dimethyl 2-[3-(2-Aminophenyl)prop-2-ynyl]-2-(prop-2-ynyl)malonate (S23). A mixture of **S22** (0.22 g, 0.58 mmol) and TBAF (1 M solution in THF; 0.64 mL, 0.64 mmol) in THF (3.0 mL) was stirred at room temperature for 1.5 h and quenched by addition of saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to give **S23** (0.12 g, 69% yield) as a pale brown solid: IR (neat) 3476 (NH), 3381 (NH), 3288 (C≡*CH*), 2260 (C≡C), 1734 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.05 (t, J = 2.7 Hz, 1H, C≡CH), 3.06 (d, J = 2.7 Hz, 2H, CH_2), 3.27 (s, 2H, CH_2), 3.79 (s, 6H, 2 × CO_2CH_3), 4.20 (br s, 2H, NH_2), 6.62−6.67 (m, 2H, Ar), 7.06−7.11 (m, 1H, Ar), 7.21 (dd, J = 7.8, 1.5 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 24.1, 53.2 (2C), 56.8, 71.8, 78.4, 80.7, 88.7, 107.5, 114.2, 117.6, 129.4, 132.1, 148.1, 169.5 (2C); HRMS (FAB) calcd for $C_{17}H_{17}NO_4$ [M^+] 299.1158, found 299.1151.

Synthesis of Dimethyl 2-[3-(2-Aminophenyl)prop-2-ynyl]-2-(3-phenylprop-2-ynyl)malonate (10c). To a solution of **S23** (94 mg, 0.32 mmol) in Et_3N (3.0 mL) were successively added CuI (6.0 mg, 0.032 mmol), $PdCl_2(PPh_3)_2$ (11 mg, 0.016 mmol), and iodobenzene (35 μL, 0.32 mmol) at room temperature under argon. The mixture was stirred at room temperature for 6 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to afford **10c** (0.11 g, 93% yield) as a pale brown solid: IR (neat) 3482 (NH), 3384 (NH), 2295 (C≡C), 2222 (C≡C), 1729 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.27 (s, 2H, CH_2), 3.32 (s, 2H, CH_2), 3.81 (s, 6H, 2 × CO_2CH_3), 4.25 (br s, 2H, NH_2), 6.62−6.67 (m, 2H, Ar), 7.07−7.11 (m, 1H, Ar), 7.22 (dd, J = 7.6, 1.2 Hz, 1H, Ar), 7.26−7.29 (m, 3H, Ar), 7.36−7.39 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 24.3, 53.1 (2C), 57.2, 80.7, 83.7, 83.9, 88.9, 107.6, 114.2, 117.6, 123.0, 128.1, 128.2 (2C), 129.4, 131.7 (2C), 132.1, 148.1, 169.6 (2C); HRMS (FAB) calcd for $C_{23}H_{22}NO_4$ [$M + H]^+$ 376.1549, found 376.1553.



Synthesis of Dimethyl 2-[3-(2-Aminophenyl)prop-2-ynyl]-2-(but-2-ynyl)malonate (12). To a solution of 2-iodoaniline (0.13 g, 0.59 mmol) in THF (1.2 mL) were successively added Et_3N (0.41 mL, 3.0 mmol), CuI (5.6 mg, 0.030 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.030 mmol), and dimethyl 2-(but-2-ynyl)-2-(prop-2-ynyl)malonate (**S24**) (0.14 g, 0.62 mmol) in THF

(1.2 mL) at room temperature under argon. The mixture was stirred at room temperature for 20 h and quenched by addition of saturated aqueous NH_4Cl at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to give **12** (68 mg, 37% yield) as a brown oil: IR (neat) 3481 (NH), 3382 (NH), 2253 (C≡C), 1734 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.77 (t, J = 2.4 Hz, 3H, $C{\equiv}CCH_3$), 2.99 (q, J = 2.4 Hz, 2H, CH_2), 3.24 (s, 2H, CH_2), 3.78 (s, 6H, 2 × CO_2CH_3), 4.22 (br s, 2H, NH_2), 6.61−6.66 (m, 2H, Ar), 7.06−7.10 (m, 1H, Ar), 7.21 (dd, J = 7.6, 1.0 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5, 23.3, 24.1, 53.0 (2C), 57.1, 72.8, 79.4, 80.4, 89.1, 107.6, 114.1, 117.5, 129.3, 132.1, 148.1, 169.8 (2C); HRMS (FAB) calcd for $C_{18}H_{19}NO_4$ [M^+] 313.1314, found 313.1310.



Synthesis of *N*-(2-{[2-(Phenylethynyl)phenyl]ethynyl}phenyl)-methanesulfonamide (S26). To a solution of **S10** (0.31 g, 1.2 mmol) in THF (2.0 mL) were successively added diisopropylamine (0.85 mL, 6.1 mmol), CuI (14 mg, 0.073 mmol), $PdCl_2(PhCN)_2$ (28 mg, 0.073 mmol), P(*t*-Bu)$_3$ (35 μL, 0.15 mmol) and **S25** (0.24 g, 1.3 mmol) at room temperature under argon. The mixture was stirred at room temperature for 19 h, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to give **S26** (0.22 g, 48% yield) as a pale brown sold: IR (neat) 3329 (NH), 2256 (C≡C), 2215 (C≡C), 1338 (S=O), 1155 (S=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.88 (s, 3H, CH_3), 7.16 (td, J = 7.7, 1.1 Hz, 1H, Ar), 7.22 (br s, 1H, NH), 7.32−7.41 (m, 6H, Ar), 7.53−7.62 (m, 6H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.5, 87.5, 87.9, 94.0, 95.3, 114.3, 119.8, 122.7, 124.2, 124.7, 126.0, 128.2, 128.4 (2C), 128.7, 128.9, 130.2, 131.8, 131.8 (2C), 132.3, 132.4, 137.8; HRMS (FAB) calcd for $C_{23}H_{17}NO_2S$ [M^+] 371.0980, found 371.0983.

Synthesis of 1-(Methylsulfonyl)-2-[2-(phenylethynyl)phenyl]-1*H*-indole (S27). To a solution of **S26** (0.20 g, 0.54 mmol) in NMP (2.5 mL) were added *N*,*N*-diisopropylethylamine (0.47 mL, 2.7 mmol). The mixture was stirred at 80 °C for 15 h and quenched by addition of H_2O at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (3:1) to give **S27** (0.18 g, 90% yield) as a pale yellow oil: IR (neat) 2294 (C≡C), 2254 (C≡C), 1370 (S=O), 1171 (S=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.94 (s, 3H, CH_3), 6.85 (s, 1H, Ar), 7.13−7.26 (m, 5H, Ar), 7.34−7.46 (m, 4H, Ar), 7.51−7.53 (m, 1H, Ar), 7.63−7.66 (m, 2H, Ar), 8.11 (dd, J = 8.0, 0.7 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.7, 88.5, 93.2, 113.2, 115.0, 121.1, 122.7, 123.6, 124.2, 125.0, 127.6, 128.3 (2C), 128.4, 128.7, 129.9, 131.3 (2C), 131.5, 131.7, 134.7, 137.0, 139.2; HRMS (FAB) calcd for $C_{23}H_{17}NO_2S$ [M^+] 371.0980, found 371.0978.

Synthesis of 2-[2-(Phenylethynyl)phenyl]-1*H*-indole (20). To a solution of **S27** (74 mg, 0.20 mmol) in MeOH (2.0 mL) was added MeONa (65 mg, 1.2 mmol) at 60 °C. The mixture was stirred at 60 °C for 18 h, and MeONa (32 mg, 0.60 mmol) was added at 80 °C. The reaction mixture was stirred at 80 °C for 19 h and quenched by addition of H_2O at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (6:1) to give **20** (40 mg, 68% yield) as a pale yellow solid: IR (neat) 3430 (NH), 2249 (C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 1.5 Hz, 1H, Ar), 7.11−7.15 (m, 1H, Ar), 7.19−7.23 (m, 1H, Ar), 7.28 (td, J = 7.6, 1.0 Hz, 1H, Ar), 7.36−7.41 (m, 5H, Ar), 7.52−7.55 (m, 2H, Ar), 7.63 (dd, J = 7.8, 1.0 Hz, 1H, Ar), 7.66 (d, J = 7.8 Hz, 1H, Ar), 7.78 (dd, J = 7.8, 0.5 Hz, 1H, Ar), 9.60 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 89.6, 93.6, 102.1, 110.9, 118.7, 120.1, 120.7, 122.5, 122.7, 127.2, 128.0, 128.4, 128.6 (2C), 128.8, 129.0, 131.3 (2C), 133.4, 134.0, 136.3, 136.8; HRMS (FAB) calcd for $C_{22}H_{15}N$ [M^+] 293.1204, found 293.1205.

Gold-Catalyzed Cascade Cyclization of Diynes. General Procedure for Synthesis of Fused Indoles. Synthesis of 6-*p*-Tolyl-11*H*-benzo[*a*]carbazole (2g) (Table 2, Entry 4). A mixture of the gold catalyst **C** (5.0 mg, 7.1 μmol, 5 mol %) and AgOTf (1.8 mg, 7.1 μmol, 5 mol %) in acetonitrile (0.71 mL) was stirred at room temperature under argon. After aniline **1g** (43 mg, 0.14 mmol) was added, the mixture was stirred at 80 °C for 45 min. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on amino silica gel with *n*-hexane/Et_2O (2:3) to afford **2g** (36 mg, 83% yield) as a brown oil. ^1H NMR spectra of **2g** were in good agreement with those previously reported.[12]

Synthesis of 6-(4-Methoxyphenyl)-11*H*-benzo[*a*]carbazole (2h) (Table 3, Entry 2). By a procedure similar to that described for the preparation of carbazole **2g**, **1h** (36 mg, 0.11 mmol) was converted into **2h** (30 mg, 83% yield) as a pale brown solid by treatment with **C** (3.9 mg, 5.6 μmol) and AgOTf (1.4 mg, 5.6 μmol) in acetonitrile (0.56 mL) at 80 °C for 30 min. ^1H NMR spectra of **2h** were in good agreement with those previously reported.[12]

Synthesis of 6-[3-(Trifluoromethyl)phenyl]-11*H*-benzo[*a*]carbazole (2i) (Table 3, Entry 3). By a procedure similar to that described for the preparation of carbazole **2g**, **1i** (31 mg, 0.087 mmol) was converted into **2i** (31 mg, 98% yield) as a brown oil by treatment with **C** (3.1 mg, 4.3 μmol) and AgOTf (1.1 mg, 4.3 μmol) in acetonitrile (0.43 mL) at 80 °C for 40 min: IR (neat) 3472 (NH) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.01−7.07 (m, 2H, Ar), 7.22 (d, J = 8.0 Hz, 1H, Ar), 7.27 (s, 1H, Ar), 7.30 (dd J = 7.4, 7.4 Hz, 1H, Ar), 7.37−7.41 (m, 2H, Ar), 7.46 (d, J = 7.4 Hz, 1H, Ar), 7.55−7.58 (m, 2H, Ar), 7.62 (d, J = 8.6 Hz, 1H, Ar), 7.78−7.79 (m, 1H, Ar), 7.92 (br s, 1H, NH), 7.96 (s, 1H, Ar); ^{13}C NMR (125 MHz, C_6D_6) δ 111.4, 116.6, 120.2, 120.9, 121.0, 121.6, 122.0, 123.9, 124.4 (q, J = 3.6 Hz), 125.0, 125.0 (q, J = 272.3 Hz), 125.6, 125.9, 126.5 (q, J = 3.6 Hz), 129.0, 129.3, 131.0 (q, J = 32.0 Hz), 132.5, 133.1, 135.1, 135.7, 139.1, 142.6; HRMS (FAB) calcd for $C_{23}H_{14}F_3N$ [M^+] 361.1078, found 361.1068.

Synthesis of 3-(11*H*-Benzo[*a*]carbazol-6-yl)benzonitrile (2j) (Table 3, Entry 4). By a procedure similar to that described for the preparation of carbazole **2g**, **1j** (33 mg, 0.10 mmol) was converted into **2j** (26 mg, 79% yield) as a yellow solid by treatment with **C** (3.7 mg, 5.2 μmol) and AgOTf (1.3 mg, 5.2 μmol) in acetonitrile (0.52 mL) at 80 °C for 30 min: IR (neat) 3344 (NH), 2234 (C≡N) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.81 (dd, J = 7.7, 7.7 Hz, 1H, Ar), 7.03 (dd, J = 7.7, 7.7 Hz, 1H, Ar), 7.11−7.15 (m, 2H, Ar), 7.27−7.34 (m, 2H, Ar), 7.38−7.45 (m, 4H, Ar), 7.50 (s, 1H, Ar), 7.69 (d, J = 6.9 Hz, 1H, Ar), 7.81 (dd, J = 6.9, 2.3 Hz, 1H, Ar), 8.09 (br s, 1H, NH); ^{13}C NMR (125 MHz, C_6D_6) δ 111.5, 113.2, 116.4, 118.9, 120.2, 121.0, 121.1,

121.5, 121.8, 123.8, 125.1, 125.7, 126.0, 128.9, 129.2, 131.0, 132.4, 132.8, 133.6, 134.3, 135.7, 139.1, 142.6; HRMS (FAB) calcd for $C_{23}H_{14}N_2$ [M^+] 318.1157, found 318.1149.

Synthesis of 6-*m*-Tolyl-11*H*-benzo[*a*]carbazole (2k) (Table 3, Entry 5). By a procedure similar to that described for the preparation of carbazole **2g**, **1k** (33 mg, 0.11 mmol) was converted into **2k** (26 mg, 76% yield) as a brown oil by treatment with **C** (3.8 mg, 5.3 μmol) and AgOTf (1.4 mg, 5.3 μmol) in acetonitrile (0.53 mL) at 80 °C for 30 min: IR (neat) 3469 (NH) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 2.21 (s, 3H, CH_3), 7.06 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.13 (d, J = 7.4 Hz, 1H, Ar), 7.23 (d, J = 8.0 Hz, 1H, Ar), 7.27 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.32 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.36−7.41 (m, 2H, Ar), 7.49 (s, 1H, Ar), 7.53−7.55 (m, 2H, Ar), 7.64 (d, J = 8.6 Hz, 1H, Ar), 7.82−7.85 (m, 2H, Ar), 7.89 (br s, 1H, NH); ^{13}C NMR (125 MHz, C_6D_6) δ 21.4, 111.2, 117.4, 120.0, 120.7, 121.0, 121.3, 122.6, 124.5, 124.8, 125.1, 125.7, 126.9, 128.5, 128.5, 129.2, 130.5, 132.8, 135.6, 137.4, 138.1, 139.2, 141.8; HRMS (FAB) calcd for $C_{23}H_{16}N$ [$M - H]^-$ 306.1283, found 306.1285.

Synthesis of 2-(11*H*-Benzo[*a*]carbazol-6-yl)benzonitrile (2l) (Table 3, Entry 6). By a procedure similar to that described for the preparation of carbazole **2g**, **1l** (41 mg, 0.13 mmol) was converted into **2l** (4.2 mg, 10% yield) as a yellow solid by treatment with **C** (4.6 mg, 6.5 μmol) and AgOTf (1.7 mg, 6.5 μmol) in acetonitrile (0.65 mL) at 80 °C for 250 min: IR (neat) 3365 (NH), 2228 (C≡N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.81 (d, J = 7.7 Hz, 1H, Ar), 6.98 (dd, J = 7.7, 7.7 Hz, 1H, Ar), 7.36 (dd, J = 7.7, 7.7 Hz, 1H, Ar), 7.57 (s, 1H, Ar), 7.62−7.80 (m, 5H, Ar), 7.94 (dd, J = 7.7, 7.7 Hz, 1H, Ar), 8.10−8.12 (m, 2H, Ar), 8.61 (d, J = 8.3 Hz, 1H, Ar), 12.49 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 111.1, 113.0, 116.1, 118.4, 119.7, 120.5, 120.7, 120.8, 121.2, 123.1, 124.7, 125.8, 126.1, 128.2, 129.0, 131.0, 131.6, 131.7, 132.6, 133.1, 135.3, 138.6, 145.1; HRMS (FAB) calcd for $C_{23}H_{14}N_2$ [M^+] 318.1157, found 318.1157.

Synthesis of 6-*o*-Tolyl-11*H*-benzo[*a*]carbazole (2m) (Table 3, Entry 7). By a procedure similar to that described for the preparation of carbazole **2g**, **1m** (30 mg, 0.096 mmol) was converted into **2m** (24 mg, 82% yield) as a brown solid by treatment with **C** (3.4 mg, 4.8 μmol) and AgOTf (1.2 mg, 4.8 μmol) in acetonitrile (0.48 mL) at 80 °C for 40 min: IR (neat) 3431 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.11 (s, 3H, CH_3), 6.95 (d, J = 8.0 Hz, 1H, Ar), 7.00 (dd, J = 8.0, 8.0 Hz, 1H, Ar), 7.32−7.36 (m, 2H, Ar), 7.39−7.45 (m, 4H, Ar), 7.52−7.60 (m, 3H, Ar), 7.99 (d, J = 8.0 Hz, 1H, Ar), 8.14 (d, J = 8.0 Hz, 1H, Ar), 8.85 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 110.8, 117.4, 120.0, 120.2, 120.2, 120.4, 121.2, 124.1, 124.6, 125.3, 125.5, 125.9, 127.8, 128.9, 129.6, 129.9, 132.2, 134.8, 135.9, 136.7, 138.5, 140.7; HRMS (FAB) calcd for $C_{23}H_{16}N$ [$M - H]^-$ 306.1283, found 306.1289.

Synthesis of 6-(Thiophen-3-yl)-11*H*-benzo[*a*]carbazole (2n) (Table 3, Entry 8). By a procedure similar to that described for the preparation of carbazole **2g**, **1n** (28 mg, 0.093 mmol) was converted into **2n** (21 mg, 74% yield) as a yellow solid by treatment with **C** (3.3 mg, 4.7 μmol) and AgOTf (1.2 mg, 4.7 μmol) in acetonitrile (0.47 mL) at 80 °C for 40 min: IR (neat) cm^{-1}: 3410 (NH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.37 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.42 (dd, J = 4.6, 1.1 Hz, 1H, Ar), 7.50−7.57 (m, 6H, Ar), 7.60 (d, J = 7.4 Hz, 1H, Ar), 7.96 (d, J = 7.4 Hz, 1H, Ar), 8.09 (d, J = 8.0 Hz, 1H, Ar), 8.85 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 110.9, 117.0, 119.7, 120.3, 120.3, 121.0, 122.0, 123.0, 123.8, 124.7, 125.4, 125.5, 125.7, 128.8, 129.3, 131.2, 132.0, 135.2, 138.6, 141.7; HRMS (FAB) calcd for $C_{20}H_{13}NS$ [M^+]: 299.0769; found: 299.0767.

Synthesis of 6-Cyclopentyl-11*H*-benzo[*a*]carbazole (2o) (Table 3, Entry 9). By a procedure similar to that described for the preparation of carbazole **2g**, **1o** (34 mg, 0.12 mmol) was converted into **2o** (31 mg, 90% yield) as a pale brown solid by treatment with **C** (4.2 mg, 6.0 μmol) and AgOTf (1.5 mg, 6.0 μmol) in acetonitrile (0.60 mL) at 80 °C for 40 min, which was recrystallized from *n*-hexane/EtOAc to give pure **2o** as pale brown crystals: mp: 147−149 °C; IR (neat) cm^{-1}: 3417 (NH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.85−2.00 (m, 6H, *c*-pentyl), 2.29−2.35 (m, 2H, *c*-pentyl), 4.07−4.13 (m, 1H, *c*-pentyl), 7.31 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.42 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.48−7.50 (m, 3H, Ar), 7.57 (d, J = 8.0 Hz, 1H, Ar), 7.94 (dd, J = 6.3, 3.4 Hz, 1H, Ar), 8.04 (dd, J = 6.3, 3.2 Hz, 1H, Ar), 8.24 (d, J = 8.0 Hz, 1H, Ar), 8.80 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0 (2C), 32.6 (2C), 42.9, 111.0, 115.2, 117.7, 119.6, 119.9, 120.1, 122.5, 124.1, 124.2, 124.7, 125.3, 128.4, 132.4, 135.1, 138.6, 140.4. Anal. Calcd for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found C, 88.18; H, 6.60; N, 4.91.

Synthesis of Methyl 6-Phenyl-11*H*-benzo[*a*]carbazole-8-carboxylate (2p) (Table 3, Entry 10). By a procedure similar to that described for the preparation of carbazole **2g**, **1p** (43 mg, 0.12 mmol) was converted into **2p** (29 mg, 68% yield) as a pale brown solid by treatment with **C** (4.4 mg, 6.2 μmol) and AgOTf (1.6 mg, 6.2 μmol) in acetonitrile (0.62 mL) at 80 °C for 120 min. ^1H NMR spectra of **2p** were in good agreement with those previously reported.[12]

Synthesis of 8-Methyl-6-phenyl-11*H*-benzo[*a*]carbazole (2q) (Table 3, Entry 11). By a procedure similar to that described for the preparation of carbazole **2g**, **1q** (29 mg, 0.096 mmol) was converted into **2q** (24 mg, 83% yield) as a brown solid by treatment with **C** (3.4 mg, 4.8 μmol) and AgOTf (1.2 mg, 4.8 μmol) in acetonitrile (0.48 mL) at 80 °C for 30 min. ^1H NMR spectra of **2q** were in good agreement with those previously reported.[12]

Synthesis of 9-Chloro-6-phenyl-11*H*-benzo[*a*]carbazole (2r) (Table 3, Entry 12). By a procedure similar to that described for the preparation of carbazole **2g**, **1r** (30 mg, 0.092 mmol) was converted into **2r** (28 mg, 92% yield) as a yellow solid by treatment with **C** (3.3 mg, 4.6 μmol) and AgOTf (1.2 mg, 4.6 μmol) in acetonitrile (0.46 mL) at 80 °C for 40 min: IR (neat) 3416 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.98 (dd, J = 8.6, 1.7 Hz, 1H, Ar), 7.31 (d, J = 8.6 Hz, 1H, Ar), 7.48−7.59 (m, 7H, Ar), 7.63 (dd, J = 8.0, 1.7 Hz, 2H, Ar), 7.97 (d, J = 7.4 Hz, 1H, Ar), 8.07 (d, J = 8.0 Hz, 1H, Ar), 8.82 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 110.8, 116.3, 120.1, 120.2, 120.3, 121.3, 122.4, 122.8, 125.7, 125.9, 127.7, 128.4 (2C), 128.9, 129.2 (2C), 130.3, 132.2, 135.6, 136.2, 139.1, 140.8; HRMS (FAB) calcd for $C_{22}H_{13}ClN$ [$M - H]^-$ 326.0737, found 326.0740.

Synthesis of 9-Chloro-6-cyclohexyl-11*H*-benzo[*a*]carbazole (2s) (Table 3, Entry 13). By a procedure similar to that described for the preparation of carbazole **2g**, **1s** (34 mg, 0.10 mmol) was converted into **2s** (33 mg, 96% yield) as a pale yellow solid by treatment with **C** (3.6 mg, 5.1 μmol) and AgOTf (1.3 mg, 5.1 μmol) in acetonitrile (0.51 mL) at 80 °C for 90 min: IR (neat) 3416 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36−1.45 (br m, 1H, Cy), 1.58−1.68 (m, 4H, Cy), 1.89−1.91 (br m, 1H, Cy), 1.96−2.01 (br m, 2H, Cy), 2.22−2.29 (br m, 2H, Cy), 3.43−3.47 (br m, 1H, Cy), 7.26 (dd, J = 8.6, 1.7 Hz, 1H, Ar), 7.46 (s, 1H, Ar), 7.50−7.52 (m, 3H, Ar), 7.93 (dd, J = 6.0, 3.2 Hz, 1H, Ar), 7.99−8.00 (m, 2H, Ar), 8.72 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 27.2 (2C), 33.1 (2C), 41.1, 110.9, 115.8, 116.7, 119.5, 120.1, 120.6, 122.4, 123.0, 124.9, 125.6, 128.6, 129.9, 132.6, 135.4, 139.0, 141.9; HRMS (FAB) calcd for $C_{22}H_{20}ClN$ [M^+] 333.1284, found 333.1277.

Synthesis of 6-Cyclohexyl-9-(trifluoromethyl)-11*H*-benzo[*a*]carbazole (2t) (Table 3, Entry 14). By a procedure similar to that described for the preparation of carbazole **2g**, **1t** (32 mg, 0.088 mmol) was converted into **2t** (28 mg, 87% yield) as a pale brown solid by treatment with **C** (3.1 mg, 4.4 μmol) and AgOTf (1.1 mg, 4.4 μmol) in acetonitrile (0.44 mL) at 80 °C for 90 min: IR (neat) 3495 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36−1.45 (br m, 1H, Cy), 1.60−1.69 (m, 4H, Cy), 1.90−1.93 (br

m, 1H, Cy), 1.99−2.01 (br m, 2H, Cy), 2.21−2.31 (br m, 2H, Cy), 3.46−3.50 (br m, 1H, Cy), 7.47 (s, 1H, Ar), 7.50−7.58 (m, 3H, Ar), 7.80 (s, 1H, Ar), 7.94 (dd, J = 5.7, 2.9 Hz, 1H, Ar), 8.02 (dd, J = 7.5, 3.2 Hz, 1H, Ar), 8.17 (d, J = 8.6 Hz, 1H, Ar), 8.89 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 27.2 (2C), 33.2 (2C), 41.1, 108.3 (q, J = 4.8 Hz), 116.1, 116.5, 116.7 (q, J = 3.6 Hz), 119.4, 120.3, 122.4, 124.8 (q, J = 241.9 Hz), 125.1, 125.9 (q, J = 32.4 Hz), 126.0, 126.2, 128.6, 133.0, 136.5, 137.5, 142.2; HRMS (FAB) calcd for $C_{23}H_{20}F_3N$ [M^+] 367.1548, found 367.1556.

Synthesis of *tert*-Butyl 6-Phenyl-11*H*-benzo[*a*]carbazole-11-carboxylate (2u) (Table 4, Entry 1). By a procedure similar to that described for the preparation of carbazole **2g**, **1u** (41 mg, 0.10 mmol) was converted into **2u** (36 mg, 89% yield) as a yellow oil by treatment with **C** (3.7 mg, 5.2 μmol) and AgOTf (1.3 mg, 5.2 μmol) in acetonitrile (0.52 mL) at 80 °C for 2 h: IR (neat) 1730 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 [s, 9H, $C(CH_3)_3$], 7.07 (dd, J = 8.0, 8.0 Hz, 1H, Ar), 7.16 (d, J = 8.0 Hz, 1H, Ar), 7.35−7.39 (m, 1H, Ar), 7.49−7.56 (m, 5H, Ar), 7.59−7.61 (m, 2H, Ar), 7.65 (s, 1H, Ar), 7.93 (d, J = 8.0 Hz, 1H, Ar), 8.19 (d, J = 8.0 Hz, 1H, Ar), 8.26 (d, J = 8.0 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2 (3C), 84.5, 114.8, 122.0, 122.1, 122.6, 122.8, 124.9, 125.0, 125.6, 126.0, 126.1, 126.2, 127.8, 128.5, 128.5 (2C), 128.7, 129.4 (2C), 133.0, 135.3, 140.6, 140.6, 151.9; HRMS (FAB) calcd for $C_{27}H_{23}NO_2$ [M^+] 393.1729, found 393.1731.

Synthesis of 11-Methyl-6-phenyl-11*H*-benzo[*a*]carbazole (2v) (Table 4, Entry 2). By a procedure similar to that described for the preparation of carbazole **2g**, **1v** (32 mg, 0.11 mmol) was converted into **2v** (30 mg, 92% yield) as a colorless solid by treatment with **C** (3.7 mg, 5.3 μmol) and AgOTf (1.3 mg, 5.3 μmol) in acetonitrile (0.53 mL) at 80 °C for 40 min, which was recrystallized from *n*-hexane to give pure **2v** as colorless crystals: mp 194−195 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 3.54 (s, 3H, CH_3), 7.04 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.13 (d, J = 8.6 Hz, 1H, Ar), 7.27−7.34 (m, 5H, Ar), 7.38 (dd, J = 5.7, 3.2 Hz, 1H, Ar), 7.52 (s, 1H, Ar), 7.66−7.71 (m, 3H, Ar), 7.88 (dd, J = 5.7, 2.9 Hz, 1H, Ar), 8.37 (dd, J = 5.7, 3.4 Hz, 1H, Ar); ^{13}C NMR (125 MHz, C_6D_6) δ 33.4, 109.1, 117.9, 119.6, 121.8, 122.4, 122.5, 122.5, 123.3, 124.7, 124.9, 125.1, 127.7, 128.6 (2C), 129.6, 129.8 (2C), 133.8, 136.3, 136.9, 141.4, 142.1. Anal. Calcd for $C_{23}H_{17}N$: C, 89.87; H, 5.57; N, 4.56. Found: C, 89.61; H, 5.79; N, 4.60.

Synthesis of 6-Cyclohexyl-2-fluoro-11*H*-benzo[*a*]carbazole (2w) (Table 4, Entry 3). By a procedure similar to that described for the preparation of carbazole **2g**, **1w** (33 mg, 0.11 mmol) was converted into **2w** (28 mg, 84% yield) as a brown solid by treatment with **C** (3.7 mg, 5.3 μmol) and AgOTf (1.3 mg, 5.3 μmol) in acetonitrile (0.53 mL) at 80 °C for 50 min: IR (neat) 3457 (NH) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35−1.44 (br m, 1H, Cy), 1.59−1.70 (m, 4H, Cy), 1.89−2.00 (m, 3H, Cy), 2.27−2.28 (br m, 2H, Cy), 3.51−3.55 (br m, 1H, Cy), 7.22−7.26 (m, 1H, Ar), 7.32 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.42−7.45 (m, 2H, Ar), 7.55 (d, J = 8.0 Hz, 1H, Ar), 7.62 (dd, J = 9.7, 1.7 Hz, 1H, Ar), 7.89 (dd, J = 8.9, 5.4 Hz, 1H, Ar), 8.14 (d, J = 8.0 Hz, 1H, Ar), 8.64 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.6, 27.2 (2C), 33.2 (2C), 41.0, 104.3 (d, J = 22.8 Hz), 111.1, 115.1, 115.1, 119.9, 120.0, 122.5, 123.7, 124.6, 129.3, 130.8, 130.8, 134.6 (d, J = 4.8 Hz), 138.7, 141.4, 160.1 (d, J = 244.7 Hz); HRMS (FAB) calcd for $C_{22}H_{20}FN$ [M^+] 317.1580, found 317.1575.

Synthesis of 6-Phenyl-11*H*-pyrido[3,2-*a*]carbazole (2x) (Table 4, Entry 4). By a procedure similar to that described for the preparation of carbazole **2g**, **1x** (41 mg, 0.14 mmol) was converted into **2x** (17 mg, 37% yield) as a brown solid by treatment with **C** (20 mg, 0.028 mmol) and AgOTf (7.1 mg, 0.028 mmol) in acetonitrile (0.69 mL) at 80 °C for 24 h. ^{1}H NMR spectra of **2x** were in good agreement with those previously reported.[12]

Synthesis of 5-Phenyl-10*H*-furo[3,2-*a*]carbazole (2y) (Table 4, Entry 5). By a procedure similar to that described for the preparation of carbazole **2g**, **1y** (34 mg, 0.12 mmol) was converted into **2y** (33 mg, 98% yield) as a colorless solid by treatment with **C** (4.2 mg, 5.9 μmol) and AgOTf (1.5 mg, 5.9 μmol) in acetonitrile (0.59 mL) at 80 °C for 75 min, which was recrystallized from *n*-hexane to give pure **2y** as colorless crystals: mp 120−121 °C; IR (neat) 3443 (NH) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98−7.01 (m, 2H, Ar), 7.29−7.32 (m, 2H, Ar), 7.36 (d, J = 8.0 Hz, 1H, Ar), 7.44−7.54 (m, 4H, Ar), 7.63−7.64 (m, 2H, Ar), 7.69 (d, J = 2.3 Hz, 1H, Ar), 8.38 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 103.4, 105.7, 110.6, 110.9, 115.7, 119.4, 121.8, 123.7, 124.4, 127.5, 128.4 (2C), 129.4 (2C), 132.6, 134.6, 139.1, 141.3, 144.1, 154.6. Anal. Calcd for $C_{20}H_{13}NO$: C, 84.78; H, 4.62; N, 4.94. Found: C, 84.55; H, 4.65; N, 4.78.

Synthesis of *tert*-Butyl 4-Phenyl-2,3-dihydro-1*H*-benzo[*g*]-indole-1-carboxylate (7) (Scheme 3). By a procedure similar to that described for the preparation of carbazole **2g**, **6** (42 mg, 0.12 mmol) was converted into **7** (41 mg, 99% yield) as a pale yellow solid by treatment with **C** (4.3 mg, 6.0 μmol) and AgOTf (1.5 mg, 6.0 μmol) in acetonitrile (0.60 mL) at 80 °C for 25 min: IR (neat) 1698 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 [s, 9H, $C(CH_3)_3$], 3.16 (t, J = 7.7 Hz, 2H, CH_2), 4.24 (t, J = 7.7 Hz, 2H, CH_2), 7.36−7.51 (m, 7H, Ar), 7.63 (s, 1H, Ar), 7.83 (d, J = 8.0 Hz, 1H, Ar), 7.98 (d, J = 8.0 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.4 (3C), 30.0, 51.9, 81.1, 124.0, 124.8, 125.2, 125.4, 125.5, 127.3, 128.2, 128.4 (2C), 128.6 (2C), 129.6, 134.0, 136.5, 139.5, 140.4, 154.5; HRMS (FAB) calcd for $C_{23}H_{23}NO_2$ [M^+] 345.1729, found 345.1734.

Synthesis of 4-Phenyl-2,3-dihydro-1*H*-benzo[*g*]indole (5) (Scheme 3). To a solution of **7** (40 mg, 0.12 mmol) in 1,4-dioxane (0.50 mL) was added 4 N HCl/1,4-dioxane (0.50 mL, 2.0 mmol) at room temperature. The mixture was stirred at room temperature for 19 h and quenched by addition of saturated aqueous $NaHCO_3$ at room temperature. The aqueous mixture was extracted with EtOAc, and the layers were separated. The organic layer was dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on amino silica gel with *n*-hexane/EtOAc (5:1) to afford **5** (26 mg, 90% yield) as a red oil: IR (neat) 3373 (NH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.27 (t, J = 8.5 Hz, 2H, CH_2), 3.73 (t, J = 8.5 Hz, 2H, CH_2), 3.95 (br s, 1H, NH), 7.32−7.46 (m, 6H, Ar), 7.52−7.55 (m, 2H, Ar), 7.62−7.66 (m, 1H, Ar), 7.79−7.83 (m, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.8, 48.0, 118.8, 120.1, 121.3, 121.8, 124.8, 125.5, 127.0, 128.3 (2C), 128.5 (2C), 128.6, 133.8, 137.4, 141.2, 147.4; HRMS (FAB) calcd for $C_{18}H_{15}N$ [M^+] 245.1204, found 245.1206.

Synthesis of 4-Phenyl-2,3-dihydronaphtho[1,2-*b*]furan (9) (Scheme 3). By a procedure similar to that described for the preparation of carbazole **2g**, **8** (42 mg, 0.17 mmol) was converted into **9** (36 mg, 85% yield) as a pale yellow solid by treatment with **C** (6.1 mg, 8.6 μmol) and AgOTf (2.2 mg, 8.6 μmol) in acetonitrile (0.86 mL) at 80 °C for 40 min: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.42 (t, J = 8.9 Hz, 2H, CH_2), 4.76 (t, J = 8.9 Hz, 2H, CH_2), 7.36 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.42−7.46 (m, 5H, Ar), 7.54−7.55 (m, 2H, Ar), 7.82 (dd, J = 6.0, 3.2 Hz, 1H, Ar), 7.96 (dd, J = 6.0, 3.4 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.7, 71.9, 118.7, 119.7, 119.8, 121.4, 125.2, 126.1, 127.2, 127.9, 128.3 (2C), 128.5 (2C), 134.2, 137.0, 140.8, 155.8; HRMS (FAB) calcd for $C_{18}H_{14}O$ [M^+] 246.1045, found 246.1050.

Synthesis of 5-Phenyl-2-tosyl-1,2,3,10-tetrahydroazepino[3,4-*b*]-indole (11a) (Table 5, Entry 2). By a procedure similar to that described for the preparation of carbazole **2g**, **10a** (33 mg, 0.079 mmol) was converted into **11a** (14 mg, 42% yield) as a brown solid by treatment with **A** (2.1 mg, 4.0 μmol) and AgOTf (1.0 mg, 4.0 μmol) in acetonitrile (0.40 mL) at 80 °C for 1.5 h: IR (neat) 3369 (NH), 1331 (S=O), 1157 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3H, $C_6H_4CH_3$), 3.92 (d, J = 6.9 Hz, 2H, CH_2), 4.60 (s, 2H, CH_2), 5.97 (t, J = 6.9 Hz, 1H, C=C*H*CH_2), 6.63 (d, J = 8.0 Hz, 1H, Ar), 6.86 (dd, J = 7.4, 7.4 Hz, 1H, Ar),

7.12 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.17 (d, J = 8.0 Hz, 2H, Ar), 7.25−7.34 (m, 6H, Ar), 7.71 (d, J = 8.0 Hz, 2H, Ar), 8.63 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 44.5, 45.8, 111.3, 114.0, 119.7, 120.0, 120.8, 122.4, 126.2, 127.3 (2C), 128.0, 128.1 (2C), 128.2 (2C), 129.7 (2C), 134.2, 135.7, 135.8, 139.6, 143.2, 143.5; HRMS (FAB) calcd for $C_{25}H_{22}N_2O_2S$ [M^+] 414.1402, found 414.1408.

Synthesis of 5-Phenyl-3,10-dihydro-1*H*-oxepino[3,4-*b*]indole (11b) (Table 5, Entry 4). By a procedure similar to that described for the preparation of carbazole **2g**, **10b** (38 mg, 0.14 mmol) was converted into **11b** (18 mg, 49% yield) as a brown oil by treatment with **C** (5.1 mg, 7.2 μmol) and AgOTf (1.8 mg, 7.2 μmol) in acetonitrile (0.72 mL) at 80 °C for 4 h: IR (neat) 3282 (NH) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.11 (d, J = 6.3 Hz, 2H, CH_2), 4.83 (s, 2H, CH_2), 6.29 (t, J = 6.3 Hz, 1H, C=C*H*CH_2), 6.75 (d, J = 8.0 Hz, 1H, Ar), 6.91 (ddd, J = 7.7, 7.7, 1.1 Hz, 1H, Ar), 7.16 (ddd, J = 7.7, 7.7, 1.1 Hz, 1H, Ar), 7.35−7.38 (m, 4H, Ar), 7.44−7.46 (m, 2H, Ar), 8.34 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.7, 64.8, 111.2, 114.6, 120.0, 121.1, 122.3, 124.1, 126.4, 127.9, 128.2 (2C), 128.2 (2C), 135.9, 138.7, 140.2, 143.5; HRMS (FAB) calcd for $C_{18}H_{15}NO$ [M^+] 261.1154, found 261.1153.

Synthesis of Dimethyl 10-Phenyl-6,8-dihydrocyclohepta[*b*]-indole-7,7(5*H*)-dicarboxylate (11c) (Table 5, Entry 5). By a procedure similar to that described for the preparation of carbazole **2g**, **10c** (35 mg, 0.092 mmol) was converted into **11c** (22 mg, 63% yield) as a colorless solid by treatment with **C** (3.3 mg, 4.6 μmol) and AgOTf (1.2 mg, 4.6 μmol) in acetonitrile (0.46 mL) at 80 °C for 2.5 h: IR (neat) 3329 (NH), 1726 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62 (d, J = 6.9 Hz, 2H, CH_2), 3.31 (s, 2H, CH_2), 3.74 (s, 6H, 2 × CO_2CH_3), 6.43 (t, J = 6.9 Hz, 1H, C=C*H*CH_2), 6.85 (d, J = 7.4 Hz, 1H, Ar), 6.91 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.12 (dd, J = 7.4, 7.4 Hz, 1H, Ar), 7.30−7.31 (br m, 3H, Ar), 7.36 (d, J = 8.0 Hz, 1H, Ar), 7.40−7.42 (br m, 2H, Ar), 8.55 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.4, 33.4, 52.8 (2C), 70.3, 110.9, 112.6, 119.7, 120.3, 121.5, 122.9, 126.6, 127.5, 127.6 (2C), 128.1 (2C), 135.6, 138.1, 139.8, 141.1, 171.7 (2C); HRMS (FAB) calcd for $C_{23}H_{21}NO_4$ [M^+] 375.1471, found 375.1471.

Synthesis of (*E*)-Dimethyl 4-Ethylidene-3,4-dihydro-1*H*-carbazole-2,2(9*H*)-dicarboxylate [(*E*)-13] (Scheme 4). By a procedure similar to that described for the preparation of carbazole **2g**, **12** (31 mg, 0.099 mmol) was converted into (***E*)-13** (17 mg, 34% yield) as a pale yellow solid by treatment with **C** (3.5 mg, 5.0 μmol) and AgOTf (1.3 mg, 5.0 μmol) in acetonitrile (0.50 mL) at 80 °C for 3 h: IR (neat) 3423 (NH), 1739 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ: 1.84 (d, J = 6.8 Hz, 3H, C*H*$_3$CH=C), 3.26 (s, 2H, CH_2), 3.28 (s, 6H, 2 × CO_2CH_3), 3.35 (s, 2H, CH_2), 6.25 (q, J = 6.9 Hz, 1H, CH_3C*H*=C), 6.68 (br s, 1H, NH), 6.99−7.03 (m, 1H, Ar), 7.15−7.20 (m, 2H, Ar), 7.91−7.94 (m, 1H, Ar); ^{13}C NMR (125 MHz, C_6D_6) δ 13.3, 30.0, 32.5, 52.4 (2C), 55.6, 111.3, 111.9, 116.2, 120.5, 120.7, 121.9, 125.5, 129.1, 132.5, 137.1, 171.2 (2C); HRMS (FAB) calcd for $C_{18}H_{19}NO_4$ [M^+] 313.1314, found 313.1305.

Synthesis of 6-Phenyl-11*H*-benzo[*a*]carbazole (2c) (Scheme 6). By a procedure similar to that described for the preparation of carbazole **2g**, **20** (30 mg, 0.102 mmol) was converted into **2c** (31 mg, quant) as a yellow solid by treatment with Ph_3PAuCl (2.5 mg, 5.1 μmol) and AgOTf (1.3 mg, 5.1 μmol) in acetonitrile (0.51 mL) at 80 °C for 40 min. ^{1}H NMR spectra of **2c** were in good agreement with those previously reported.[12]

Antifungal Susceptibility Tests. Antifungal susceptibility assay was performed by the CLSI M38-A2 microdilution method.[41] Compounds were assayed at 0.05−100 μM concentrations (2-fold serial dilutions). The inoculum size was 1×10^3 to 3×10^3 CFU/mL as a final concentration. Ninety-six-well microplates were incubated at 35 °C for 4 days. MICs were determined as the minimal inhibitory concentration of drug that produced visually 80% reduction of turbidity compared to that of the growth control (drug-free medium). *T. mentagrophytes* KD-1031 (MYA-4439) and *T. rubrum* KD-1137 (MYA-4438) were used as quality control strains recommended for use in CLSI method (M38-A2).

Cytotoxicity Assays. Cytotoxicity to human embryonic lung cell (HEL cell) was determined with the MTT assay. Cells were seeded into 96-well microplates at 1×10^5 cells/mL as a final concentration. Then, cells were treated with 0.05 to 100 μM concentration of each compound. Microplates were incubated at 37 °C for 72 h under 5% CO_2. After incubation, the medium was removed from the cells. The MTT solution (Eagle's MEM supplemented with 0.45 mg/mL MTT and 1% fetal bovine serum) were added into 96-well microplates and incubated for 4 h. After incubation, the medium was removed, and formazan crystals were solubilized with DMSO. Its optical density was measured at 540 nm, and then the LD_{50} (lethal doses 50%) was calculated.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

(41) Clinical and Laboratory Standards Institute (CLSI). *Reference method for broth dilution antifungal susceptibility testing of filamentous fungi; Approved standard*, 2nd ed.; M38-A2; Clinical and Laboratory Standards Institute: Wayne, PA, 2008.