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A Method for the Synthesis of Substituted Quinolines via Electrophilic Cyclization of 1-Azido-2-(2-propynyl)benzene

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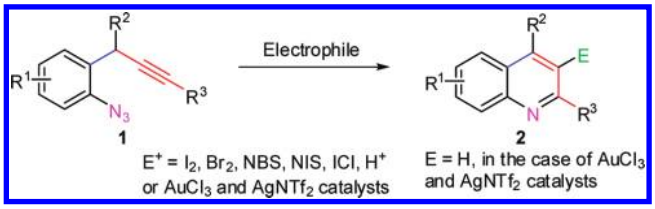

A new and efficient strategy for the synthesis of substituted quinolines via electrophilic cyclization is developed. The intramolecular cyclization of 1-azido-2-(2-propynyl)benzene **1** proceeds smoothly in the presence of electrophilic reagents (I_2, Br_2, ICl, NBS, NIS, and $HNTf_2$) in CH_3NO_2 at room temperature or in the presence of catalytic amounts of $AuCl_3/AgNTf_2$ in THF at 100 °C to afford the corresponding quinolines **2** in good to high yields. In the case of the electrophilic reagents, E of **2** is either I, Br, or H, depending on the reagent type, while E of **2** is H in the case of the electrophilic catalyst.

Introduction

Quinolines represent an important class of alkaloids because of their wide utility. Substituted quinolines are often found as structural frameworks in a large number of biologically active natural products and pharmaceuticals.[1] Examples include anti-Alzheimer agents,[2] anticancer agents,[3] and antimalarial drugs.[4] Furthermore, quinoline derivatives have been shown to be outstanding organocatalysts and are recognized as useful tools for the highly enantioselective syntheses of chiral molecules.[5] Because of their importance, much attention has been paid to development efficient methods for the synthesis of substituted quinolines. In recent years, a number of syntheses of quinoline derivatives have been reported.[6]

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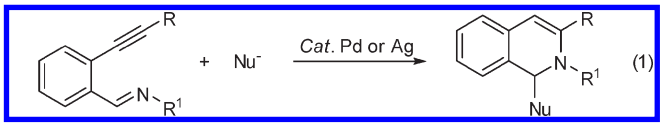
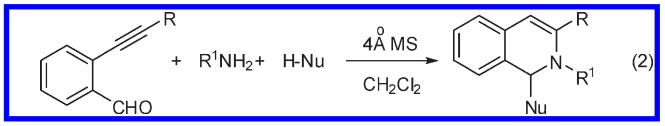
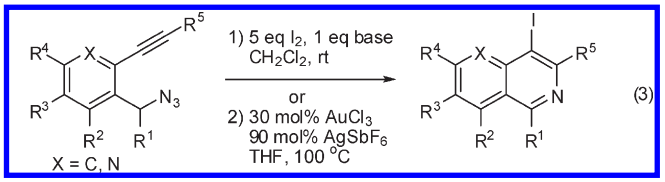
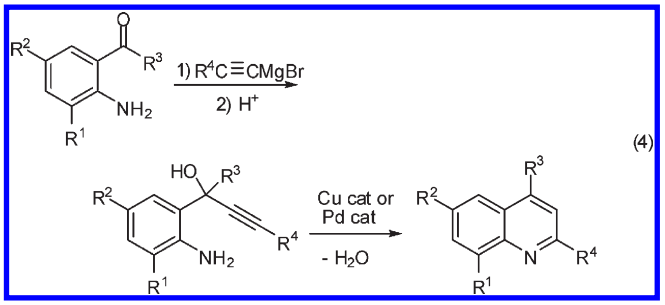
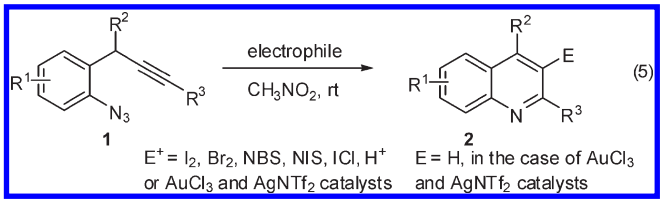
We recently reported metal-catalyzed or nonmetal-catalyzed synthesis of substituted dihydroisoquinolines (eqs 1 and 2),[7] and an entirely new method for the synthesis of substituted isoquinolines through iodine-mediated[8] or gold-catalyzed[9] cyclization of 2-alkynyl benzyl azides (eq 3). A novel and practical synthesis of substituted quinolines via a two-step procedure involving Grignard addition of alkynylmagnesium bromides to 2-aminoaryl ketones followed by regioselective copper- or palladium-catalyzed 6-*endo-dig* cyclodehydration of the corresponding 1-(2-aminophenyl)-2-yn-1-ols (eq 4) was reported by Gabriele and co-workers.[10] Accordingly, it occurred to us that the electrophilic cyclization of 1-azido-2-(2-propynyl)benzene would give substituted quinolines. Herein, we report a new method for the synthesis of substituted quinolines **2** from 1-azido-2-(2-propynyl)benzene **1** in the presence of I_2, Br_2, NIS, and ICl in CH_3NO_2 at room temperature or in the presence of catalytic amounts of $AuCl_3$/$AgNTf_2$ and $HNTf_2$ in THF at 100 °C (eq 5).







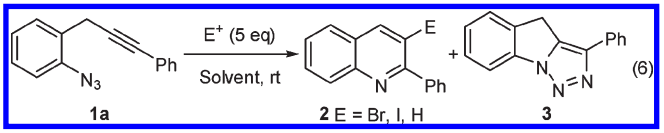




Results and Discussion

Initially, we screened the reaction conditions for the electrophilic cyclization of substrate **1a**. For cyclization,

TABLE 1. Optimization of Electrophilic Reagents (I_2, Br_2, NIS, ICl, NBS, H^+) for Cyclization of 1a



entry	E^+	solvent	time (h)	**2**[a] (%)	**3**[a] (%)	**1a**[a] (%)
1	I_2	CH_2Cl_2	12	56	23	0
2	I_2	DMF	12	31	0	38
3	I_2	toluene	12	28	31	6
4	I_2	THF	12	23	16	37
5	I_2	CH_3CN	12	45	18	7
6	I_2	CH_3NO_2	24	74 (69)	13 (7)	0
7[b]	I_2	CH_2Cl_2	12	73	11	0
8	Br_2	CH_3NO_2	1	(96)	0	0
9[c]	Br_2	CH_3NO_2	12	84	0	3
10	NBS	CH_3NO_2	0.5	(84)	0	0
11	ICl	CH_3NO_2	0.5	(55)	0	0
12	NIS	CH_3NO_2	12	(82)	0	0
13	TfOH (1 equiv)	THF	24	13	0	50
14	HCl (1 equiv)	THF	24	0	0	81
15	$TsOH \cdot H_2O$ (1 equiv)	THF	24	0	0	77
16	HBF_4 (1 equiv)	THF	24	0	0	76
17	TFA (1 equiv)	THF	24	10	0	44
18	AcOH (1 equiv)	THF	24	0	37	50
19	$HNTf_2$ (1 equiv)	THF	24	54(49)	0	7(5)
20	$HNTf_2$ (1.2 equiv)	THF	24	(62)	0	0
21[d]	$HNTf_2$ (1 equiv)	THF	24	37	0	0

[a] ^1H NMR yield was determined by using CH_2Br_2 as an internal standard. Isolated yield is shown in parentheses. [b] $NaHCO_3$ (2 equiv) as additive was used. [c] 3 equiv of Br_2 was used. [d] Reaction temperature was 120 °C.

promoted by electrophilic reagents, the results are summarized in Table 1. Table 2 outlines the results for the use of Lewis acids as catalysts. As observed in the case of the electrophilic cyclization of 1-azido-2-(2-propynyl)benzene (eq), the cyclization of **1a** produced **2** along with the 1,3-dipolar adduct **3** under certain conditions. The iodocyclization with I_2 gave **3** as a minor product (Table 1, entries 1 and 3−7), but the bromocyclization with Br_2 and NBS and the iodocyclization with ICl and NIS did not produce **3** at all (entries 8−12). Especially, the bromocyclization by the use of Br_2 afforded **2** with an excellent yield (96% isolated yield) (entry 8). The use of Bronsted acids did not afford good results (entries 13−19). The use of acetic acid gave **3** without formation of **2**. A better result was obtained by the use of $HNTf_2$ as a protic acid (entry 20).

The electrophilic catalysts, such as $AgSbF_6$, PPh_3AuCl, CuI, and $PtCl_2$, gave **3** as a major product, although the combined yields of **2** and **3** were low (Table 2, entries 6, 8, 18, and 21). Among the catalysts examined, $AuCl_3$/$AgNTf_2$ (1:3, 30 mol %) gave **2** in 85% isolated yield without formation of **3** (entry 16). To understand how the regio- and

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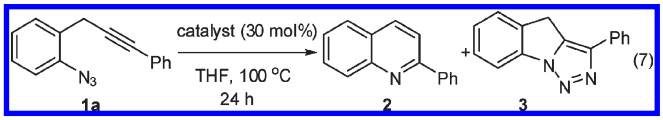
TABLE 2. Optimization of Electrophilic Catalysts for Cyclization of 1a



entry	catalyst	2[a] (%)	3[a] (%)	1a[a] (%)
1	AgOTf	9	0	45
2	$AgPF_6$	0	0	83
3	$AgBF_4$	0	0	89
4	$AgNTf_2$	5	0	33
5	$AgClO_4$	0	0	56
6	$AgSbF_6$	11	12	13
7	$AgSbF_6$/TFA (2 equiv)	5	0	53
8	PPh_3AuCl	0	45	19
9	AuCl	19	0	31
10	AuCl/AgOTf (1:1)	35	0	24
11	AuCl/$AgSbF_6$ (1:1)	51	0	13
12	AuCl/$AgNTf_2$ (1:1)	(49)	0	17
13	$AuCl_3$	32	0	61
14	$AuCl_3$/$AgSbF_6$ (1:3)	66 (64)	0	0
15	$AuCl_3$/AgOTf (1:3)	58 (57)	0	0
16	$AuCl_3$/$AgNTf_2$ (1:3)	(85)	0	0
17	$PdCl_2$	(50)	0	0
18[b]	CuI	(6)	(31)	0
19	$Cu(OTf)_2$	35	0	11
20	$In(OTf)_3$	0	0	87
21	$PtCl_2$	12	16	5

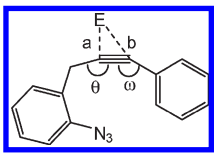
[a] ^{1}H NMR yield was determined by using CH_2Br_2 as an internal standard. Isolated yield is shown in parentheses. [b] 1.5 equiv of CuI, CH_3CN, 110 °C, 60 h.

chemoselectivities depend on the reagents and catalysts, we carried out a computation study similar to that performed previously for the case of isoquinoline synthesis.[11] Computed enthalpies of formation and selected structural parameters of the optimized structures of associates between diaryl acetylene **1a** and various electrophilic reagents/catalysts are shown in the Table 3.

Comparing the data of Table 3 with the synthetic results, one can elucidate the structural features of an associate between the alkyne and the electrophiles that plays a critical role for the selective cyclization to the corresponding quinolines. Thus, it is clear that the strength of the electrophile binding is not significant for the successful quinoline synthesis, since either very strongly binding electrophiles (e.g. $AuNTf_2$ or AuOTf, entries 12 and 13) or weakly binding bromine (entry 1) can give selectively high yields of quinolines, and vice versa: both strongly binding (e.g. AgOTf, entry 8) and weakly binding (I_2, entry 2) electrophiles can be poor catalysts and/or provide significant amounts of the side product **3**. On the other hand, one can see a clear correlation between the performance of the catalyst and its ability to bind to the triple bond in a nonsymmetrical manner, leaving the acetylene moiety uninvolved. Thus, the best performing catalyst, viz. Br_2, coordinates to the triple bond only weakly, but strongly nonsymmetrically (the angle ω is most close to 180°), and the difference between θ and ω (and a and b) is the largest among the reagents examined (entries 1−6). Similar values of ω are seen only for NIS and ICl (coordinating by iodine), which also are nice reagents and can be used for synthetic purposes. The nonsymmetrical factor is also

(11) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075–5087.

TABLE 3. Selected Structural Parameters of the Optimized Structures of Associates between Diaryl Acetylene 1a and Various Electrophilic Reagents[a]



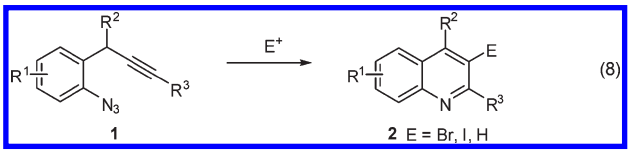
entry	electrophile	ΔH, kcal/mol	a, Å	b, Å	θ, deg	ω, deg
1	Br_2	−6.3	2.759	2.968	169.7	179.1
2	I_2	−5.1	3.029	3.201	170.9	178.6
3	ICl (coordination by I^+)	−7.6	2.905	3.111	168.5	178.7
4	ClI (coordination by Cl^+	−3.8	2.782	2.962	173.5	179.7
5	NBS	−3.7	3.058	3.187	177.3	175.6
6	NIS	−4.1	3.185	3.290	170.5	177.7
7	AgCl	−23.8	2.317	2.342	167.9	166.8
8	AgOTf	−28.6	2.300	2.293	167.5	165.6
9	CuCl	−34.6	2.037	2.049	165.9	164.2
10	CuOTf	−41.9	2.022	2.052	163.8	168.3
11	AuCl	−36.6	2.213	2.225	163.3	161.2
12	$AuNTf_2$	−40.4	2.208	2.286	161.0	168.2
13	AuOTf	−51.6	2.192	2.200	163.0	161.7
14	$AuPPh_3$	−37.5	2.307	2.313	166.4	163.7

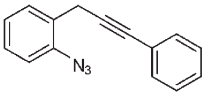
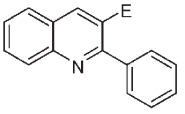
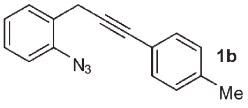
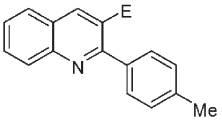
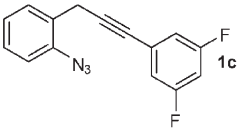
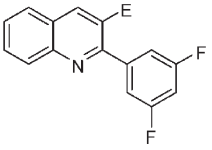
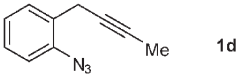
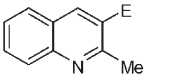
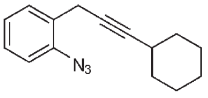
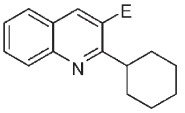
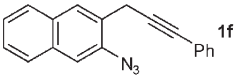
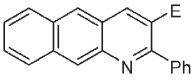
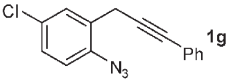
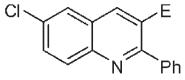
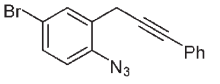
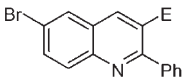
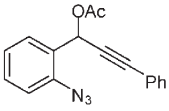
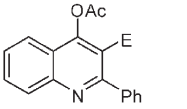
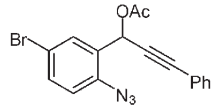
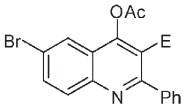
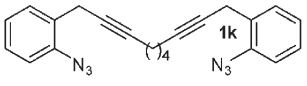
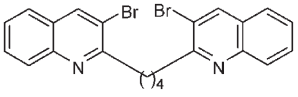
[a] Optimizations were done on the B3LYP/SDD level of theory.

important for obtaining better chemical yields of **2**. The difference between θ and ω is the largest in the case of $AuNTf_2$ among the catalysts examined (entry 12). In the case of $AuClPPh_3$, the chemoselectivity was changed; **3** was formed as an isolable product and the desired **2** was not obtained at all (Table 2, entry 8). Accordingly, we carried out the computation for the $AuClPPh_3$ case, and the result is shown in entry 14. However, the reason for the switch of the chemoselectivity is not clear at present.

With the optimized conditions in hand, the scope of the electrophilic cyclization of various substrates, reagents, and catalysts was studied. The results are summarized in Table 4. The substrate **1a** was cyclized in the presence of 5 equiv of I_2 in CH_3NO_2 within 24 h to afford a mixture of product **2aa** in 69% yield and the triazole **3** in 7% yield (entry 1). Other electrophiles such as NIS and ICl were also investigated. The reactions proceeded smoothly to produce **2aa** without formation of **3** (entries 2 and 3). The use of NIS gave **2aa** in a higher yield than ICl. Bromo-substituted quinoline **2ab** was obtained with Br_2 or NBS at shorter reaction times in higher yields as compared to the case of iodo-substituted quinoline (entries 4 and 5). The quinoline **2ac** was obtained in 85% or 62% isolated yield, respectively, in the presence of 30 mol % of $AuCl_3$/90 mol % of $AgNTf_2$ or in the presence of 1.2 equiv of $HNTf_2$ (entries 6 and 7). Substrate **1b** having methyl at the para-position of the aromatic ring afforded the corresponding cyclized products **2ba** and **2bb** with use of NIS and Br_2, respectively, in high yields (entries 8 and 9). The substrate **1c** bearing a 3,5-difluoro group on the aromatic ring afforded the corresponding cyclized products **2ca**−**2cc** in good to high yields (entries 10−12). The reactions of substrates **1d** and **1e**, having a methyl and a cyclohexyl group at the alkyne terminus, proceeded smoothly under the standard condition to give quinolines **2da**, **2db**, and **2ea**−**2ec** in good yields (entries 13−17). The cyclization of **1f** afforded the bromo-substituted **2fa** and H-substituted **2fb** upon treatment with

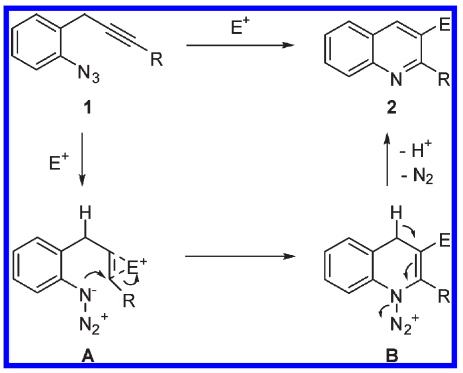
TABLE 4. Synthesis of Substituted Quinolines with Various Substrates and Electrophiles[a]



Entry	Substrate	Electrophile	Time (h)	Product **2** (E)		yield %[b]
1	 **1a**	I_2	24		**2aa (I)**	69[c]
2		ICl	0.5		**2aa (I)**	55
3		NIS	12		**2aa (I)**	82
4		Br_2	1		**2ab (Br)**	96
5		NBS	0.5		**2ab (Br)**	84
6		$Au(NTf_2)_3$[d]	24		**2ac (H)**	85
7		$HNTf_2$[e]	24		**2ac (H)**	62
8	 **1b**	NIS	1		**2ba (I)**	90
9		Br_2	3		**2bb (Br)**	99
10	 **1c**	ICl	2		**2ca (I)**	82
11		Br_2	1		**2cb (Br)**	89
12		$Au(NTf_2)_3$[d]	24		**2cc (H)**	83
13	 **1d**	NIS	12		**2da (I)**	47
14		Br_2	2		**2db (Br)**	46
15	 **1e**	NIS	12		**2ea (I)**	51
16		Br_2	2		**2eb (Br)**	56
17		$Au(NTf_2)_3$[d]	24		**2ec (H)**	57
18	 **1f**	Br_2	2		**2fa (Br)**	92
19		$Au(NTf_2)_3$[d]	12		**2fb (H)**	70
20	 **1g**	NIS	60		**2ga (I)**	82
21		Br_2[f]	24		**2gb (Br)**	87
22	 **1h**	NIS	42		**2ha (I)**	80
23		Br_2[f]	24		**2hb (Br)**	87
24		$Au(NTf_2)_3$[d]	24		**2hc (H)**	71
25		$HNTf_2$[e]	24		**2hc (H)**	60
26	 **1i**	NIS	12		**2ia (I)**	78
27		Br_2	2		**2ib (Br)**	73
28	 **1j**	NIS	48		**2ja (I)**	70
29		NBS	48		**2jb (Br)**	74
30	 **1k**	Br_2[g]	1		**2ka (Br)**	59

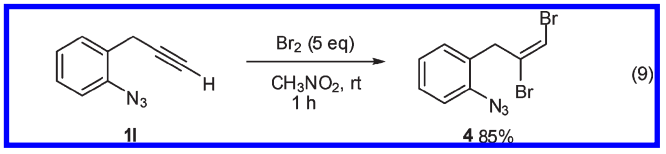
[a]The reaction of **1** (0.2 mmol) was carried out in the presence of 5 equiv of electrophile (I2, ICl, NIS, Br_2, or NBS) in CH_3NO_2 (0.1 M) at room temperature for the indicated reaction time under argon unless otherwise noted. [b]Isolated yield. [c]Triazole was obtained in 7% as a minor product. [d]Substrate **1** (0.2 mmol) was treated with 30 mol % of $AuCl_3$ and 90 mol % of $AgNTf_2$ in THF (2 mL) at 100 °C under argon. [e]Substrate **1** (0.2 mol) was treated with 1.2 equiv of $HNTf_2$ in THF (2 mL) at 100 °C under argon. [f]7 equiv of Br_2 was used. [g]10 equiv of Br_2 was used.

SCHEME 1. A Plausible Mechanism



Br_2 and $Au(NTf_2)_3$, respectively, in good to high yields (entries 18 and 19). The substrates **1g** and **1h**, in which the aromatic ring was substituted with chloro and bromo groups, gave the corresponding quinolines **2ga**, **2gb**, and **2ha**−**2hc** in good to high yields irrespective of the use of Br_2, NIS, $Au(NTf_2)_3$, or $HNTf_2$ as electrophiles (entries 20−25). In both cases, increased amounts of bromine were used to obtain good chemical yields. Substitution of the OAc group at R^2 did not exert any significant influence on the cyclization: the reaction proceeded very smoothly to afford the products **2ia**, **2ib** and **2ja**, **2jb** in good yields (entries 26−29). The use of NBS, instead of Br_2, was also effective for the formation of quinoline **2jb** (entry 29). A biquinoline was synthesized by the electrophilic cyclization: the substrate **1k** was treated with Br_2 at room temperature, leading to the desired product **2ka** in 59% yield (entry 30).

When **1*l*** (R^3 = H) was treated with Br_2, the dibromination of the triple bond took place, leading to the bis-bromine adduct **4** selectively in 85% yield (eq 9).



(9)

A plausible mechanism for the formation of quinoline **2** via electrophilic cyclization of 1-azido-2-(2-propynyl)benzene **1** is illustrated in Scheme 1. Coordination of the triple bond of **1** to an electrophile E^+ is presumed to generate an intermediate **A**, and subsequent nucleophilic attack of a nitrogen atom to the electron-deficient alkyne would form an intermediate **B**. Elimination of N_2 and H^+ then results in the formation of quinoline **2**.

In conclusion, we have developed a new and efficient strategy for the synthesis of quinolines via electrophilic cyclization of 1-azido-2-alkynylbenzene derivatives. This reaction provides a useful method for the synthesis of multisubstituted quinolines in good to high yields. Particularly, the easy synthesis of bisquinoline **2ka** is interesting and we are now extending this methodology for the synthesis of polyaromatic rings.

Experimental Section

General Procedure for the Electrophilic Cyclization of 1-Azido-2-(3-phenylprop-2-ynyl)benzene 1a by Br_2. To a 5 mL screw capped vial equipped with a magnetic stirring bar were added 1-azido-2-(3-phenylprop-2-ynyl)benzene (**1a**, 46.7 mg, 0.2 mmol) and CH_3NO_2 (1.5 mL) under an argon atmosphere. Bromine (0.052 mL, 1.0 mmol, 5 equiv) in 0.5 mL of CH_3NO_2 was added dropwise to the vial with a syringe. The reaction mixture was stirred at room temperature for 1 h, and the progress of the reaction was monitored by TLC (hexane/ethyl acetate, 5/1). After complete consumption of the starting material, saturated aqueous $Na_2S_2O_3$ was added, and stirring was continued for 5−15 min. The mixture was extracted with CH_2Cl_2 (2 × 10 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate; 20/1−10/1) to afford product **2ab** in 96% yield (54.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61−7.44 (m, 4H), 7.81−7.71 (m, 4H), 8.13 (d, J = 8.5 Hz, 1H), 8.51 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.8, 126.4, 127.4, 128.0, 128.2, 128.8, 129.3, 129.5, 130.0, 139.8, 139.9, 146.5, 158.1. IR (KBr) 3050, 2921, 1615, 1462, 1078, 743, 689 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{10}BrN$ (M + Na) 305.9889, found 305.9888.

General Procedure for the Electrophilic Cyclization of 1-Azido-2-(3-phenylprop-2-ynyl)benzene 1a by $AuCl_3/AgNTf_2$. To a THF (2 mL, 0.1 M) solution of $AuCl_3$ (18.2 mg, 0.06 mmol) and $AgNTf_2$ (70.9 mg, 0.18 mmol), which were weighed in a glovebox, was added 1-azido-2-(3-phenylprop-2-ynyl)benzene (**1a**, 46.7 mg, 0.2 mmol) at room temperature under an Ar atmosphere in a pressured vial. The mixture was stirred at 100 °C for 24 h. The reaction progress was monitored by TLC (hexane/ethyl acetate, 5/1). After consumption of **1a**, the reaction mixture was cooled to room temperature and filtered through a short Florisil pad with use of ethyl acetate as eluent. After concentration, the residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 20/1−10/1) to afford product **2ac** in 85% yield as a white solid (34.9 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.41 (m, 4H), 7.71 (tt, J = 7.5, 1.5 Hz, 1H), 7.90−7.78 (m, 2H), 8.24−8.11 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.0, 126.2, 127.4, 127.4, 127.5, 128.7, 128.8, 128.8, 129.3, 129.6, 129.7, 136.7, 157.3. IR (KBr) 3054, 3034, 2925, 2119, 1580, 1445, 827, 762, 691 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{11}N$ (M + Na) 228.0784, found 228.0784.

General Procedure for the Electrophilic Cyclization of 1-Azido-2-(3-phenylprop-2-ynyl)benzene 1a by $HNTf_2$. To a THF (2 mL, 0.1 M) solution of $HNTf_2$ (67.5 mg, 0.24 mmol), which was weighed in a glovebox, was added 1-azido-2-(3-phenylprop-2-ynyl)benzene (**1a**, 46.7 mg, 0.2 mmol) at room temperature under an Ar atmosphere in a pressured vial. The mixture was stirred at 100 °C for 24 h. The reaction progress was monitored by TLC (hexane/ethyl acetate, 5/1). After consumption of **1a**, the reaction mixture was cooled to room temperature and filtered through a short Florisil pad with use of ethyl acetate as eluent. After concentration, the residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 20/1−10/1) to afford product **2ac** in 62% yield as a white solid (25.5 mg).

Supporting Information Available: Characterization data for all new compounds and details of computation. This material is available free of charge via the Internet at http://pubs.acs.org.