Tetrahedron 67 (2011) 5168–5175

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Direct synthesis of highly fused perimidines by copper(I)-catalyzed hydroamination of 2-ethynylbenzaldehydes

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ARTICLE INFO

Article history:
Received 11 April 2011
Accepted 12 May 2011
Available online 18 May 2011

Keywords:
C–H arylation
Polyarene
Isoquinoline
Perimidine
Multi-component reaction

ABSTRACT

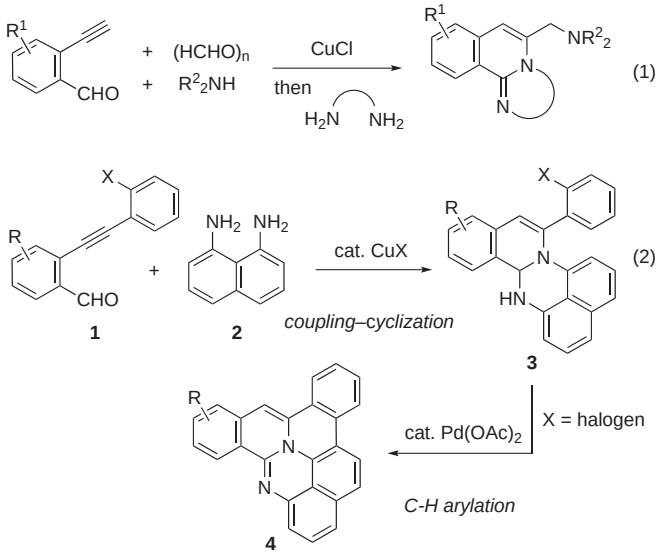
A novel synthesis of highly fused perimidine derivatives was achieved in two steps from 2-alkynylbenzaldehydes. Copper-catalyzed annulation of 2-[(2-bromophenyl)ethynyl]benzaldehydes with 1,8-diaminonaphthalene produced dihydroisoquinolino[2,1-*a*]perimidines bearing a 2-bromophenyl group. Subsequent palladium-catalyzed C–H arylation provided dibenzo[1,2:7,8]quinolizino[3,4,5,6-*kla*]perimidine derivatives in moderate to good yields.

1. Introduction

Because of their charge mobility, highly-conjugated polycyclic compounds are important in practical applications for electronic materials, such as in dye lasers and electroluminescent materials.[1–5] Compounds with a cyclic amidine moiety, such as fused perimidine derivatives,[6] are particularly useful because they have high π-stacking ability, electron affinity, and reduction potential, and can be used as core structures of biologically active compounds.[7–9]

We have an ongoing program directed toward fused isoquinoline synthesis based on four-component coupling and cyclization cascade (Scheme 1, Eq. 1).[10,11] We postulated that a fused perimidine skeleton could be readily constructed by copper-catalyzed annulation of 2-ethynylbenzaldehyde **1** with 1,8-diaminonaphthalene **2** (Eq. 2). Use of 2-alkynylbenzaldehydes **1** bearing an aryl halide moiety (X=halogen) with palladium-catalyzed C–H arylation[4,5,12–21] of the resulting perimidines **3** would provide facile access to a new class of highly fused perimidines **4**.

Recently, several syntheses of isoquinoline-fused compounds using a diamine component have been reported (Scheme 2). Dyker et al. used 1,2-phenylenediamine for construction of a benzimidazo[2,1-*a*]isoquinoline skeleton from 2-alkynylbenzaldehydes (Eq. 3).[22,23] Yanada et al. reported palladium-catalyzed direct synthesis of benzimidazo[2,1-*a*]isoquinolines through one-pot Sonogashira coupling between 2-bromobenzaldehydes and an alkyne, followed by cyclization with 1,2-phenylenediamine (Eq. 4).[24] Patil et al. reported a gold-catalyzed reaction of 2-alkynylbenzaldehydes with aniline, which had another nucleophilic functionality, such as pyrrole/indole/imidazole rings or amino/sulfonamide/hydroxy groups (Eq. 5).[25] However, annulation of 2-alkynylbenzaldehydes with a diamine component in which each of amino groups is located on a different benzene ring is unprecedented.[26] Here, we



Scheme 1. Strategy for direct synthesis of highly fused perimidines.

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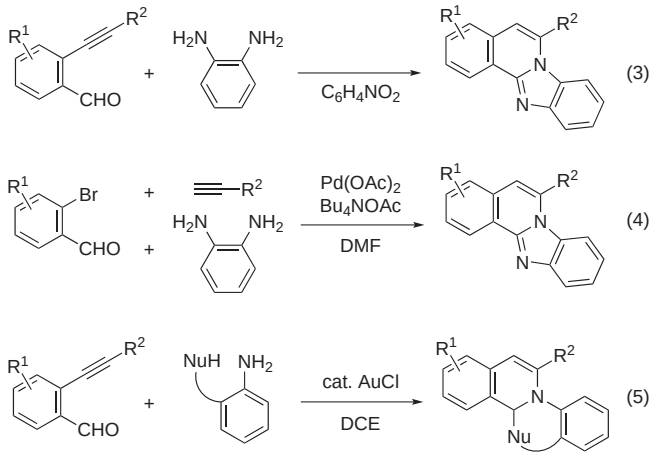
doi:10.1016/j.tet.2011.05.051



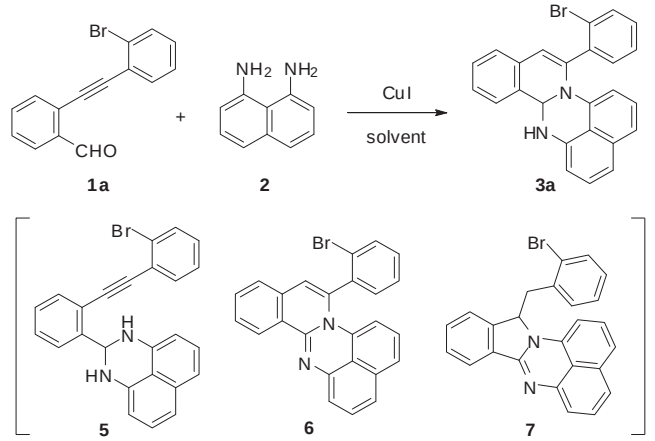
Scheme 2. Related reactions for synthesis of fused isoquinolines.

report a novel synthesis of highly fused perimidines **4** by copper-catalyzed coupling and cyclization of 2-alkynylbenzaldehydes **1** and 1,8-diaminonaphthalene **2**, followed by palladium-catalyzed C–H arylation (Scheme 1).

2. Results and discussion

The reaction conditions for the copper-catalyzed annulation using 2-[(2-bromophenyl)ethynyl]benzaldehyde **1a** and 1,8-diaminonaphthalene **2** were optimized (Table 1). When the aldehyde **1a** was treated with **2** in the presence of CuI (10 mol %) in DMF, the isoquinoline **6** was obtained as the oxidized form in 53% yield (entry 1). The use of dioxane as the solvent at 80 °C under an Ar or O_2 atmosphere was less effective, and produced the intermediate aminal **5** as the major product (56–67% yield) along with unoxidized isoquinoline **3a** (18–20% yield, entries 2 and 3). Although the reaction at higher temperature (120 °C) increased the yield of **3a** to 92% (entry 4), scaling up the reaction from 0.11 mmol to 1.1 mmol was unsuccessful (entry 5). The use of microwave irradiation solved this problem, and **3a** was produced in 91% yield on the 1.1 mmol scale (entry 6). Because microwave conditions in DMF led to an unsatisfactory result (entry 7), the conditions shown in entry 6 were used for further investigations.

Table 1
Optimization of reaction conditions for the coupling–cyclization[a]

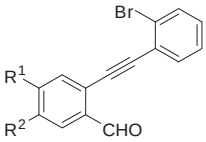
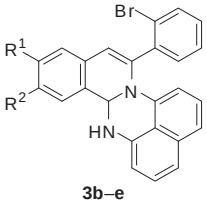
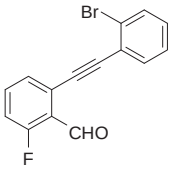
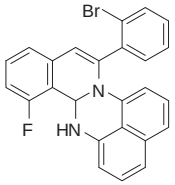
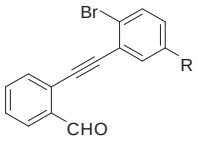
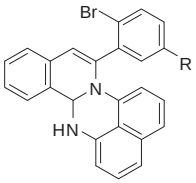
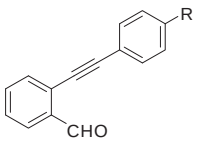
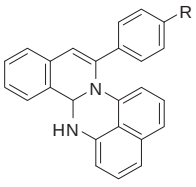


Entry	Solvent	Conditions	Yield[c] (%)			
			3a	**5**	**6**	**7**
1	DMF	110 °C, 20 h	–	–	53	–
2	Dioxane	80 °C, 10 h	20	67	–	–
3[d]	Dioxane	80 °C, 30 h	18	56	7	–
4	Dioxane	reflux 12 h	92	–	–	5
5[e]	Dioxane	reflux 24 h	54	34	–	–
6[e]	Dioxane	MW[b], 150 °C, 1 h	91	–	–	5
7	DMF	MW[b], 140 °C, 1 h	56	–	7	31

[a] Unless otherwise stated the reactions were conducted with **1a** (0.11 mmol) and **2** (1.2 equiv) in the presence of CuI (10 mol %) under Ar.
[b] MW=microwave irradiation.
[c] Isolated yields.
[d] The reaction was conducted under an O_2 atmosphere.
[e] The reactions were conducted on a 1.1 mmol scale.

The substrate scope of the copper-catalyzed annulation was then examined using substituted 2-alkynylbenzaldehydes **1b**–**h** (Table 2). These substrates were readily prepared by Sonogashira coupling of substituted 2-ethynylbenzaldehydes with 2-iodobromobenzene (see the Experimental section). The substrates **1b**–**e**, bearing an

Table 2
Coupling–cyclization of various 2-alkynylbenzaldehydes[a]

Entry	Substrate	Product	Yield[b] (%)
	 **1b–e**	 **3b–e**	
1	**1b**/**3b**: R^1=F, R^2=H		97
2	**1c**/**3c**: R^1=Me, R^2=H		97
3	**1d**/**3d**: R^1=H, R^2=F		89
4	**1e**/**3e**: R^1=H, R^2=OMe		71
5	 **1f**	 **3f**	89
	 **1g**, **h**	 **3g**, **h**	
6	**1g**/**3g**: R=F		73
7	**1h**/**3h**: R=Me		91
	 **1i**, **j**	 **3i**, **j**	
8	**1i**/**3i**: R=H		91
9	**1j**/**3j**: R=Me		91

[a] Compounds **1** (50 mg) and **2** (1.5 equiv) in dioxane were stirred for 1 h at 150 °C under microwave irradiation in the presence of CuI (10 mol %).
[b] Isolated yields.

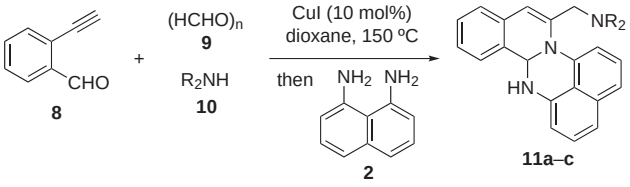
electron-withdrawing (fluoro) or -donating (methyl or methoxy) substituent at the *para*- or *meta*-position to the formyl group, underwent the desired annulation under the standard reaction conditions. The corresponding fused perimidines **3b**–**e** were produced in good to excellent yields (71–97%, entries 1–4). Substitution with a fluoro group at the *ortho* position was also tolerated (entry 5). Influence of the benzene substitution at the alkyne terminus with a fluoro or methyl group was less important (entries 6 and 7). The substrates **1i** and **1j** without a bromo substituent also gave the desired products **3i** and **3j** in high yields (91%, entries 8 and 9).

In order to expand the use of 1,8-diaminonaphthalene **2** as a precursor of other perimidine derivatives, we examined four-component annulation using 2-ethynylbenzaldehyde **8**, formaldehyde **9**, and secondary amine **10**. As shown in Table 3, the reaction with diisopropylamine, piperidine, and morpholine as the secondary amine component produced perimidines **11a**–**c** bearing an aminomethyl group (52–70% yield).

Next, palladium-catalyzed C–H arylation for the synthesis of highly fused perimidines was investigated. Isoquinoline **3a** was chosen as the model substrate for optimization of the cyclization conditions (Table 4). When isoquinoline **3a** was allowed to react with $Pd(OAc)_2$ (10 mol %) in the presence of PPh_3 (25 mol %) and Cs_2CO_3 (2 equiv) in dioxane, the desired heptacyclic perimidine **4a** as the oxidized form was obtained in 40% yield (entry 1). The use of P(*t*-Bu)$_3$·HBF$_4$ as a ligand slightly improved the yield (43%, entry 2). Reaction in the absence of phosphine as the ligand (entry 3) or under microwave irradiation at 160 °C (entry 4) was less effective. DMF was promising as the reaction solvent, and produced **4a** in 65% yield (entry 5). Among the palladium catalysts and phosphine ligands tested (entries 5–8), $Pd(OAc)_2/PPh_3$ was the most effective in DMF (entry 5). Other solvents (toluene, DMSO, propan-2-ol, and EtOH, entries 9–12) and bases (Na_2CO_3, K_2CO_3, K_3PO_4, and KOAc, entries 13–16) were also examined, and K_3PO_4 in DMF was the most effective (78% yield, entry 15).

Finally, a series of substrates with various substituent patterns were applied to the C–H arylation under the optimized conditions for **3a** (Table 5). All the substituted substrates **3b**–**h** afforded the desired products **4b**–**h** as the oxidized form (45–62% yield, entries 1–7). This result was independent of the substituents on the two benzene rings. The moderate yields were partly because crystallization was required for purification. Poor solubility of **4** in various nonpolar or polar solvents, including aromatic solvents, did not allow easy purification by column chromatography. These results show that copper-catalyzed annulation of 2-alkynylbenzaldenydes **1** with 1,8-diaminonaphthalene **2**, and subsequent palladium-catalyzed arylation provides convenient access to highly fused perimidine derivatives.

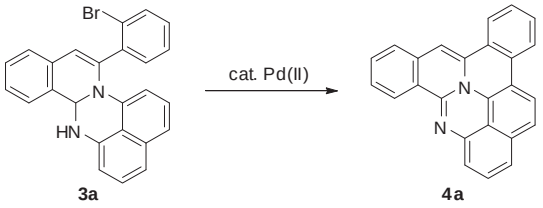
Table 3
Four-component synthesis of fused perimidines[a]



Entry	R_2NH	Conditions[b]	Product	Yield[c] (%)
1	(*i*-Pr)$_2$NH	rt, 1 h	**11a**	52
2		rt, 6 h	**11b**	70
3		rt, 4 h	**11c**	61

[a] After the three-component reaction of **8** (0.23 mmol), **9** (2 equiv), and **10** (2 equiv) in the presence of CuI (10 mol %) in dioxane, **2** (3 equiv) was added and the reaction mixture was stirred for 1 h at 150 °C under microwave irradiation.
[b] Conditions for the reaction of **8** with **9** and **10**.
[c] Isolated yields.

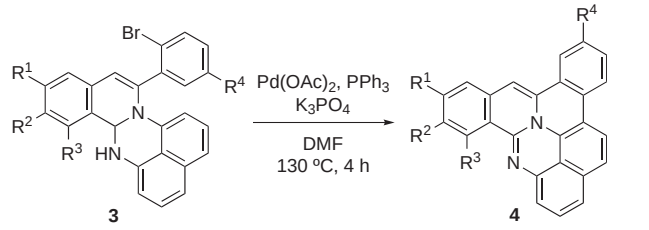
Table 4
Optimization of reaction conditions for palladium-catalyzed C–H arylation[a]



Entry	Catalyst	Ligand	Solvent	Base	Temp	Time	Yield[b] (%)
1	$Pd(OAc)_2$	PPh_3	Dioxane	Cs_2CO_3	Reflux	5 h	40
2	$Pd(OAc)_2$	P(*t*-Bu)$_3$·HBF$_4$	Dioxane	Cs_2CO_3	Reflux	5 h	43
3	$Pd(OAc)_2$	None	Dioxane	Cs_2CO_3	Reflux	5 h	0
4	$Pd(OAc)_2$	PPh_3	Dioxane	Cs_2CO_3	MW,[c] 160 °C	15 min	27
5	$Pd(OAc)_2$	PPh_3	DMF	Cs_2CO_3	130 °C	4 h	65
6	$Pd(OAc)_2$	P(*t*-Bu)$_3$·HBF$_4$	DMF	Cs_2CO_3	130 °C	6 h	56
7	$Pd(PPh_3)_2Cl_2$	PPh_3	DMF	Cs_2CO_3	130 °C	5 h	22
8	$Pd(PPh_3)_4$	PPh_3	DMF	Cs_2CO_3	130 °C	5 h	0
9	$Pd(OAc)_2$	PPh_3	Toluene	Cs_2CO_3	Reflux	6 h	<60[d]
10	$Pd(OAc)_2$	PPh_3	DMSO	Cs_2CO_3	130 °C	6 h	<65[d]
11	$Pd(OAc)_2$	PPh_3	Propan-2-ol	Cs_2CO_3	Reflux	6 h	0
12	$Pd(OAc)_2$	PPh_3	EtOH	Cs_2CO_3	Reflux	4 h	0
13	$Pd(OAc)_2$	PPh_3	DMF	Na_2CO_3	130 °C	4 h	39
14	$Pd(OAc)_2$	PPh_3	DMF	K_2CO_3	130 °C	4 h	<57[d]
15	$Pd(OAc)_2$	PPh_3	DMF	K_3PO_4	130 °C	4 h	78
16	$Pd(OAc)_2$	PPh_3	DMF	KOAc	130 °C	4 h	<60[d]

[a] All reactions were conducted using **3a** (0.06–0.07 mmol) in the presence of a palladium catalyst (10 mol %), ligand (25 mol %), and base (2 equiv).
[b] Isolated yields.
[c] MW=microwave irradiation.
[d] Contained inseparable impurities.

Table 5
Synthesis of highly fused perimidines[a]



Entry	Substrate/Product	R^1	R^2	R^3	R^4	Yield[b] (%)
1	**3b**/**4b**	F	H	H	H	45
2	**3c**/**4c**	Me	H	H	H	53
3	**3d**/**4d**	H	F	H	H	53
4	**3e**/**4e**	H	OMe	H	H	61
5	**3f**/**4f**	H	H	F	H	51
6	**3g**/**4g**	H	H	H	F	49
7	**3h**/**4h**	H	H	H	Me	62

[a] All reactions were conducted with **3** (30 mg) in the presence of K_3PO_4 (2 equiv), $Pd(OAc)_2$ (10 mol %), and PPh_3 (25 mol %) in DMF.
[b] Isolated yields after recrystallization.

3. Conclusions

Fused perimidine derivatives were synthesized by copper-catalyzed annulation of 2-alkynylbenzaldenydes **1** with 1,8-diaminonaphthalene **2**. The four-component approach was applied to this reaction to produce perimidine derivatives bearing an aminomethyl group. Palladium-catalyzed C–H arylation of perimidines bearing an aryl bromide moiety produced a new class of highly fused perimidine derivatives in moderate to good yields.

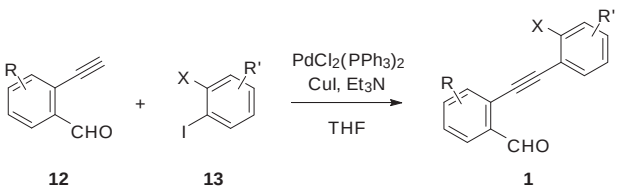
4. Experimental

4.1. General

^{1}H NMR spectra were recorded using a JEOL AL-500 spectrometer at 500 MHz frequency. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in $CDCl_3$ or CD_3OD) as internal standard. ^{13}C NMR spectra were recorded using a JEOL AL-500 and referenced to the residual $CHCl_3$ or MeOH signal. Melting points were measured by a hot stage melting points apparatus (uncorrected). For column chromatography, Wakogel C-300E was employed. Microwave reaction was conducted in a sealed glass vessel (capacity 10 mL) using CEM Discover microwave reactor with a run time of no more than 10 min at below 300 W. The commercially available compounds including **2, 9**, **10a**–**c**, **13a**–**e**, and **14** were used without further purification.

The compounds **12a**–**e**[10] and **12f**[27] were prepared according to the literature.

4.2. Preparation of starting materials



*4.2.1. 2-[(2-Bromophenyl)ethynyl]benzaldehyde (**1a**).* A mixture of 2-ethynylbenzaldehyde (**12a**) (1.00 g, 7.68 mmol), 1-bromo-2-iodobenzene (**13a**) (1.18 mL, 9.22 mmol), CuI (146 mg, 0.77 mmol), $PdCl_2(PPh_3)_2$ (107 mg, 0.15 mmol), and Et_3N (15 mL) in THF (15 mL) was stirred at 80 °C for 2 h under argon, and filtrated through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with hexane–EtOAc (15:1) to give **1a** (1.81 g, 83%) as a colorless solid: mp 69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (ddd, J=8.0, 8.0, 1.7 Hz, 1H, Ar), 7.33 (ddd, J=8.0, 8.0, 1.1 Hz, 1H, Ar), 7.48 (dd, J=8.0, 8.0 Hz, 1H, Ar), 7.58–7.62 (m, 2H, Ar), 7.64 (dd, J=8.0, 1.1 Hz, 1H, Ar), 7.70 (d, J=8.0 Hz, 1H, Ar), 7.97 (dd, J=8.0, 1.1 Hz, 1H, Ar), 10.76 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 89.3, 94.6, 124.6, 125.8, 126.5, 127.2 (2C), 129.0, 130.1, 132.6, 133.4, 133.5, 133.8, 136.1, 191.9. Anal. Calcd for $C_{15}H_9BrO$: C, 63.18; H, 3.18. Found: C, 63.20; H, 3.28.

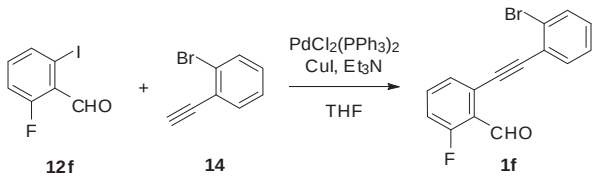
*4.2.2. 2-[(2-Bromophenyl)ethynyl]-4-fluorobenzaldehyde (**1b**).* By a procedure identical with that described for the preparation of **1a**, 2-ethynyl-4-fluorobenzaldehyde (**12b**) (100 mg, 0.68 mmol) was converted to **1b** (169 mg, 83%) by the reaction with 1-bromo-2-iodobenzene (**13a**) (104 μL, 0.81 mmol), CuI (6.4 mg, 0.034 mmol), $PdCl_2(PPh_3)_2$ (23.7 mg, 0.034 mmol), and Et_3N (1.0 mL) in THF (1.0 mL) at 80 °C for 1.5 h: colorless solid: mp 109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (ddd, J=8.0, 8.0, 2.1 Hz, 1H, Ar), 7.26 (ddd, J=8.0, 8.0, 1.7 Hz, 1H, Ar), 7.33–7.38 (m, 2H, Ar), 7.60 (dd, J=8.0, 1.7 Hz, 1H, Ar), 7.65 (d, J=8.0 Hz, 1H, Ar), 8.00 (dd, J=8.6, 5.7 Hz, 1H, Ar), 10.67 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 88.0 (d, J=2.4 Hz), 95.6, 116.9 (d, J=21.6 Hz), 119.8 (d, J=22.8 Hz), 124.1, 125.9, 127.2, 128.9 (d, J=10.8 Hz), 130.0 (d, J=9.6 Hz), 130.5, 132.7, 132.9, 133.6, 165.6 (d, J=256.7 Hz), 190.2. Anal. Calcd for $C_{15}H_8BrFO$: C, 59.43; H, 2.66. Found: C, 59.49; H, 2.80.

*4.2.3. 2-[(2-Bromophenyl)ethynyl]-4-methylbenzaldehyde (**1c**).* By a procedure identical with that described for the preparation of **1a**, 2-ethynyl-4-methylbenzaldehyde (**12c**) (50 mg, 0.35 mmol) was converted to **1c** (78 mg, 75%) by the reaction with 1-bromo-2-iodobenzene (**13a**) (53.4 μL, 0.42 mmol), CuI (3.3 mg, 0.017 mmol), $PdCl_2(PPh_3)_2$ (12.2 mg, 0.017 mmol), and Et_3N (0.75 mL) in THF (0.75 mL) at 80 °C for 1 h: colorless solid: mp 79 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H, CCH_3) 7.22 (ddd, J=8.0, 8.0, 1.5 Hz, 1H, Ar), 7.27 (d, J=8.0 Hz, 1H, Ar), 7.32 (ddd, J=8.0, 8.0, 1.1 Hz, 1H, Ar), 7.50 (s, 1H, Ar), 7.58 (dd, J=8.0, 1.7 Hz, 1H, Ar), 7.63 (dd, J=8.0, 1.1 Hz, 1H, Ar), 7.86 (d, J=8.0 Hz, 1H, Ar), 10.69 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 89.5, 94.1, 124.7, 125.8, 126.4, 127.1, 127.2, 130.0 (2C), 132.6, 133.4, 133.7, 134.0, 144.8, 191.5. Anal. Calcd for $C_{16}H_{11}BrO$: C, 64.24; H, 3.71. Found: C, 64.15; H, 3.82.

*4.2.4. 2-[(2-Bromophenyl)ethynyl]-5-fluorobenzaldehyde (**1d**).* By a procedure identical with that described for the preparation of **1a**, 2-ethynyl-5-fluorobenzaldehyde (**12d**) (100 mg, 0.68 mmol) was converted to **1d** (174 mg, 85%) by the reaction with 1-bromo-2-iodobenzene (**13a**) (104 μL, 0.81 mmol), CuI (6.4 mg, 0.034 mmol), $PdCl_2(PPh_3)_2$ (23.7 mg, 0.034 mmol), and Et_3N (1.0 mL) in THF (1.0 mL) at 80 °C for 1.5 h: colorless solid: mp 93 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (ddd, J=7.7, 7.7, 1.5 Hz, 1H, Ar), 7.28–7.34 (m, 2H, Ar), 7.58 (dd, J=7.7, 1.4 Hz, 1H, Ar), 7.62–7.64 (m, 2H, Ar), 7.69 (dd, J=8.6, 5.2 Hz, 1H, Ar), 10.70 (d, J=3.4 Hz, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 88.2, 94.4, 113.7 (d, J=22.8 Hz), 121.3 (d, J=22.8 Hz), 122.5 (d, J=3.6 Hz), 124.4, 125.7, 127.2, 130.2, 132.6, 133.4, 135.4 (d, J=7.2 Hz), 138.1 (d, J=7.2 Hz), 162.6 (d, J=253.1 Hz), 190.6. Anal. Calcd for $C_{15}H_8BrFO$: C, 59.43; H, 2.66. Found: C, 59.60; H, 2.92.

*4.2.5. 2-[(2-Bromophenyl)ethynyl]-5-methoxylbenzaldehyde (**1e**).* By a procedure identical with that described for the preparation of **1a**, 2-ethynyl-5-methoxybenzaldehyde (**12e**) (100 mg, 0.62 mmol) was converted to **1e** (167 mg, 85%) by the reaction with 1-bromo-2-iodobenzene (**13a**) (95.9 μL, 0.75 mmol), CuI (5.9 mg, 0.031 mmol), $PdCl_2(PPh_3)_2$ (21.9 mg, 0.031 mmol), and Et_3N (1.0 mL) in THF (1.0 mL) at 80 °C for 1 h: colorless solid: mp 102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 3H, CH_3), 7.14 (dd, J=8.6, 2.9 Hz,

1H, Ar), 7.20 (ddd, *J*=7.7, 7.7, 1.3 Hz, 1H, Ar), 7.31 (ddd, *J*=7.7, 7.7, 1.1 Hz, 1H, Ar), 7.44 (d, *J*=2.9 Hz, 1H, Ar), 7.56 (dd, *J*=8.0, 1.7 Hz, 1H, Ar), 7.60–7.63 (m, 2H, Ar), 10.72 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.6, 89.4, 93.3, 109.8, 119.1, 121.7, 124.9, 125.6, 127.1, 129.7, 132.5, 133.2, 134.7, 137.6, 160.1, 191.8. Anal. Calcd for $C_{16}H_{11}BrO_2$: C, 60.98; H, 3.52. Found: C, 60.95; H, 3.41.



*4.2.6. 2-[(2-Bromophenyl)ethynyl]-6-fluorobenzaldehyde (**1f**).* By a procedure similar to that described for the preparation of **1a**, 2-fluoro-6-iodobenzaldehyde (**12f**) (50 mg, 0.20 mmol) was converted to **1f** (56 mg, 92%) by the reaction with 1-bromo-2-ethynylbenzene (**14**) (43.4 mg, 0.24 mmol), CuI (1.9 mg, 0.012 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.012 mmol), and Et_3N (0.5 mL) in THF (0.5 mL) at 50 °C for 2 h: colorless solid: mp 74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (ddd, *J*=7.7, 7.7, 3.6 Hz, 1H, Ar), 7.24 (ddd, *J*=7.7, 7.7, 1.7 Hz, 1H, Ar), 7.33 (ddd, *J*=7.7, 7.7, 1.1 Hz, 1H, Ar), 7.50–7.57 (m, 2H, Ar), 7.61–7.64 (m, 2H, Ar), 10.70 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 89.2 (d, *J*=4.8 Hz), 95.2, 117.2 (d, *J*=21.6 Hz), 124.4 (d, *J*=9.6 Hz), 125.8, 127.0, 127.1 (d, *J*=25.2 Hz), 129.7 (2C), 130.4, 132.6, 133.7, 134.8 (d, *J*=10.8 Hz), 162.4 (d, *J*=262.7 Hz), 188.5. Anal. Calcd for $C_{15}H_8BrFO$: C, 59.43; H, 2.66. Found: C, 59.42; H, 2.93.

*4.2.7. 2-[(2-Bromo-5-fluorophenyl)ethynyl]benzaldehyde (**1g**).* By a procedure identical with that described for the preparation of **1a**, 2-ethynylbenzaldehyde (**12a**) (100 mg, 0.77 mmol) was converted to **1g** (177 mg, 91%) by the reaction with 1-bromo-4-fluoro-2-iodobenzene (**13b**) (83.7 μL, 0.64 mmol), CuI (6.1 mg, 0.032 mmol), $PdCl_2(PPh_3)_2$ (22.5 mg, 0.032 mmol), and Et_3N (1.5 mL) in THF (1.5 mL) at 50 °C for 2 h: colorless solid: mp 89–90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (ddd, *J*=8.3, 8.3, 3.1 Hz, 1H, Ar), 7.29 (dd, *J*=8.3, 2.9 Hz, 1H, Ar), 7.49 (dd, *J*=7.4, 7.4 Hz, 1H, Ar), 7.55–7.61 (m, 2H, Ar), 7.68 (d, *J*=7.4 Hz, 1H, Ar), 7.96 (dd, *J*=7.4, 1.1 Hz, 1H, Ar), 10.71 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 90.2, 93.4 (d, *J*=3.6 Hz), 117.7 (d, *J*=22.8 Hz), 112.1 (d, *J*=24.0 Hz), 120.3 (d, *J*=3.6 Hz), 125.7, 126.0 (d, *J*=9.6 Hz), 127.2, 129.3, 133.4, 133.7, 133.8 (d, *J*=9.6 Hz), 136.2, 161.3 (d, *J*=248.3 Hz), 191.4. Anal. Calcd for $C_{15}H_8BrFO$: C, 59.43; H, 2.66. Found: C, 59.64; H, 2.95.

*4.2.8. 2-[(2-Bromo-5-methylphenyl)ethynyl]benzaldehyde (**1h**).* By a procedure identical with that described for the preparation of **1a**, 2-ethynylbenzaldehyde (**12a**) (200 mg, 1.54 mmol) was converted to **1h** (331 mg, 72%) by the reaction with 1-bromo-2-iodo-4-methylbenzene (**13c**) (182 μL, 1.28 mmol), CuI (12.2 mg, 0.064 mmol), $PdCl_2(PPh_3)_2$ (44.9 mg, 0.064 mmol), and Et_3N (3.0 mL) in THF (3.0 mL) at 80 °C for 1 h: colorless solid: mp 93–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3H, CCH_3), 7.04 (dd, *J*=8.0, 2.0 Hz, 1H, Ar), 7.42 (d, *J*=1.7 Hz, 1H, Ar), 7.46–7.51 (m, 2H, Ar), 7.60 (ddd, *J*=7.4, 7.4, 1.1 Hz, 1H, Ar), 7.69 (d, *J*=8.0 Hz, 1H, Ar), 7.97 (dd, *J*=8.0, 1.1 Hz, 1H, Ar), 10.76 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 88.9, 94.9, 122.4, 124.2, 126.6, 127.1, 128.9, 131.2, 132.3, 133.3, 133.7, 134.0, 136.1, 137.2, 192.0. Anal. Calcd for $C_{16}H_{11}BrO$: C, 64.24; H, 3.71. Found: C, 64.44; H, 3.88.

*4.2.9. 2-(Phenylethynyl)benzaldehyde (**1i**).* By a procedure identical with that described for the preparation of **1a**, 2-ethynylbenzaldehyde (**12a**) (100 mg, 0.77 mmol) was converted to **1i** (111 mg, 70%) by the reaction with iodobenzene (**13d**) (103 μL, 0.92 mmol), CuI (7.3 mg, 0.038 mmol), $PdCl_2(PPh_3)_2$ (26.9 mg, 0.038 mmol), and Et_3N (1.0 mL) in THF (1.0 mL) at 80 °C for 1 h: yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.39 (m, 3H, Ar), 7.44 (dd, *J*=7.7, 7.7 Hz, 1H, Ar), 7.55–7.59 (m, 3H, Ar), 7.64 (d, *J*=7.4 Hz, 1H, Ar), 7.95 (d, *J*=7.4 Hz, 1H, Ar), 10.65 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.9, 96.3, 122.3, 126.8, 127.2, 128.5 (2C), 128.6, 129.0, 131.7 (2C), 133.2, 133.7, 135.8, 191.6; HRMS (FAB) calcd for $C_{15}H_{11}O$ (MH^+): 207.0810; found: 207.0810.

*4.2.10. 2-[(4-Methylphenyl)ethynyl]benzaldehyde (**1j**).* By a procedure identical with that described for the preparation of **1a**, 2-ethynylbenzaldehyde (**12a**) (100 mg, 0.77 mmol) was converted to **1j** (120 mg, 71%) by the reaction with 1-iodo-2-methylbenzene (**13e**) (201 mg, 0.92 mmol), CuI (7.3 mg, 0.038 mmol), $PdCl_2(PPh_3)_2$ (26.9 mg, 0.038 mmol), and Et_3N (1.0 mL) in THF (1.0 mL) at 80 °C for 1 h: colorless solid: mp 48 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H, CCH_3), 7.18 (d, *J*=8.0 Hz, 2H, Ar), 7.40–7.46 (m, 3H, Ar), 7.56 (ddd, *J*=7.6, 7.6, 1.3 Hz, 1H, Ar), 7.62 (d, *J*=6.9 Hz, 1H, Ar), 7.93 (dd, *J*=7.6, 1.1 Hz, 1H, Ar), 10.65 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 84.3, 96.6, 119.2, 127.1 (2C), 128.3, 129.2 (2C), 131.5 (2C), 133.1, 133.7, 135.7, 139.3, 191.7. Anal. Calcd for $C_{16}H_{12}O$: C, 87.25; H, 5.49. Found: C, 87.11; H, 5.74.

4.3. Copper-catalyzed coupling–cyclization

*4.3.1. General procedure: synthesis of 13-(2-Bromophenyl)-7,7a,12,13-dihydroisoquinolino[2,1-a]perimidine (**3a**) (Table 1, entry 6).* A mixture of **1a** (50 mg, 0.18 mmol), 1,8-diaminonaphthalene (**2**) (41.5 mg, 0.26 mmol), and CuI (3.3 mg, 0.018 mmol) in dioxane (1.0 mL) was stirred for 60 min at 150 °C under microwave irradiation (300 W). The reaction mixture was concentrated under reduced pressure and purified by column chromatography over silica gel with hexane–EtOAc (15:1) to give **3a** (68 mg, 91%) as a pale yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (br s, 1H, NH), 5.68 (s, 1H, NCHN), 6.15 (s, 1H, C=CH), 6.36 (d, *J*=7.4 Hz, 1H, Ar), 6.66 (dd, *J*=6.6, 2.0 Hz, 1H, Ar), 6.96 (dd, *J*=8.0, 8.0 Hz, 1H, Ar), 7.04–7.09 (m, 3H, Ar), 7.16 (d, *J*=7.4 Hz, 1H, Ar), 7.21 (ddd, *J*=7.4, 7.4, 1.1 Hz, 1H, Ar), 7.29–7.36 (m, 4H, Ar), 7.38–7.40 (m, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.3, 103.2, 107.6, 117.1, 118.5, 120.1, 123.0, 124.2, 124.4, 124.9, 125.8, 126.3, 126.4, 126.6, 126.7, 129.2 (2C), 131.9, 132.2, 132.3, 134.4, 137.8, 138.3, 142.1, 142.4; HRMS (FAB) calcd for $C_{25}H_{18}BrN_2$ (MH^+): 425.0653; found: 425.0649.

*4.3.2. 13-(2-Bromophenyl)-10-fluoro-7,7a-dihydroisoquinolino[2,1-a]perimidine (**3b**) (Table 2, entry 1).* By a procedure identical with that described for the preparation of **3a**, **1b** (50 mg, 0.17 mmol) was converted into **3b** (70 mg, 97%) by the reaction with 1,8-diaminonaphthalene (**2**) (39.1 mg, 0.25 mmol) and CuI (3.1 mg, 0.017 mmol): yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (br s, 1H, NH), 5.57 (s, 1H, NCHN), 6.12 (s, 1H, C=CH), 6.32 (d, *J*=7.4 Hz, 1H, Ar), 6.67 (dd, *J*=6.9, 1.7 Hz, 1H, Ar), 6.82 (dd, *J*=9.5, 2.6 Hz, 1H, Ar), 6.88 (ddd, *J*=8.6, 8.6, 2.3 Hz, 1H, Ar), 6.93 (dd, *J*=8.0, 8.0 Hz, 1H, Ar), 7.04–7.10 (m, 3H, Ar), 7.26–7.32 (m, 3H, Ar), 7.37–7.38 (m, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.0, 102.2, 108.0, 110.4 (d, *J*=21.6 Hz), 112.5 (d, *J*=22.8 Hz), 117.5, 118.8, 120.3, 122.1 (d, *J*=2.4 Hz), 123.5, 124.4, 124.9, 126.5, 126.8, 128.5 (d, *J*=9.6 Hz), 129.5, 131.9, 132.4, 134.5, 134.6 (d, *J*=9.6 Hz), 137.6, 138.0, 142.0, 143.7, 163.5 (d, *J*=245.9 Hz); HRMS (FAB) calcd for $C_{25}H_{17}BrFN_2$ (MH^+): 443.0560; found: 443.0558.

*4.3.3. 13-(2-Bromophenyl)-10-methyl-7,7a-dihydroisoquinolino[2,1-a]perimidine (**3c**) (Table 2, entry 2).* By a procedure identical with that described for the preparation of **3a**, **1c** (50 mg, 0.17 mmol) was converted into **3c** (71 mg, 97%) by the reaction with 1,8-diaminonaphthalene (**2**) (39.6 mg, 0.25 mmol) and CuI (3.2 mg, 0.017 mmol): yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H, CCH_3), 4.43 (br s, 1H, NH), 5.59 (s, 1H, NCHN), 6.10 (s,

1H, C=CH), 6.29 (d, *J*=7.4 Hz, 1H, Ar), 6.64 (dd, *J*=6.9, 1.1 Hz, 1H, Ar), 6.92 (dd, *J*=7.7, 7.7 Hz, 1H, Ar), 6.95 (br s, 1H, Ar), 7.00–7.07 (m, 4H, Ar), 7.20 (d, *J*=7.4 Hz, 1H, Ar), 7.24–7.30 (m, 2H, Ar), 7.34 (d, *J*=8.0 Hz, 1H, Ar), 7.37 (d, *J*=7.4 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 69.3, 103.2, 107.6, 117.2, 118.5, 120.2, 123.0, 123.8, 124.5, 124.8, 124.9, 126.4, 126.6, 126.7 (2C), 129.2, 132.0, 132.1, 132.4, 134.5, 138.0, 138.5, 139.0, 142.3, 142.4; HRMS (FAB) calcd for $C_{26}H_{20}BrN_2$ (MH^+): 439.0810; found: 439.0805.

*4.3.4. 13-(2-Bromophenyl)-9-fluoro-7,7a-dihydroisoquinolino[2,1-a] perimidine (**3d**) (Table 2, entry 3).* By a procedure identical with that described for the preparation of **3a**, **1d** (50 mg, 0.17 mmol) was converted into **3d** (65 mg, 89%) by the reaction with 1,8-diaminonaphthalene (**2**) (39.1 mg, 0.25 mmol) and CuI (3.1 mg, 0.017 mmol): yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (br s, 1H, NH), 5.67 (s, 1H, NCHN), 6.09 (s, 1H, C=CH), 6.31 (d, *J*=7.4 Hz, 1H, Ar), 6.69 (dd, *J*=6.6, 1.4 Hz, 1H, Ar), 6.93 (dd, *J*=7.7, 7.7 Hz, 1H, Ar), 7.01–7.12 (m, 6H, Ar), 7.28–7.39 (m, 4H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.1 (d, *J*=2.4 Hz), 103.1, 108.2, 113.6 (d, *J*=22.8 Hz), 116.3 (d, *J*=21.6 Hz), 117.1, 118.9, 120.1, 123.1, 124.4, 125.0, 126.0 (d, *J*=8.4 Hz), 126.5, 126.8, 128.3 (d, *J*=7.2 Hz), 128.7 (d, *J*=2.4 Hz), 129.4, 131.9, 132.5, 134.4, 137.6, 138.1, 141.7, 141.9 (d, *J*=2.4 Hz), 161.2 (d, *J*=244.7 Hz); HRMS (FAB) calcd for $C_{25}H_{17}BrFN_2$ (MH^+): 443.0560; found: 443.0552.

*4.3.5. 13-(2-Bromophenyl)-9-methoxy-7,7a-dihydroisoquinolino [2,1-a]perimidine (**3e**) (Table 2, entry 4).* By a procedure identical with that described for the preparation of **3a**, **1e** (50 mg, 0.16 mmol) was converted into **3e** (51 mg, 71%) by the reaction with 1,8-diaminonaphthalene (**2**) (37.6 mg, 0.24 mmol) and CuI (3.0 mg, 0.016 mmol): yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (s, 3H, OCH_3), 4.54 (br s, 1H, NH), 5.68 (s, 1H, NCHN), 6.09 (s, 1H, C=CH), 6.30 (d, *J*=7.4 Hz, 1H, Ar), 6.68 (dd, *J*=6.9, 1.1 Hz, 1H, Ar), 6.89–6.91 (m, 2H, Ar), 6.93 (dd, *J*=8.0, 8.0 Hz, 1H, Ar), 7.03–7.06 (m, 1H, Ar), 7.09–7.11 (m, 3H, Ar), 7.26–7.34 (m, 3H, Ar), 7.39 (d, *J*=8.0 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.5, 69.5, 103.9, 107.8, 112.2, 114.9, 116.8, 118.6, 120.0, 122.7, 124.6, 125.1, 125.5, 125.8, 126.4, 126.8, 128.3, 129.2, 132.1, 132.5, 134.5, 138.1, 138.5, 140.5, 142.0, 158.3; HRMS (FAB) calcd for $C_{26}H_{20}BrN_2O$ (MH^+): 455.0759; found: 455.0756.

*4.3.6. 13-(2-Bromophenyl)-8-fluoro-7,7a-dihydroisoquinolino[2,1-a] perimidine (**3f**) (Table 2, entry 5).* By a procedure identical with that described for the preparation of **3a**, **1f** (50 mg, 0.17 mmol) was converted into **3f** (65 mg, 89%) by the reaction with 1,8-diaminonaphthalene (**2**) (39.1 mg, 0.25 mmol) and CuI (3.1 mg, 0.017 mmol): yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (br s, 1H, NH), 5.62 (d, *J*=1.7 Hz, 1H, NCHN), 6.33 (br s, 1H, Ar), 6.46 (s, 1H, C=CH), 6.70 (dd, *J*=6.9, 1.7 Hz, 1H, Ar), 6.89–6.95 (m, 3H, Ar), 7.05–7.08 (m, 2H, Ar), 7.27–7.33 (m, 3H, Ar), 7.38–7.40 (m, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 64.3, 102.2, 107.8, 112.2 (d, *J*=21.6 Hz), 113.0 (d, *J*=15.6 Hz), 117.6, 118.7, 120.0 (d, *J*=2.4 Hz), 123.6, 124.4, 124.8, 126.5, 126.8, 129.4, 130.6 (d, *J*=9.6 Hz), 131.8, 132.4, 134.4, 134.6 (d, *J*=4.8 Hz), 137.5, 138.1, 140.9, 142.6, 143.5, 159.9 (d, *J*=245.9 Hz); HRMS (FAB) calcd for $C_{25}H_{17}BrFN_2$ (MH^+): 443.0560; found: 443.0555.

*4.3.7. 13-(2-Bromo-5-fluorophenyl)-7,7a-dihydroisoquinolino[2,1-a] perimidine (**3g**) (Table 2, entry 6).* By a procedure identical with that described for the preparation of **3a**, **1g** (50 mg, 0.17 mmol) was converted into **3g** (53 mg, 73%) by the reaction with 1,8-diaminonaphthalene (**2**) (39.1 mg, 0.25 mmol) and CuI (3.1 mg, 0.017 mmol): pale yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (br s, 1H, NH), 5.64 (s, 1H, NCHN), 6.12 (s, 1H, C=CH), 6.33 (d, *J*=7.4 Hz, 1H, Ar), 6.66 (dd, *J*=6.3, 1.7 Hz, 1H, Ar), 6.79 (ddd, *J*=8.4, 8.4, 3.2 Hz, 1H, Ar), 6.89 (br s, 1H, Ar), 6.97 (dd, *J*=7.7, 7.7 Hz, 1H, Ar), 7.13 (d, *J*=7.4 Hz, 1H, Ar), 7.21 (ddd, *J*=7.4, 7.4, 1.1 Hz, 1H, Ar), 7.27–7.34 (m, 5H, Ar), 7.38 (d, *J*=7.4 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.3, 103.5, 107.9, 116.6 (d, *J*=22.8 Hz), 116.9, 118.7, 118.9 (d, *J*=3.6 Hz), 119.0 (d, *J*=22.8 Hz), 120.2, 123.3, 124.5, 124.9, 126.2, 126.5, 126.6, 126.7, 129.3, 132.0, 133.7 (d, *J*=7.2 Hz), 134.5, 137.6, 140.1 (d, *J*=8.4 Hz), 141.5, 142.0, 161.3 (d, *J*=248.3 Hz); HRMS (FAB) calcd for $C_{25}H_{17}BrFN_2$ (MH^+): 443.0560; found: 443.0560.

*4.3.8. 13-(2-Bromo-5-methylphenyl)-7,7a-dihydroisoquinolino[2,1-a]perimidine (**3h**) (Table 2, entry 7).* By a procedure identical with that described for the preparation of **3a**, **1h** (50 mg, 0.17 mmol) was converted into **3h** (67 mg, 91%) by the reaction with 1,8-diaminonaphthalene (**2**) (39.6 mg, 0.25 mmol) and CuI (3.2 mg, 0.017 mmol): yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (s, 3H, CCH_3), 4.52 (br s, 1H, NH), 5.64 (s, 1H, NCHN), 6.15 (s, 1H, C=CH), 6.31 (d, *J*=7.4 Hz, 1H, Ar), 6.67 (dd, *J*=6.6, 1.4 Hz, 1H, Ar), 6.87 (dd, *J*=8.3, 2.0 Hz, 1H, Ar), 6.95 (dd, *J*=8.0, 8.0 Hz, 1H, Ar), 6.98 (br s, 1H, Ar), 7.13 (d, *J*=7.4 Hz, 1H, Ar), 7.18–7.22 (m, 2H, Ar), 7.26–7.33 (m, 4H, Ar), 7.36 (d, *J*=8.0 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 69.4, 103.2, 107.8, 117.0, 118.6, 120.3, 121.0, 123.0, 124.3, 124.9, 125.8, 126.4, 126.5, 126.6, 129.3, 130.2, 132.1, 132.4, 132.6, 134.5, 136.7, 137.9, 138.0, 142.2, 142.7; HRMS (FAB) calcd for $C_{26}H_{20}BrN_2$ (MH^+): 439.0810; found: 439.0807.

*4.3.9. 13-Phenyl-7,7a-dihydroisoquinolino[2,1-a]perimidine (**3i**) (Table 2, entry 8).* By a procedure identical with that described for the preparation of **3a**, **1i** (50 mg, 0.24 mmol) was converted into **3i** (76 mg, 91%) by the reaction with 1,8-diaminonaphthalene (**2**) (57.5 mg, 0.36 mmol) and CuI (4.6 mg, 0.024 mmol): pale yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (br s, 1H, NH), 5.80 (s, 1H, NCHN), 6.14 (d, *J*=7.4 Hz, 1H, Ar), 6.55 (br s, 1H, C=CH), 6.77 (d, *J*=7.4 Hz, 1H, Ar), 6.92 (dd, *J*=7.7, 7.7 Hz, 1H, Ar), 7.14 (dd, *J*=7.4, 7.4 Hz, 1H, Ar), 7.18–7.22 (m, 4H, Ar), 7.27–7.32 (m, 5H, Ar), 7.49 (m, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.3, 107.5, 113.2, 116.7, 118.2, 120.3 (2C), 124.4 (2C), 125.1, 125.9, 126.6, 126.9, 127.1 (2C), 128.3 (2C), 128.4 (2C), 133.5, 134.3, 136.6, 138.1, 139.7, 144.5; HRMS (FAB) calcd for $C_{25}H_{19}N_2$ (MH^+): 347.1548; found: 347.1547.

*4.3.10. 13-(p-Tolyl)-7,7a-dihydroisoquinolino[2,1-a]perimidine (**3j**) (Table 2, entry 9).* By a procedure identical with that described for the preparation of **3a**, **1j** (50 mg, 0.23 mmol) was converted into **3j** (75 mg, 91%) by the reaction with 1,8-diaminonaphthalene (**2**) (53.8 mg, 0.34 mmol) and CuI (4.3 mg, 0.023 mmol): yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3H, CCH_3), 4.97 (br s, 1H, NH), 5.76 (s, 1H, NCHN), 6.15 (d, *J*=7.4 Hz, 1H, Ar), 6.58 (br s, 1H, C=CH), 6.77 (d, *J*=7.4 Hz, 1H, Ar), 6.93 (dd, *J*=8.0, 8.0 Hz, 1H, Ar), 7.08–7.14 (m, 3H, Ar), 7.17–7.21 (m, 4H, Ar), 7.27 (d, *J*=7.4 Hz, 1H, Ar), 7.30 (dd, *J*=7.7, 7.7 Hz, 1H, Ar), 7.43 (m, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 68.2, 107.5, 112.8, 116.4, 118.1, 120.0 (2C), 124.2 (2C), 125.0, 126.0, 126.6, 126.8, 126.9 (2C), 128.2, 129.2 (2C), 132.3, 133.8, 134.2, 138.2, 138.3, 139.6, 144.7; HRMS (FAB) calcd for $C_{26}H_{21}N_2$ (MH^+): 361.1705; found: 361.1705.

*4.3.11. General procedure for four-component coupling–cyclization: synthesis of N-[(7,7a-dihydroisoquinolino[2,1-a]perimidin-13-yl) methyl]-N-isopropylpropan-2-amine (**11a**) (Table 3, entry 1).* A mixture of 2-ethynylbenzaldehyde (**8**) (30 mg, 0.23 mmol), paraformaldehyde (**9**) (13.8 mg, 0.46 mmol), diisopropylamine (**10a**) (65.3 μL, 0.46 mmol), and CuI (4.4 mg, 0.023 mmol) in dioxane (1.0 mL) was stirred at rt for 1 h. After the Mannich-type reaction was completed (monitored by TLC), 1,8-diaminonaphthalene (**2**) (109 mg, 0.69 mmol) was added, and the mixture was stirred for additional 60 min at 150 °C under microwave irradiation (300 W). The mixture was concentrated under reduced pressure and purified by column chromatography over silica gel with hexane–EtOAc

(25:1) to give **11a** (46 mg, 52% yield) as a pale yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (d, J=6.3 Hz, 6H, 2× CCH_3), 0.87 (d, J=6.3 Hz, 6H, 2× CCH_3), 2.88–2.97 (m, 3H, 2× N–CH and N–C*H*H), 3.37 (d, J=16.0 Hz, 1H, N–CH*H*), 4.25 (br s, 1H, NH), 5.87 (s, 1H, NCHN), 6.10 (s, 1H, C=CH), 6.58 (dd, J=5.7, 2.3 Hz, 1H, Ar), 7.09–7.13 (m, 3H, Ar), 7.21 (d, J=6.9 Hz, 1H, Ar), 7.27–7.31 (m, 3H, Ar), 7.36 (dd, J=7.7, 7.7 Hz, 1H, Ar), 7.57 (d, J=8.6 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4 (2C), 20.5 (2C), 47.5, 48.0 (2C), 70.1, 101.4, 107.3, 118.0, 118.1, 120.0, 123.7, 124.0, 124.9, 125.5, 126.4 (2C), 126.6, 129.2, 133.2, 134.7, 138.6, 142.8, 144.0; HRMS (FAB) calcd for $C_{26}H_{30}N_3$ (MH^+): 384.2440; found: 384.2438.

*4.3.12. 13-(Piperidin-1-ylmethyl)-7,7a-dihydroisoquinolino[2,1-a] perimidine (**11b**) (Table 3, entry 2).* By a procedure identical with that described for the preparation of **11a**, **8** (30 mg, 0.23 mmol) was converted into **11b** (60 mg, 70%) by the reaction with piperidine (**10b**) (45.6 μL, 0.46 mmol): pale yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00–1.04 (m, 4H, 2× CH_2), 1.13 (br t, J=5.4 Hz, 2H, CH_2), 2.03–2.16 (m, 4H, 2× NCH_2), 2.73 (d, J=13.2 Hz, 1H, NC*H*H), 3.10 (d, J=13.2 Hz, 1H, N–CH*H*), 4.17 (br s, 1H, NH), 5.72 (s, 1H, NCHN), 5.88 (s, 1H, C=CH), 6.54 (dd, J=6.9, 1.1 Hz, 1H, Ar), 7.09 (d, J=7.4 Hz, 1H, Ar), 7.13 (ddd, J=7.4, 7.4, 1.1 Hz, 1H, Ar), 7.19 (d, J=6.9 Hz, 1H, Ar), 7.22–7.35 (m, 5H, Ar), 7.55 (dd, J=7.7, 2.0 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3, 25.7 (2C), 53.5 (2C), 60.8, 69.7, 103.1, 107.1, 117.6, 118.1, 120.5, 123.7, 124.0, 125.4 (2C), 126.3, 126.5, 126.7, 129.2, 132.6, 134.6, 139.5, 141.2, 142.6; HRMS (FAB) calcd for $C_{25}H_{26}N_3$ (MH^+): 368.2127; found: 368.2130.

*4.3.13. 4-[(7,7a-Dihydroisoquinolino[2,1-a]perimidin-13-yl)methyl] morpholine (**11c**) (Table 3, entry 3).* By a procedure identical with that described for the preparation of **11a**, **8** (30 mg, 0.23 mmol) was converted into **11c** (52 mg, 61%) by the reaction with morpholine (**10c**) (40.2 μL, 0.46 mmol): yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.95 (br m, 2H, 2× N–C*H*H), 2.25 (br m, 2H, 2× N–CH*H*), 2.72 (d, J=13.2 Hz, 1H, N–C*H*H), 2.93–3.00 (m, 4H, 2× OCH_2), 3.33 (d, J=13.2 Hz, 1H, N–CH*H*), 4.19 (br s, 1H, NH), 5.72 (s, 1H, NCHN), 5.90 (s, 1H, C=CH), 6.56 (d, J=6.9 Hz, 1H, Ar), 7.11 (d, J=7.4 Hz, 1H, Ar), 7.17 (dd, J=7.2, 7.2 Hz, 1H, Ar), 7.21–7.35 (m, 6H, Ar), 7.57 (d, J=8.6 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.3 (2C), 60.2, 66.6 (2C), 69.7, 104.0, 107.1, 117.1, 118.1, 120.8, 123.9, 124.2, 125.3, 125.7, 126.6 (2C), 127.0, 129.4, 132.4, 134.7, 139.8, 140.4, 142.5; HRMS (FAB) calcd for $C_{24}H_{24}N_3O$ (MH^+): 370.1919; found: 370.1921.

4.4. Palladium-catalyzed C–H arylation

*4.4.1. General procedure: synthesis of dibenzo[1,2:7,8]quinolizino [3,4,5,6-kla]perimidine (**4a**) hydrochloride (Table 4, entry 15).* A mixture of **3a** (50 mg, 0.12 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol), PPh_3 (7.7 mg, 0.029 mmol), and K_3PO_4 (50.2 mg, 0.24 mmol) in DMF (1.5 mL) was stirred for 4 h at 130 °C. The reaction mixture was concentrated under reduced pressure and purified by column chromatography over silica gel with toluene–EtOAc (200:1) to give **4a** (32 mg, 78%) as a red solid. When the C–H arylation products were poorly soluble in various organic solvents, their hydrochlorides were prepared as follows: the solid was dissolved in $CHCl_3$, and 4 N solution of HCl in dioxane was added to the mixture. The precipitates were collected by filtration to give **4a**·HCl as a brown solid: mp 124–126 °C; ^{1}H NMR (500 MHz, CD_3OD, 60 °C) δ 6.58 (d, J=7.4 Hz, 1H, Ar), 6.69 (d, J=6.9 Hz, 1H, Ar), 6.74–6.79 (m, 2H, Ar), 6.93 (br s, 2H, Ar), 7.19 (d, J=8.0 Hz, 1H, Ar), 7.25 (br s, 1H, Ar), 7.44–7.50 (m, 3H, Ar), 7.58 (br s, 1H, Ar), 7.67 (dd, J=6.6, 6.6 Hz, 1H, Ar), 8.18 (d, J=8.0 Hz, 1H, Ar); ^{13}C NMR (125 MHz, CD_3OD, 60 °C) δ 110.9, 111.2, 116.1, 116.9, 119.7, 122.5, 123.4, 123.8, 124.7, 125.6, 125.7, 126.8, 128.1, 128.4, 129.2, 131.0, 131.2, 131.3, 133.0 (2C), 134.8, 134.9, 137.1, 137.2, 148.9; HRMS (FAB) calcd for $C_{25}H_{15}N_2$ (MH^+): 343.1235; found: 343.1233.

*4.4.2. 12-Fluorodibenzo[1,2:7,8]quinolizino[3,4,5,6-kla]perimidine (**4b**) (Table 5, entry 1).* A mixture of **3b** (30 mg, 0.068 mmol), $Pd(OAc)_2$ (1.5 mg, 0.007 mmol), PPh_3 (4.4 mg, 0.017 mmol), and K_3PO_4 (28.7 mg, 0.14 mmol) in DMF (1.0 mL) was stirred for 4 h at 130 °C. The reaction mixture was concentrated under reduced pressure and purified by column chromatography over silica gel with toluene–EtOAc (200:1) to gave **4b** including some impurities. Recrystallization from pyridine gave pure **4b** (11 mg, 45%) as red crystals: mp 298–300 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 6.57 (s, 1H, Ar), 6.63 (d, J=7.4 Hz, 1H, Ar), 6.79 (dd, J=4.6, 4.6 Hz, 1H, Ar), 6.90 (dd, J=8.3, 8.3 Hz, 2H, Ar), 7.09–7.14 (m, 2H, Ar), 7.22–7.28 (m, 1H, Ar), 7.36 (dd, J=7.4, 7.4 Hz, 1H, Ar), 7.56 (d, J=9.2 Hz, 1H, Ar), 7.70 (d, J=8.0 Hz, 1H, Ar), 7.75 (d, J=8.0 Hz, 1H, Ar), 8.33 (dd, J=8.9, 6.0 Hz, 1H, Ar); ^{13}C NMR assignment was difficult due to the poor solubility of **4b** as well as C–F couplings; HRMS (FAB) calcd for $C_{25}H_{14}FN_2$ (MH^+): 361.1141; found: 361.1143.

*4.4.3. 12-Methyldibenzo[1,2:7,8]quinolizino[3,4,5,6-kla]perimidine (**4c**) hydrochloride (Table 5, entry 2).* By a procedure identical with that described for the preparation of **4b**, **3c** (30 mg, 0.068 mmol) was converted into **4c** (13 mg, 53%) by the reaction with $Pd(OAc)_2$ (1.5 mg, 0.007 mmol), PPh_3 (4.5 mg, 0.017 mmol), and K_3PO_4 (29.0 mg, 0.14 mmol) as red crystals. The crystals were dissolved in $CHCl_3$, and 4 N solution of HCl in dioxane was added to the mixture. After hexane was added to the mixture, the precipitates were collected by filtration to give **4c**·HCl as a brown solid: mp 128–130 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 2.39 (s, 3H, CCH_3), 6.61 (d, J=5.7 Hz, 1H, Ar), 6.73 (d, J=8.0 Hz, 1H, Ar), 6.88 (dd, J=7.4, 7.4 Hz, 1H, Ar), 6.96 (d, J=9.2 Hz, 1H, Ar), 7.00 (dd, J=7.4, 7.4 Hz, 1H, Ar), 7.07 (dd, J=7.4, 7.4 Hz, 1H, Ar), 7.17 (s, 1H, Ar), 7.29 (d, J=8.0 Hz, 1H, Ar), 7.39 (d, J=8.6 Hz, 1H, Ar), 7.43–7.45 (m, 2H, Ar), 7.60 (d, J=7.4 Hz, 1H, Ar), 7.97 (d, J=8.0 Hz, 1H, Ar); ^{13}C NMR (125 MHz, CD_3OD) δ 22.1, 110.3, 110.9, 113.9, 116.9, 119.5, 122.6, 123.5, 123.7, 124.7, 125.4, 125.5, 126.9, 128.0, 128.3, 128.4, 130.9, 131.2, 132.9, 133.0, 133.1, 134.9, 135.0, 137.1, 148.5, 149.3; HRMS (FAB) calcd for $C_{26}H_{17}N_2$ (MH^+): 357.1392; found: 357.1390.

*4.4.4. 13-Fluorodibenzo[1,2:7,8]quinolizino[3,4,5,6-kla]perimidine (**4d**) (Table 5, entry 3).* By a procedure identical with that described for the preparation of **4b**, **3d** (30 mg, 0.068 mmol) was converted into **4d** (13 mg, 53%) by the reaction with $Pd(OAc)_2$ (1.5 mg, 0.007 mmol), PPh_3 (4.4 mg, 0.017 mmol), and K_3PO_4 (28.7 mg, 0.14 mmol) as red crystals: mp 283–285 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 6.60–6.62 (m, 2H, Ar), 6.87 (d, J=8.0 Hz, 1H, Ar), 7.06–7.16 (m, 4H, Ar), 7.20 (dd, J=8.3, 8.3 Hz, 1H, Ar), 7.32 (dd, J=7.7, 7.7 Hz, 1H, Ar), 7.52 (d, J=9.2 Hz, 1H, Ar), 7.66 (dd, J=8.0, 2.9 Hz, 1H, Ar), 7.71 (d, J=8.0 Hz, 1H, Ar), 7.98 (dd, J=10.3, 2.3 Hz, 1H, Ar); ^{13}C NMR assignment was difficult due to the poor solubility of **4d** as well as C–F couplings; HRMS (FAB) calcd for $C_{25}H_{14}FN_2$ (MH^+): 361.1141; found: 361.1140.

*4.4.5. 13-Methoxydibenzo[1,2:7,8]quinolizino[3,4,5,6-kla]perimidine (**4e**) hydrochloride (Table 5, entry 4).* By a procedure identical with that described for the preparation of **4b**, **3e** (30 mg, 0.066 mmol) was converted into **4e** (15 mg, 61%) by the reaction with $Pd(OAc)_2$ (1.5 mg, 0.007 mmol), PPh_3 (4.3 mg, 0.017 mmol), and K_3PO_4 (28.0 mg, 0.13 mmol) as red crystals. The crystals were dissolved in $CHCl_3$, and 4 N solution of HCl in dioxane was added to the mixture. Hexane was added to the mixture and the precipitates were collected by filtration to give **4e**·HCl as a brown solid: mp 140–141 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 4.03 (s, 3H, OCH_3), 6.92 (d, J=6.9 Hz, 1H, Ar), 7.02 (d, J=8.0 Hz, 1H, Ar), 7.09 (dd, J=7.4, 7.4 Hz, 1H, Ar), 7.34 (m, 2H, Ar), 7.40 (dd, J=7.4, 7.4 Hz, 1H, Ar), 7.47 (d, J=9.2 Hz, 1H, Ar),

7.67 (d, *J*=9.2 Hz, 1H, Ar), 7.71 (s, 1H, Ar), 7.79 (d, *J*=9.2 Hz, 1H, Ar), 7.85 (m, 1H, Ar), 7.91 (s, 1H, Ar), 7.96 (d, *J*=7.4 Hz, 1H, Ar); ^{13}C NMR (125 MHz, CD_3OD) δ 57.3, 104.5, 110.5, 110.9, 117.9, 118.1, 120.8, 123.1, 123.6, 123.9, 125.7, 126.1, 127.7, 127.8, 128.1, 129.1, 131.0, 131.3, 132.7, 132.8, 132.9, 134.1, 134.4, 135.7, 148.7, 162.6; HRMS (FAB) calcd for $C_{26}H_{17}N_2O$ (MH^+): 373.1341; found: 373.1341.

*4.4.6. 14-Fluorodibenzo[1,2:7,8]quinolizino[3,4,5,6-kla]perimidine (**4f**) hydrochloride (Table 5, entry 5).* By a procedure identical with that described for the preparation of **4b**, **3f** (30 mg, 0.068 mmol) was converted into **4f** (13 mg, 51%) by the reaction with $Pd(OAc)_2$ (1.5 mg, 0.007 mmol), PPh_3 (4.4 mg, 0.017 mmol), and K_3PO_4 (28.7 mg, 0.14 mmol) as red crystals. The crystals were dissolved in $CHCl_3$, and 4 N solution of HCl in dioxane was added to the mixture. After hexane was added to the mixture, the precipitates were collected by filtration to give **4f**·HCl as a brown solid: mp 130–131 °C; ^{1}H NMR (500 MHz, CD_3OD, 50 °C) δ 6.75 (d, *J*=7.4 Hz, 1H, Ar), 7.07 (d, *J*=8.0 Hz, 1H, Ar), 7.16 (dd, *J*=8.0, 8.0 Hz, 1H, Ar), 7.31–7.34 (m, 2H, Ar), 7.38 (dd, *J*=7.4, 7.4 Hz, 1H, Ar), 7.44 (dd, *J*=14.0, 7.7 Hz, 1H, Ar), 7.61 (d, *J*=8.0 Hz, 1H, Ar), 7.81 (d, *J*=9.2 Hz, 1H, Ar), 7.86–7.89 (m, 2H, Ar), 8.00 (s, 1H, Ar), 8.07 (d, *J*=8.0 Hz, 1H, Ar); ^{13}C NMR (125 MHz, CD_3OD, 50 °C) δ 107.3 (d, *J*=7.2 Hz), 110.5, 111.7, 116.7 (d, *J*=22.8 Hz), 117.6, 120.6, 123.2, 123.9, 124.4, 125.2, 125.7 (d, *J*=3.6 Hz), 126.4, 128.1, 128.3, 129.5, 131.2, 131.5, 133.1, 133.6, 135.5, 136.7, 138.6 (d, *J*=10.8 Hz), 139.7 (d, *J*=8.4 Hz), 148.7, 160.8 (d, *J*=257.9 Hz); HRMS (FAB) calcd for $C_{25}H_{14}FN_2$ (MH^+): 361.1141; found: 361.1143.

*4.4.7. 8-Fluorodibenzo[1,2:7,8]quinolizino[3,4,5,6-kla]perimidine (**4g**) hydrochloride (Table 5, entry 6).* By a procedure identical with that described for the preparation of **4b**, **3g** (30 mg, 0.068 mmol) was converted into **4g** (12 mg, 49%) by the reaction with $Pd(OAc)_2$ (1.5 mg, 0.007 mmol), PPh_3 (4.4 mg, 0.017 mmol), and K_3PO_4 (28.7 mg, 0.14 mmol) as red crystals. The crystals were dissolved in $CHCl_3$, and 4 N solution of HCl in dioxane was added to the mixture. After hexane was added to the mixture, the precipitates were collected by filtration to give **4g**·HCl as a brown solid: mp 280–281 °C; ^{1}H NMR (500 MHz, CD_3OD, 60 °C) δ 6.75 (d, *J*=6.9 Hz, 1H, Ar), 6.83 (d, *J*=8.0 Hz, 1H, Ar), 6.93–6.98 (m, 2H, Ar), 7.05 (d, *J*=8.6 Hz, 1H, Ar), 7.46 (d, *J*=9.2 Hz, 1H, Ar), 7.55–7.58 (m, 3H, Ar), 7.64–7.67 (m, 2H, Ar), 7.75 (dd, *J*=7.4, 7.4 Hz, 1H, Ar), 8.25 (d, *J*=8.0 Hz, 1H, Ar); ^{13}C NMR (125 MHz, CD_3OD, 60 °C) δ 110.9, 111.6, 111.9 (d, *J*=25.2 Hz), 116.3, 117.5, 120.4, 120.8 (d, *J*=22.8 Hz), 122.7, 123.7, 124.4, 125.7, 126.6 (d, *J*=8.4 Hz), 127.6 (d, *J*=8.4 Hz), 127.8, 129.0, 129.1, 129.2, 131.0, 131.2, 134.4, 135.2, 136.9, 137.0, 149.7, 164.5 (d, *J*=250.7 Hz); HRMS (FAB) calcd for $C_{25}H_{14}FN_2$ (MH^+): 361.1141; found: 361.1141.

*4.4.8. 8-Methyldibenzo[1,2:7,8]quinolizino[3,4,5,6-kla]perimidine (**4h**) hydrochloride (Table 5, entry 7).* By a procedure identical with that described for the preparation of **4b**, **3h** (30 mg, 0.068 mmol) was converted into **4h** (15 mg, 62%) by the reaction with $Pd(OAc)_2$ (1.5 mg, 0.007 mmol), PPh_3 (4.5 mg, 0.017 mmol), and K_3PO_4 (29.0 mg, 0.14 mmol) as red crystals. The crystals were dissolved in $CHCl_3$, and 4 N solution of HCl in dioxane was added to the mixture. After hexane was added to the mixture, the precipitates were collected by filtration to give **4h**·HCl as a brown solid: mp 165–166 °C; ^{1}H NMR (500 MHz, CD_3OD, 60 °C) δ 2.22 (s, 3H, Ar), 6.79 (d, *J*=7.4 Hz, 1H, Ar), 6.89 (d, *J*=8.0 Hz, 1H, Ar), 7.00–7.04 (m, 2H, Ar), 7.09 (d, *J*=8.6 Hz, 1H, Ar), 7.50–7.53 (m, 2H, Ar), 7.59–7.63 (m, 3H, Ar), 7.74–7.80 (m, 2H, Ar), 8.25 (d, *J*=8.6 Hz, 1H, Ar); ^{13}C NMR (125 MHz, CD_3OD, 60 °C) δ 21.6, 110.4, 110.9, 116.7, 117.3, 120.5, 122.7, 123.6, 123.8, 125.2, 125.5, 125.7, 127.9, 128.9, 129.1, 130.8, 131.0, 133.9 (2C), 134.3, 135.2, 135.5, 136.9, 137.5, 142.0, 149.7; HRMS (FAB) calcd for $C_{26}H_{17}N_2$ (MH^+): 357.1392; found: 357.1390.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas 'Integrated Organic Synthesis' (H.O.) and Targeted Proteins Research Program from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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