JOC The Journal of Organic Chemistry

Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo302471z • Publication Date (Web): 28 Dec 2012

Nucleophilic Addition of Benzimidazoles to Alkynyl Bromides/Palladium-Catalyzed Intramolecular C-H Vinylation: Synthesis of Benzo[4,5]imidazo[2,1-*a*]isoquinolines

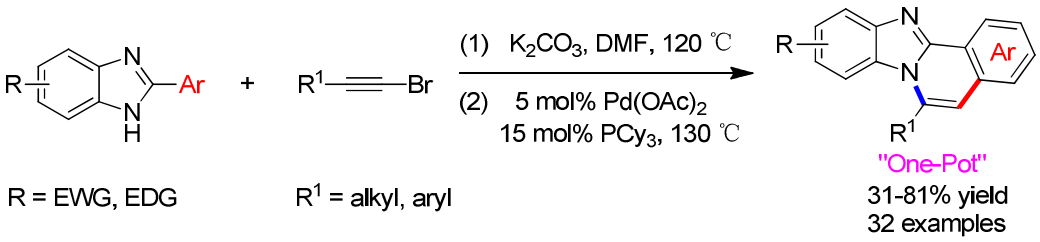
Jinsong Peng,[†,‡] Guoning Shang,[†] Chunxia Chen,[†] Zhongshuo Miao[†] and Bin Li[*,†,‡]

[†]Department of Chemistry and Chemical Engineering, College of Science, Northeast Forestry University, Harbin, 150040, P. R. China

[‡]Post-doctoral Mobile Research Station of Forestry Engineering, Northeast Forestry University, Harbin, 150040, P. R. China

[*]E-mail: libinzh62@163.com

ABSTRACT



An efficient "one-pot" route for the synthesis of benzo[4,5]imidazo[2,1-*a*] isoquinolines has been developed via nucleophilic addition of 2-aryl benzimidazoles to alkynyl bromides and subsequent palladium-catalyzed intramolecular C-H vinylation.

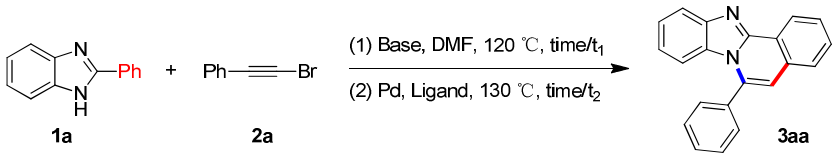
Benzimidazole-fused isoquinoline frameworks are an important class of pharmacophores and many derivatives display a wide range of biological and therapeutical activities, such as anticancer, antimicrobial, anti-HIV-1 and antifungal properties.[1] Therefore, molecules containing this motif have attracted considerable

attention in medicinal chemistry and much effort has been focused on the synthetic methods of isoquinoline-fused benzimidazole ring system. The commonly used synthetic routes involve cascade cyclization strategies with 2-ethynylbenzaldehydes and benzenediamines as substrates to give isoquinoline-fused polycyclic skeleton.[2-8] Other approaches such as a multistep route,[9] palladium-catalyzed cross-coupling protocols,[10-12] copper-catalyzed tandem process[13] and rhodium-catalyzed dual C-H bond activation strategy[14] for the synthesis of isoquinoline or benzimidazole-fused heterocyclic scaffolds have been reported.

Sequential one-pot reactions in which several bond-forming steps take place play an important role in synthetic organic chemistry.[15] Recent studies reveal that haloacetylenes can undergo addition by certain nucleophiles to give halo-substituted olefins.[16-22] These in-situ functionalized adducts have become a valuable source for various synthetic processes to provide the desired products in one-pot with a sequential manner.[23-25] In parallel with our continuing efforts to develop synthetic methods of nitrogen heterocycles,[26-28] we report here an efficient protocol for the synthesis of isoquinoline-fused benzimidazoles by the nucleophilic addition of 2-arylbenzimidazoles to alkynyl bromides with subsequent palladium-catalyzed cyclization reaction of the resultant bromoalkenes *via* intramolecular aromatic C-H bond vinylation.

For the initial experiments, 2-phenylbenzimidazole (**1a**) and bromoethynylbenzene (**2a**) as model substrates were selected for sequential nucleophilic addition/ Pd-catalyzed intramolecular C−H vinylation reaction (Table 1).

Table 1. Sequential One-Pot Reaction Condition Optimization[a]



1a 2a 3aa

entry	base	catalyst	ligand	t_1/t_2 (h)	yield[b]
1[c]	K_2CO_3	$Pd(OAc)_2$	PCy_3	2/12	44
2	K_2CO_3	$Pd(OAc)_2$	PCy_3	2/12	58
3	K_2CO_3	$Pd(OAc)_2$	PCy_3	2/16	68
4	K_3PO_4	$Pd(OAc)_2$	PCy_3	2/16	60
5[d]	K_2CO_3/ K_3PO_4	$Pd(OAc)_2$	PCy_3	2/16	69
6[d]	K_2CO_3/ K_3PO_4	$PdCl_2$	PCy_3	2/16	60
7[d]	K_2CO_3/ K_3PO_4	$PdCl_2(MeCN)_2$	PCy_3	2/16	67
8[d]	K_2CO_3/ K_3PO_4	$Pd_2(dba)_3$	PCy_3	2/16	60
9	K_2CO_3	$Pd(OAc)_2$	PCy_3	4/20	68 (35[e])
10	K_2CO_3	$Pd(OAc)_2$	PPh_3	2/16	39
11	K_2CO_3	$Pd(OAc)_2$	$P(tBu)_3$	2/16	56

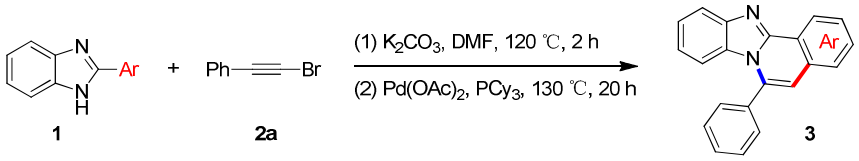
[a] Reaction conditions: 1.0 equiv of bromoethynylbenzene **2a** (0.2 mmol), 1.2 equiv of 2-phenyl-1*H*-benzo[*d*]imidazole **1a** (0.24 mmol), 2.0 equiv of base, 5 mol % of Pd catalyst, 15 mol % of ligand, DMF (2 mL). [b] Yield of isolated product after chromatography. [c] 5 mol % of Pd catalyst and 10 mol % of ligand were used. [d] K_2CO_3 and K_3PO_4 were used in 1:1 ratio. [e] Chloroethynylbenzene was used.

In fact, the nucleophilic addition of benzimidazoles to alkynyl halides in DMF can proceed regio- and stereoselectively to give (*Z*)-*N*-(1-halo-1-alken-2-yl)benzimid-azoles as reported in the literature.[16] On the basis of this chemistry, we expected that the *cis* relationship between the halides and benzimidazole moieties in the adduct gave the possibility of cyclization through palladium-catalyzed intramolecular

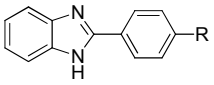
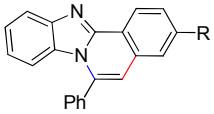
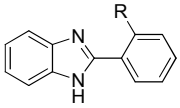
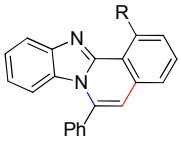
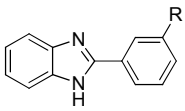
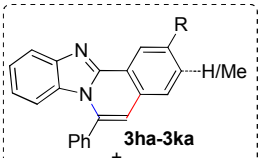
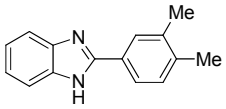
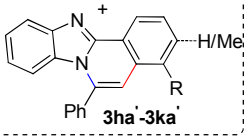
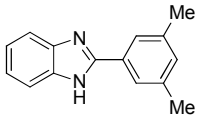
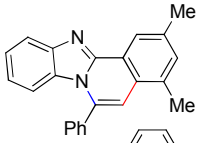
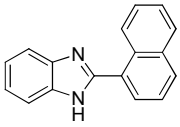
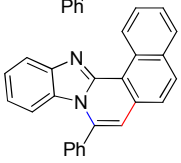
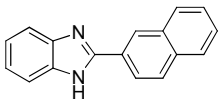
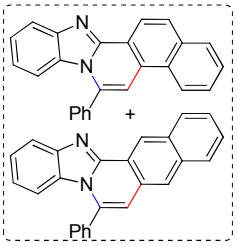
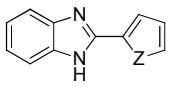
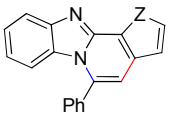
aromatic C-H vinylation. The second annulation step was then examined, in which an isoquinoline ring can be formed in one-pot fashion. Some fundamental data from that study are summarized in Table 1, including the catalyst, ligand and other reaction conditions such as base, temperature and reaction period. Upon treating the in-situ formed adduct with a mixture of $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol%) and K_2CO_3 at 130 ℃ for 12 h, the desired cyclization took place providing benzo[4,5]imidazo [2,1-*a*]isoquinoline **3aa** in 44% yield (entry 1, Table 1). A higher ratio of ligand to Pd (3:1) is preferable to afford good yields (58% vs 44%, entries 1 and 2, Table 1). The effect of cyclization time (t_2) on reaction yields was then examined: with the reaction time increasing, higher yields were obtained for this sequential process (entries 2, 3 and 9, Table 1). Compared to K_2CO_3, the use of K_3PO_4 as the base gave inferior results, K_2CO_3/K_3PO_4 (in 1:1 ratio) provided similar results (entries 3-5, Table 1). Finally, we investigated the effect of palladium sources [$PdCl_2$, $Pd(OAc)_2$, $PdCl_2(MeCN)_2$ and $Pd_2(dba)_3$] and ligands [PCy_3, PPh_3 and P(*t*Bu)$_3$] on the reaction (entries 5-11, Table 1). $Pd(OAc)_2$/ PCy_3 was found to be a very effective catalyst for such transformations with the best yield (entry 5, Table 1). When $Pd(OAc)_2$, PCy_3 and K_2CO_3 were added along with two substrates **1a** and **2a** in a one-step manner, the reaction provided an inseparable mixture. Additionally, the nature of halogen on the substrate was very important to the reaction outcome. The use of alkynyl chloride afforded inferior result than bromo analogue (entry 9, Table 1).

With the optimized reaction conditions in hand, we then explored the scope and generality of the present process. A variety of substituents (such as Me, OMe, Cl and

Table 2. Variation of the Benzimidazole Derivative[a]



1 2a 3

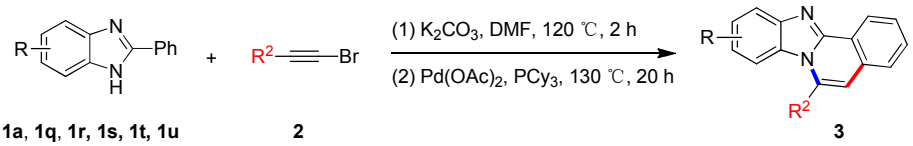
entry	substrate/**1**		products		yield (%)[b]
1		R = H **1a**		**3aa**	68
2		R = Me **1b**		**3ba**	60
3[c]		R = MeO **1c**		**3ca**	56
4		R = Cl **1d**		**3da**	45
5		R = CN **1e**		**3ea**	50
6		R = Me **1f**		**3fa**	56
7		R = Cl **1g**		**3ga**	31
8[d]		R = Me **1h**		**3ha** **3ha'**	66
9[e]		R = MeO **1i**		**3ia**	72
10		R = Cl **1j**		**3ja** **3ja'**	67 (39) (28)
11[f]		**1k**		**3ka** **3ka'**	35
12		**1l**		**3la**	60
13		**1m**		**3ma**	62
14		**1n**		**3na** **3na'**	72 (38) (34)
15		Z = O **1o**		**3oa**	67
16		Z = S **1p**		**3pa**	61

[a] Reaction conditions: 1.0 equiv of bromoethynylbenzene **2a** (0.2 mmol), 1.2 equiv of benzimidazoles **1** (0.24 mmol), 2.0 equiv of K_2CO_3, 5 mol % of $Pd(OAc)_2$, 15 mol % of PCy_3, DMF (2 mL). [b] Yield of isolated product after chromatography. [c] 4 h/24 h. [d] **3ha**:**3ha'** = 3:1. [e] Only one isomer was isolated. [f] 4 h/20 h, **3ka**:**3ka'** = 4.5:1.

CN) on the 2-arylbenzimidazole moiety were applicable, affording the cyclized products in good yields (entries 1−12, Table 2). It is worthnoting that the compatibility of 2-(chlorophenyl)-substituted benzimidazoles is particularly appealing, since this substituent offers great opportunities for further synthetic manipulations (entries 4, 7 and 10, Table 2). In addition, 2-heteroarylbenzimidazole substrates (**1o** and **1p**) were efficiently transformed into the corresponding products in good yields (entry 15 and 16, Table 2). The influence of sterics and electronics on vinylation regioselectivity of nonsymmetrical arenes was studied. In general, a small alkyl substituent such as a methyl group (entries 8 and 11, Table 2) in *meta*-positions seemed not to hamper the reaction and vinylation preferentially occured at the most sterically accessible site to give the corresponding regioisomers **3ha** and **3ka** (**3ha**: **3ha′** = 3:1, **3ka**: **3ka′** = 4.5:1). In the case of a larger substituent such as a methoxy group (entry 9, Table 2) only one product was detected by NMR. A chlorine substituent gave poorer regioselectivity, a 1.4:1 ratio in favor of isomer **3ja** was observed, which might be the result of a relatively small size of chlorine (entry 10, Table 2). When naphthyl substrate **1n** was reacted under the standard vinylation conditions, a 1.1:1 ratio of **3na**:**3na′** was obtained (entry 14, Table 2). Such low selectivities imply that this is not a characteristic outcome of electrophilic aromatic substitutions on this substrate class.

Bromoacetylene substrates **2** were then examined in this process. As shown in table 3, this method is effective for the conversion of diverse substituted bromoacetylenes such as aryl (entries 1-6, 10 and 11, Table 3), heteroaryl (entry 12,

Table 3. Variation of the Alkynyl Bromide [a]



1a, **1q**, **1r**, **1s**, **1t**, **1u** R = H, Me, Cl, MeO, CF_3 | **2** | **3**

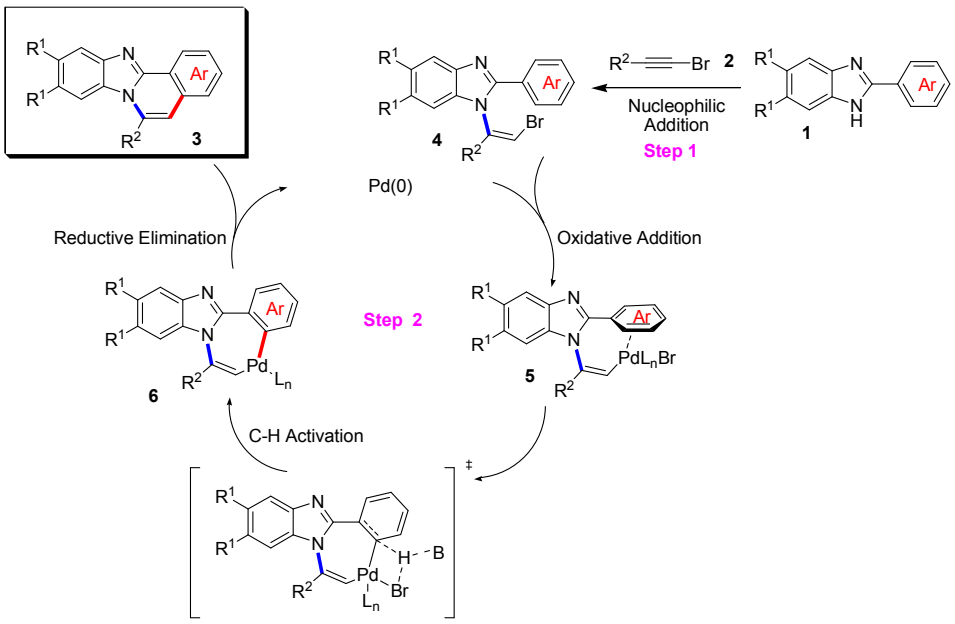
entry	substrate/**2**	products			yield (%)[b]
1			R^1 = H	**3aa**	68
2	Ph—≡—Br **2a**	R^1, R^1, Ph	R^1 = Me	**3qa**	56
3[c]			R^1 = Cl	**3ra**	55
4			R^1 = H	**3ab**	75
5	Me—≡—Br **2b**	R^1, R^1, *p*-MeC_6H_4	R^1 = Me	**3qb**	64
6[c]			R^1 = Cl	**3rb**	65
7[d]			R^1 = H	**3ac**	81
8	—≡—Br **2c**	R^1, R^1, *n*-Bu	R^1 = Me	**3qc**	50
9[c]			R^1 = Cl	**3rc**	47
10	MeO—≡—Br **2d**	*p*-$MeOC_6H_4$		**3ad**	76
11	F—≡—Br **2e**	*p*-FC_6H_4		**3ae**	81
12	S—≡—Br **2f**	S		**3af**	63
13	O, O, Ph —≡—Br **2g**	$PhCO_2$		**3ag**	67
14		Me, Ph		**3sa**	51
15[e]	Ph—≡—Br **2a**	R, Ph	R = MeO	**3ta** (23) **3ta'** (31)	54
16[e]		R, Ph	R = CF_3	**3ua** (33) **3ua'** (40)	73

[a] Reaction conditions: 1.0 equiv of alkynyl bromide **2** (0.2 mmol), 1.2 equiv of benzimidazoles **1** (0.24 mmol), 2.0 equiv of K_2CO_3, 5 mol % of $Pd(OAc)_2$, 15 mol % of PCy_3, DMF (2 mL). [b] Yield of isolated product after chromatography. [c] 10 mol % of $Pd(OAc)_2$, 30 mol % of PCy_3 and 30 mol % 2,2-dimethylpropionic acid were used; 4 h/72 h. [d] 3 h/20 h. [e] 5-Monosubstituted benzimidazole was used.

Table 3), alkyl (entries 7-9 and 13, Table 3). Furthermore, the mild reaction conditions were compatible with various functionalities including methoxy, fluorine, chlorine, and ester (entries 3, 6, 9-11 and 13, Table 3). Both **1a** and 5,6-dimethyl analogue **1q** can smoothly undergo sequential nucleophilic addition/cyclization to afford the desired product in good yields; however, the use of 5,6-dichloro substrate **1r** to effect such transformations afforded inferior results under standard reaction conditions. The reactive activity of **1r** can be improved by the combined use of an insoluble K_2CO_3 and a catalytic quantity of soluble carboxylate base (in this case via deprotonation of the 30 mol % pivalic acid in situ)[29], affording the corresponding products in 47-65% yields (entries 3, 6 and 9, Table 3). Various 4 or 5-monosubstituted benzimidazoles were then used to investigate the influence of sterics and electronics on regioselectivity of the *N* atoms in the nucleophilic addition step (entries 14-16, Table 3). In the case of 4-methyl substituted benzimidazole **1s**, nucleophilic addition occurred specifically at the sterically accessible *N* atom to give only one product **3sa** (entry 14, Table 3). Diminished selectivity was obtained when using 5-monosubstituted substrates **1t** and **1u** (entries 15 and 16, Table 3). In addition, electron-withdrawing CF_3 group at 5 position of benzimidazole ring gave a better yield than electron-donating MeO group, which might be the result of the increased nucleophilicity of nitrogen atom.

A proposed reaction mechanism was shown in Scheme 1. The nucleophilic addition of benzimidazole **1** to 1-bromo-1-alkynes **2** took place in a highly regio- and stereoselective manner to give (Z)-alkenyl bromide **4**. Oxidative addition of the vinyl

Scheme 1. Proposed Mechanism for Sequential Nucleophilic Addition/ Palladium-Catalyzed C-H Vinylation Process



bromide **4** to Pd(0) followed by approach of the aromatic ring led to a concerted metalationdeprotonation (CMD) transition state[30] to form the palladacycle **6**. Palladacycle intermediate **6** underwent C−C bond-forming reductive elimination to afford the desired benzo[4,5]imidazo[2,1-*a*]isoquinoline **3** and regenerate the active catalytic species.

In conclusion, we have developed an efficient protocol for the one-pot synthesis of benzimidazole-fused isoquinolines. The process is based on nucleophilic addition of 2-arylbenzimidazoles to alkynyl bromides and subsequent palladium-catalyzed intramolecular C-H vinylation. The result presented here should be of considerable interest of the valuable synthetic building blocks for medicinal and material science.

EXPERIMENTAL SECTION

General procedures for the one-pot synthesis of benzo[4,5]imidazo[2,1-*a*] isoquinolines. A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with alkynyl bromides (0.2 mmol, 1.0 equiv), 2-arylbenzimidazoles (0.24 mmol, 1.2 equiv) and K_2CO_3 (55 mg, 0.4 mmol, 2.0 equiv), then 1.2 mL DMF was added via syringe at room temperature. The tube was sealed and put into a pre-heated oil bath at 120 ℃ for 2-4 h. $Pd(OAc)_2$ (0.01 mmol, 2.3 mg), PCy_3 (0.03 mmol, 8.4 mg) and DMF (0.8 mL) were then added, and the reaction mixture was heated to 130 ℃ for another 20 h. Finally, the mixture was cooled to room temperature, quenched with water (3 mL), and diluted with ethyl acetate (5 mL). The layers were separated and the aqueous layer was extracted with (2 × 5 mL) ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel (H), eluting with 3-10% ethyl acetate/ petroleum ether.

6-Phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3aa).[3, 4, 8] White solid (40 mg, 68%), mp 178-179 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.91-8.89 (1H, dd, *J* = 9.2, 4.0 Hz), 8.00 (1H, d, *J* = 8.4 Hz), 7.73-7.67 (3H, m), 7.64-7.59 (5H, m), 7.39 (1H, t, *J* = 7.6 Hz), 7.01 (1H, quint, *J* = 8.0, 1.2 Hz), 6.91 (1H, s), 6.49 (1H, d, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.3, 144.3, 137.5, 134.7, 131.6, 130.7, 130.1, 129.9, 129.4, 129.0, 127.9, 126.7, 125.1, 124.2, 122.9, 121.3, 119.7, 114.1, 112.6. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{21}H_{14}N_2Na$ 317.1055; found 317.1057.

3-Methyl-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ba).[4] Pale yellow solid (37 mg, 60%), mp 193-195 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.77 (1H, d, *J* = 8.4

Hz), 7.96 (1H, d, *J* = 8.0 Hz), 7.63-7.58 (5H, m), 7.52-7.50 (2H, m), 7.37 (1H, t, *J* = 8.0 Hz), 6.98 (1H, t, *J* = 8.0 Hz), 6.84 (1H, s), 6.46 (1H, d, *J* = 8.0 Hz), 2.55 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.5, 144.3, 140.5, 137.5, 134.8, 131.8, 130.7, 129.8, 129.5, 129.4, 128.9, 126.5, 125.1, 124.1, 121.0, 120.6, 119.5, 114.0, 112.5, 21.9. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{16}N_2Na$ 331.1211; found 331.1213.

3-Methoxy-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ca). Pale yellow solid (36 mg, 56%), mp 181-183 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (1H, d, *J* = 8.4 Hz), 7.94 (1H, d, *J* = 8.4 Hz), 7.64-7.59 (5H, m), 7.36 (1H, t, *J* = 8.0 Hz), 7.29-7.27 (1H, dd, *J* = 8.8, 2.4 Hz), 7.11 (1H, d, *J* = 2.4 Hz), 6.96 (1H, t, *J* = 8.0 Hz), 6.83 (1H, s), 6.45 (1H, t, *J* = 8.4 Hz), 3.95 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.2, 148.5, 144.4, 138.05, 134.6, 133.4, 130.6, 129.8, 129.3, 128.9, 126.9, 124.0, 120.7, 119.3, 117.2, 116.7, 113.9, 112.3, 108.1, 55.5. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{16}N_2NaO$ 347.1160; found 347.1158.

3-Chloro-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3da). White solid (30 mg, 45%), mp 175-177 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.80 (1H, d, *J* = 8.8 Hz), 7.96 (1H, d, *J* = 8.0 Hz), 7.69-7.59 (7H, m), 7.39 (1H, t, *J* = 7.6 Hz), 7.00 (1H, t, *J* = 8.0 Hz), 6.81 (1H, s), 6.46 (1H, d, *J* = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.6, 144.2, 138.8, 136.1, 134.2, 132.7, 130.6, 130.1, 129.2, 129.0, 128.3, 126.7, 125.9, 124.4, 121.5, 121.2, 119.7, 114.1, 111.3. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{21}H_{13}ClN_2Na$ 351.0665; found 351.0663.

6-Phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline-3-carbonitrile (3ea). Pale yellow solid (32 mg, 50%), mp 223-225 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.96 (1H, d, *J* =

8.4 Hz), 8.03 (1H, s), 8.00 (1H, d, J = 8.4 Hz), 7.85 (1H, d, J = 8.4 Hz), 7.68-7.59 (5H, m), 7.43 (1H, t, J = 7.6 Hz), 7.07 (1H, t, J = 8.0 Hz), 6.90 (1H, s), 6.50 (1H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.6, 144.2, 139.5, 133.8, 131.2, 131.1, 130.6, 130.4, 129.6, 129.2, 128.9, 126.0, 125.5, 124.9, 122.4, 120.2, 118.4, 114.2, 113.3, 111.1. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{13}N_3Na$ 342.1007; found 342.1008.

1-Methyl-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3fa). White solid (35 mg, 56%), mp 212-214 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (1H, d, J = 8.0 Hz), 7.64-7.59 (5H, m), 7.55-7.54 (2H, m), 7.52-7.49 (1H, m), 7.38 (1H, t, J = 8.0 Hz), 7.00 (1H, t, J = 8.0 Hz), 6.88 (1H, s), 6.48 (1H, d, J = 8.4 Hz), 3.35 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.8, 144.2, 138.7, 137.1, 134.9, 132.8, 130.4, 129.8, 129.7, 129.3, 129.1, 128.9, 124.6, 123.7, 121.9, 121.1, 120.0, 113.9, 113.4, 24.5. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{16}N_2Na$ 331.1211; found 331.1213.

1-Chloro-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ga). Pale yellow solid (21 mg, 31%), mp 239-241 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (1H, d, J = 8.0 Hz), 7.73 (1H, d, J = 7.6 Hz), 7.65-7.58 (6H, m), 7.55-7.51 (1H, m), 7.39 (1H, t, J = 8.0 Hz), 7.02 (1H, t, J = 8.0 Hz), 6.89 (1H, s), 6.45 (1H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.1, 144.0, 138.2, 134.3, 134.1, 132.5, 130.6, 130.0, 129.7, 129.5, 129.2, 129.0, 125.6, 124.1, 121.9, 120.7, 120.5, 113.8, 112.6. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{21}H_{13}ClN_2Na$ 351.0665; found 351.0663.

Mixture of 2-methyl-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ha) and 4-methyl-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ha′). Inseparable yellow solid (41 mg, 66%, **3ha**:**3ha′** = 3:1). **3ha**+**3ha′**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.77

(0.22H, d, J = 8.0 Hz), 8.70 (0.67H, s), 7.97 (0.90H, d, J = 8.0 Hz), 7.63-7.54 (5.65H, m), 7.48 (1H, t, J = 8.0 Hz), 7.37 (1H, t, J = 7.2 Hz), 7.02-6.96 (1.2H, m), 6.85 (0.68H, s), 6.48 (0.92H, d, J = 8.8 Hz), 2.62 (0.7H, s), 2.59 (2.0H, s). **3ha**+**3ha′**: ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 148.2, 144.3, 144.2, 138.1, 137.1, 136.6, 134.9, 134.7, 133.9, 131.6, 131.1, 130.7, 130.6, 130.4, 129.8, 129.7, 129.4, 129.3, 129.0, 128.9, 127.6, 126.5, 124.8, 124.2, 124.1, 123.1, 122.8, 121.1, 119.6, 114.1, 112.5, 109.2, 21.6, 19.3. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{16}N_2Na$ 331.1211; found 331.1213.

2-Methoxy-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ia). Pale yellow solid (47 mg, 72%), mp 186-188 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (1H, d, J = 2.4 Hz), 7.99 (1H, d, J = 8.4 Hz), 7.63-7.57 (6H, m), 7.38 (1H, t, J = 8.0 Hz), 7.29-7.26 (1H, dd, J = 8.4, 2.4 Hz), 6.99 (1H, t, J = 8.0 Hz), 6.86 (1H, s), 6.50 (1H, d, J = 8.4 Hz), 4.04 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5, 148.0, 144.1, 135.2, 134.8, 130.7, 129.7, 129.5, 128.9, 128.3, 125.7, 124.2, 124.1, 121.1, 120.9, 119.6, 114.2, 112.4, 105.2, 55.9. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{16}N_2NaO$ 347.1160; found 347.1158.

2-Chloro-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ja). Pale yellow solid (26 mg, 39%), mp 217-219 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.88 (1H, s), 7.98 (1H, d, J = 8.4 Hz), 7.67-7.59 (7H, m), 7.40 (1H, t, J = 7.6 Hz), 7.02 (1H, t, J = 8.0 Hz), 6.87 (1H, s), 6.49 (1H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.1, 144.1, 137.8, 134.3, 133.8, 130.6, 130.5, 130.0, 129.8, 129.3, 129.0, 128.0, 124.6, 124.4, 124.0, 121.6, 119.8, 114.1, 111.7. HRMS-ESI (m/z): $[M + Na]^+$ calcd for

$C_{21}H_{13}ClN_2Na$ 351.0665; found 351.0663.

4-Chloro-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ja′). Pale yellow solid (18 mg, 28%), mp 154-156 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.81 (1H, d, *J* = 8.0 Hz), 7.98 (1H, d, *J* = 8.0 Hz), 7.73 (1H, d, *J* = 7.6 Hz), 7.66-7.56 (6H, m), 7.40 (1H, t, *J* = 7.6 Hz), 7.31 (1H, s), 7.02 (1H, t, *J* = 8.0 Hz), 6.50 (1H, d, *J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.6, 144.3, 138.6, 134.4, 131.2, 130.5, 130.3, 130.1, 129.3, 129.0, 128.0, 124.5, 124.4, 123.9, 121.7, 119.8, 114.2, 108.5. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{21}H_{13}ClN_2Na$ 351.0665; found 351.0663.

Mixture of 2,3-dimethyl-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ka) and 3,4-dimethyl-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ka′). Inseparable pale yellow solid (23 mg, 35%, **3ka**:**3ka′** = 4.5:1). **3ka**+**3ka′**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.67 (0.2H, d, *J* = 8.0 Hz), 8.64 (0.97H, s), 7.96 (1.2H, d, *J* = 8.0 Hz), 7.63-7.56 (6.14H, m), 7.48 (0.32H, t, *J* = 8.0 Hz), 7.45 (1H, s), 7.35 (1.3H, t, *J* = 8.0 Hz), 7.07 (0.22H, s), 6.96 (1H, t, *J* = 8.0 Hz), 6.80 (1H, s), 6.46 (1.2H, d, *J* = 8.4 Hz), 2.51 (0.75H, s), 2.50 (3.5H, s), 2.43 (3H, s). **3ka**+**3ka′**: ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.8, 148.3, 144.3, 144.2, 139.9, 138.5, 137.6, 136.9, 136.6, 135.1, 134.9, 131.7, 130.7, 130.5, 130.4, 130.2, 129.9, 129.8, 129.7, 129.4, 129.0, 128.9, 126.9, 125.2, 124.1, 124.0, 122.6, 121.1, 120.9, 120.8, 119.4, 114.1, 114.0, 112.3, 109.5, 21.1, 20.2, 20.0. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{23}H_{18}N_2Na$ 345.1368; found 345.1369.

2,4-Dimethyl-6-phenylbenzo[4,5]imidazo[2,1-a]isoquinoline (3la). Pale yellow solid (39 mg, 60%), mp 188-190 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.59 (1H, s), 7.97 (1H, d, *J* = 8.4 Hz), 7.63-7.59 (5H, m), 7.39-7.34 (2H, m), 6.99-6.96 (2H, m), 6.48

(1H, d, J = 8.4 Hz), 2.58 (3H, s), 2.55 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 144.2, 137.8, 136.1, 135.1, 133.8, 132.8, 130.6, 129.7, 129.5, 128.9, 128.1, 124.1, 122.9, 122.8, 120.9, 119.5, 114.0, 109.3, 21.5, 19.2. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{23}H_{18}N_2Na$ 345.1368; found 345.1369.

8-Phenylbenzo[*h*]benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ma). Pale yellow solid (43 mg, 62%), mp 198-200 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.01 (1H, d, J = 8.8 Hz), 8.14 (1H, d, J = 8.4 Hz), 8.05-7.94 (3H, m), 7.73-7.70 (2H, m), 7.66-7.62 (5H, m), 7.46 (1H, t, J = 7.6 Hz), 7.06 (1H, s), 7.04 (1H, t, J = 7.6 Hz), 6.59 (1H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.4, 144.7, 138.1, 134.8, 132.8, 131.7, 131.2, 130.2, 129.9, 129.4, 129.3, 129.0, 128.8, 128.3, 128.2, 126.6, 124.9, 124.4, 121.0, 120.0, 117.9, 114.3, 113.4. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{25}H_{16}N_2Na$ 367.1211; found 367.1213.

8-Phenylbenzo[*f*]benzo[4,5]imidazo[2,1-*a*]isoquinoline (3na). Pale yellow solid (26 mg, 38%), mp 238-240 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.91 (1H, d, J = 8.8 Hz), 8.54-8.52 (1H, m), 8.08-7.99 (3H, m), 7.74 (1H, s), 7.69-7.65 (7H, m), 7.43 (1H, t, J = 7.6 Hz), 7.03 (1H, t, J = 7.6 Hz), 6.60 (1H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 144.6, 138.1, 134.9, 133.9, 130.9, 130.4, 130.0, 129.4, 129.1, 128.9, 128.8, 128.7, 128.6, 127.5, 127.1, 124.6, 123.3, 122.2, 121.0, 120.6, 119.7, 114.2, 108.0. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{25}H_{16}N_2Na$ 367.1211; found 367.1213.

6-Phenylbenzo[*g*]benzo[4,5]imidazo[2,1-*a*]isoquinoline (3na′). Pale yellow solid (23.5 mg, 34%), mp 174-176 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.43 (1H, s), 8.16-8.13 (2H, m), 8.00-7.97 (2H, m), 7.64-7.57 (7H, m), 7.37 (1H, t, J = 7.6 Hz),

7.01 (1H, t, J = 7.6 Hz), 6.97 (1H, s), 6.44 (1H, d, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.5, 144.0, 136.9, 134.7, 134.0, 132.6, 131.2, 130.9, 129.8, 129.5, 128.9, 128.8, 127.8, 127.3, 126.4, 125.2, 124.9, 123.9, 121.7, 121.3, 119.7, 113.8, 112.8. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{25}H_{16}N_2Na$ 367.1211; found 367.1213.

5-Phenylbenzo[4,5]imidazo[1,2-*a*]furo[2,3-c]pyridine (3oa). Pale yellow solid (38 mg, 67%), mp 218-219 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (1H, d, J = 8.4 Hz), 7.88 (1H, d, J = 2.0 Hz), 7.64-7.54 (5H, m), 7.39 (1H, t, J = 7.6 Hz), 6.96 (1H, t, J = 7.6 Hz), 6.89-6.88 (2H, m), 6.45 (1H, d, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.9, 144.9, 141.7, 140.4, 137.3, 134.8, 130.2, 129.8, 129.5, 129.0, 125.3, 124.7, 120.6, 119.9, 114.2, 107.6, 106.3. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{19}H_{12}N_2NaO$ 307.0847; found 307.0848.

5-Phenylbenzo[4,5]imidazo[1,2-a]thieno[2,3-c]pyridine (3pa).[4] Yellow solid (37 mg, 61%), mp 208-210 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (1H, d, J = 8.0 Hz), 7.69 (1H, d, J = 5.2 Hz), 7.64-7.56 (5H, m), 7.40-7.37 (2H, m), 7.05 (1H, s), 6.97 (1H, t, J = 7.6 Hz), 6.49 (1H, d, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.8, 144.7, 138.7, 137.7, 134.6, 130.2, 130.0, 129.9, 129.4, 129.0, 125.9, 124.6, 124.5, 120.7, 119.5, 114.3, 108.7. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{19}H_{12}N_2NaS$ 323.0619; found 323.0621.

9,10-Dimethyl-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3qa).[4] Pale yellow solid (36 mg, 56%), mp 210-212 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86-8.84 (1H, m), 7.74 (1H, s), 7.71-7.61 (4H, m), 7.60-7.58 (4H, m), 6.87 (1H, s), 6.19 (1H, s), 2.37 (3H, s), 2.13 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.6, 142.7, 137.4, 134.7,

133.4, 131.4, 131.0, 130.3, 129.7, 129.4, 129.1, 128.8, 127.7, 126.6, 124.9, 122.9, 119.4, 114.2, 112.1, 20.7, 20.4. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{23}H_{18}N_2Na$ 345.1368; found 345.1365.

9,10-Dichloro-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ra). White solid (40 mg, 55%), mp 285-286 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.83-8.81 (1H, m), 8.03 (1H, s), 7.75-7.62 (6H, m), 7.59-7.57 (2H, m), 6.96 (1H, s), 6.50 (1H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.8, 143.5, 137.0, 133.7, 131.7, 130.7, 130.4, 129.6, 129.2, 128.4, 128.3, 126.8, 125.2, 124.8, 122.5, 120.4, 115.3, 113.2. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{21}H_{12}Cl_2N_2Na$ 385.0275; found 385.0277.

6-(*p*-Tolyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ab).[4] White solid (46 mg, 75%), mp 151-153 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.92-8.89 (1H, m), 8.00 (1H, d, J = 8.4 Hz), 7.72-7.65 (3H, m), 7.49-7.47 (2H, m), 7.41-7.37 (3H, m), 7.02 (1H, quint, J = 8.0, 0.8 Hz), 6.88 (1H, s), 6.57 (1H, d, J = 8.8 Hz), 2.54 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.3, 144.2, 139.9, 137.6, 131.7, 131.6, 130.7, 130.0, 129.6, 129.2, 127.7, 126.6, 125.1, 124.1, 122.8, 121.1, 119.6, 114.2, 112.5, 21.5. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{16}N_2Na$ 331.1211; found 331.1212.

9,10-Dimethyl-6-(*p*-tolyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3qb). Yellow solid (43 mg, 64%), mp 173-175 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.85-8.83 (1H, m), 7.73 (1H, s), 7.67-7.61 (3H, m), 7.46 (2H, d, J = 8.0 Hz), 7.38 (2H, d, J = 7.6 Hz), 6.83 (1H, s), 6.28 (1H, s), 2.53 (3H, s), 2.36 (3H, s), 2.14 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.6, 142.6, 139.8, 137.5, 133.3, 131.9, 131.5, 130.3, 129.7, 129.4, 129.3, 129.1, 127.6, 126.5, 124.9, 122.8, 119.4, 114.3, 112.1, 21.5, 20.8, 20.4.

HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{24}H_{20}N_2Na$ 359.1524; found 359.1526.

9,10-Dichloro-6-(*p*-tolyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3rb). Pale yellow solid (49 mg, 65%), mp 240-242 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.79 (1H, dd, *J* = 6.0, 2.4 Hz), 8.00 (1H, s), 7.72-7.65 (3H, m), 7.47-7.42 (4H, m), 6.91 (1H, s), 6.58 (1H, s), 2.55 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.8, 143.4, 140.5, 137.1, 131.8, 130.8, 130.7, 129.8, 129.6, 129.1, 128.2, 128.1, 126.7, 125.2, 124.7, 122.4, 120.3, 115.4, 113.2, 21.5. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{14}Cl_2N_2Na$ 399.0432; found 399.0435.

6-Butylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ac).[3, 4] White solid (45 mg, 81%), mp 124-126 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.82-8.81 (1H, m), 8.04 (1H, d, *J* = 8.0 Hz), 7.98 (1H, d, *J* = 8.0 Hz), 7.65-7.59 (3H, m), 7.50 (1H, t, *J* = 7.6 Hz), 7.37 (1H, t, *J* = 7.6 Hz), 6.77 (1H, s), 3.30 (2H, t, *J* = 7.6 Hz), 1.90 (2H, quint, *J* = 7.6 Hz), 1.61 (2H, sext, *J* = 7.6 Hz), 1.04 (3H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 144.3, 139.0, 131.6, 130.7, 129.9, 127.1, 125.9, 125.0, 124.1, 122.3, 121.7, 120.0, 114.2, 109.6, 33.1, 29.4, 22.3, 13.9. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{19}H_{18}N_2Na$ 297.1368; found 297.1366.

6-Butyl-9,10-dimethylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3qc).[4] Pale yellow solid (30 mg, 50%), mp 167-168 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.79-8.77 (1H, m), 7.77 (1H, s), 7.71 (1H, d, *J* = 6.4 Hz), 7.61-7.57 (3H, m), 6.70 (1H, d, *J* = 6.4 Hz), 3.26 (2H, quart, *J* = 8.0 Hz), 2.46 (3H, s), 2.45 (3H, s), 1.87 (2H, m), 1.63-1.57 (2H, m), 1.04 (3H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.9, 142.8, 138.9, 133.2, 131.5, 130.8, 129.5, 129.1, 127.0, 125.8, 124.8, 122.3, 119.7, 114.3, 109.3,

33.1, 29.5, 22.3, 21.0, 20.4, 13.9. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{21}H_{22}N_2Na$ 325.1681; found 325.1682.

6-Butyl-9,10-dichlorobenzo[4,5]imidazo[2,1-*a*]isoquinoline (3rc). White solid (32 mg, 47%), mp 170-172 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.72 (1H, d, *J* = 7.6 Hz), 8.04 (1H, s), 8.00 (1H, s), 7.66-7.61 (3H, m), 6.77 (1H, s), 3.18 (2H, t, *J* = 7.6 Hz), 1.86 (2H, quint, *J* = 7.6 Hz), 1.61 (2H, sext, *J* = 7.6 Hz), 1.06 (3H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.0, 143.6, 138.3, 131.7, 130.6, 129.5, 128.2, 127.5, 126.1, 125.2, 125.1, 121.8, 120.6, 115.4, 110.4, 32.7, 29.1, 22.3, 13.9. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{19}H_{16}Cl_2N_2Na$ 365.0588; found 365.0590.

6-(4-Methoxyphenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ad). White solid (49 mg, 76%), mp 185-186 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (1H, dd, *J* = 5.6, 3.6 Hz), 7.99 (1H, d, *J* = 8.4 Hz), 7.73-7.66 (3H, m), 7.52 (2H, d, *J* = 8.4 Hz), 7.40 (1H, t, *J* = 7.6 Hz), 7.11 (2H, d, *J* = 8.8 Hz), 7.03 (1H, t, *J* = 7.6 Hz), 6.88 (1H, s), 6.60 (1H, d, *J* = 8.4 Hz), 3.96 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.7, 148.3, 144.2, 137.4, 131.7, 130.8, 130.7, 130.0, 127.7, 127.0, 126.5, 125.1, 124.1, 122.8, 121.2, 119.6, 114.3, 114.1, 112.6, 55.5. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{16}N_2NaO$ 347.1160; found 347.1161.

6-(4-Fluorophenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ae). Pale yellow solid (51 mg, 81%), mp 140-142 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.92 (1H, dd, *J* = 5.6, 3.6 Hz), 8.02 (1H, d, *J* = 8.0 Hz), 7.76-7.70 (3H, m), 7.63-7.60 (2H, m), 7.43 (1H, quint, *J* = 7.6, 0.8 Hz), 7.34-7.28 (2H, m), 7.07 (1H, quint, *J* = 7.6, 1.2 Hz), 6.91 (1H, s), 6.54 (1H, d, *J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.8, 162.3, 148.2, 144.2,

136.4, 131.5, 131.4, 131.3, 130.8, 130.7, 130.6, 130.1, 128.0, 126.6, 125.1, 124.2, 123.0, 121.3, 119.8, 116.3, 116.0, 113.8, 112.9. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{21}H_{13}FN_2Na$ 335.0960; found 335.0961.

6-(Thiophen-2-yl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3af). Pale yellow solid (38 mg, 63%), mp 146-148 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.89 (1H, d, *J* = 6.4 Hz), 7.99 (1H, d, *J* = 8.0 Hz), 7.75-7.68 (3H, m), 7.65-7.63 (1H, m), 7.42 (1H, t, *J* = 7.6 Hz), 7.38-7.37 (1H, m), 7.30-7.29 (1H, m), 7.10-7.07 (2H, m), 6.56 (1H, d, *J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.1, 144.1, 134.6, 131.0, 130.6, 130.1, 129.9, 129.8, 128.4, 128.0, 127.5, 126.8, 125.1, 124.3, 123.3, 121.5, 119.7, 115.2, 113.7. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{19}H_{12}N_2NaS$ 323.0619; found 323.0621.

3-(Benzo[4,5]imidazo[2,1-*a*]isoquinolin-6-yl)propyl benzoate (3ag). Pale yellow solid (51 mg, 67%), mp 141-143 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.81-8.80 (1H, m), 8.09-8.03 (4H, m), 7.63-7.57 (4H, m), 7.51-7.44 (3H, m), 7.33-7.29 (1H, m), 6.83 (1H, s), 4.58 (2H, t, *J* = 6.0 Hz), 3.50-3.48 (2H, m), 2.42-3.38 (2H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 148.5, 144.2, 137.5, 133.2, 131.4, 130.5, 130.1, 130.0, 129.5, 128.5, 127.5, 126.0, 125.0, 124.3, 122.3, 122.0, 120.1, 113.9, 110.3, 63.8, 30.3, 26.9. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{25}H_{20}N_2NaO_2$ 403.1422; found 403.1423.

11-Methyl-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3sa). White solid (31.5 mg, 51%), mp 182-184 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.95-8.92 (1H, m), 7.71-7.65 (3H, m), 7.62-7.57 (5H, m), 7.18 (1H, d, *J* = 7.2 Hz), 6.91-6.88 (2H, m), 6.31 (1H, d, *J* = 8.4 Hz), 2.84 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.6, 143.6,

137.6, 134.7, 131.4, 130.3, 129.8, 129.7, 129.6, 129.4, 128.9, 127.7, 126.5, 125.2, 124.2, 123.1, 121.1, 112.4, 111.5, 17.1. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{16}N_2Na$ 331.1211; found 331.1213.

10-Methoxy-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ta). White solid (15 mg, 23%), mp 156-158 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.83-8.81 (1H, m), 7.85 (1H, d, *J* = 9.2 Hz), 7.72-7.62 (8H, m), 7.03 (1H, dd, *J* = 8.8, 2.4 Hz), 6.89 (1H, s), 5.90 (1H, d, *J* = 2.4 Hz), 3.47 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 147.6, 138.7, 137.2, 134.5, 131.1, 130.9, 129.8, 129.7, 129.6, 128.8, 127.8, 126.6, 124.6, 123.2, 120.0, 114.2, 112.2, 97.2, 55.2. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{16}N_2NaO$ 347.1160; found 347.1161.

9-Methoxy-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ta′). Yellow sticky liquid (20 mg, 31%); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.86-8.84 (1H, m), 7.73-7.72 (1H, m), 7.68-7.66 (2H, m), 7.64-7.59 (5H, m), 7.43 (1H, m), 6.91 (1H, s), 6.64 (1H, dd, *J* = 9.2, 2.4 Hz), 6.35 (1H, d, *J* = 9.2 Hz), 3.88 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.3, 148.5, 145.4, 137.2, 134.6, 131.4, 129.9, 129.8, 129.3, 129.0, 127.8, 126.6, 125.2, 124.9, 122.7, 114.5, 112.3, 111.5, 101.0, 55.6. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{16}N_2NaO$ 347.1160; found 347.1161.

6-Phenyl-10-(trifluoromethyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ua). Yellow solid (24 mg, 33%), mp 195-197 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.89-8.86 (1H, m), 8.25 (1H, m), 7.85-7.70 (3H, m), 7.69-7.58 (5H, m), 7.25-7.23 (1H, m), 6.98 (1H, s), 6.54-6.52 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.8, 143.7, 137.2, 134.1, 132.4, 131.7, 130.7, 130.2, 129.3, 129.2, 128.3, 126.8, 125.3, 123.5, 122.6, 117.84,

117.81, 117.3, 117.2, 114.4, 113.4. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{13}F_3N_2Na$ 385.0929; found 385.0931.

6-Phenyl-9-(trifluoromethyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ua′). Yellow solid (29 mg, 40%), mp 217-219 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.90-8.88 (1H, m), 8.04-8.02 (1H, m), 7.77-7.72 (3H, m), 7.69-7.59 (6H, m), 7.02 (1H, s), 6.69 (1H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.2, 146.2, 137.3, 133.8, 131.9, 130.8, 130.3, 129.9, 129.4, 129.3, 128.2, 126.8, 125.3, 123.1, 122.8, 122.6, 121.1, 121.0, 119.9, 113.1, 112.0, 111.9. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{13}F_3N_2Na$ 385.0929; found 385.0931.

ACKNOWLEDGMENT. We are grateful to the funds supported by the Fundamental Research Funds for the Central Universities (DL12DB03), China Postdoctoral Science Foundation (20110491013, 2012T50319) and Heilongjiang Postdoctoral Grant (LBH-Z11251).

Supporting Information Available: General experimental methods and ^{1}H and ^{13}C NMR spectra of the products **3aa-3ag**. This material is available free of charge via the Internet http://pubs.acs.org.

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