JOC The Journal of Organic Chemistry

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Synthesis of Polyfunctionalized Quinolines via the Sequence of Propargyl−Allenyl Isomerization and Aza-electrocyclization

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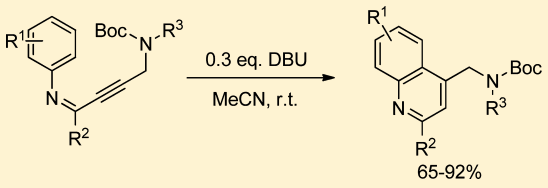
Supporting Information

ABSTRACT: Quinoline derivatives are important heterocyclic compounds because of their natural occurrence and applications in pharmaceutical fields. In this paper, a sequence of propargyl−allenyl isomerization and aza-electrocyclization for the synthesis of polyfunctionalized quinolines are described.



Quinoline derivatives, due to their natural occurrence[1] and applications in pharmaceutical fields,[2−4] such as antimalarial,[2] antitumor,[3] and antibacterial[4] activities, may be one of the most important heterocyclic compounds. Many famous molecules in the quinoline family, especially for the 4-substituted quinoline amine derivatives, for example, quinine, mefloquine, chloroquine, and amodiaquine (Figure 1), occupy a prominent place in medicinal chemistry.

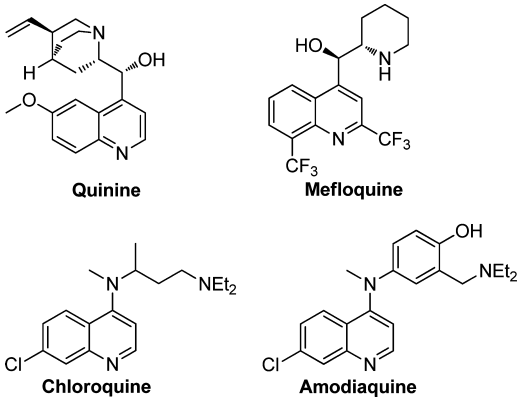


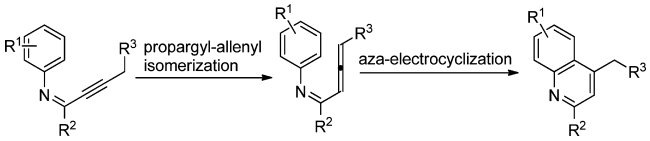
Figure 1. 4-Substituted quinoline amines.

Generally, there are only three ways to prepare quinolines: direct functionalization to quinoline, construction of a new pyridine ring from a benzenoid aromatic compound, or construction of a new benzene ring from a pyridine. Direct functionalization to quinoline, due to the effect of the substituent(s) and the difference of the pyridine ring with benzene ring, might encounter difficulty in some cases. Considering the much higher availability of benzenoid aromatic compounds than pyridine derivatives, construction of a new pyridine ring from a benzenoid aromatic compound may be an attractive protocol to access quinolines.

Allene-promoted cyclization reactions, in which the allene moiety could enhance the reaction possibility compared with that of a normal olefin, offer a facile route to cyclic compounds,[5] and the in situ propargyl−allenyl isomerization, which means the preparation of stable and readily accessible propargyl substrates instead of active and complicated allenes, has been a useful and efficient method attracting much attention by organic chemists.[6]

During our research on the in situ propargyl−allenyl isomerization,[7] we developed a 6π-electrocyclization protocol to construct the skeleton of a benzene ring.[7a,b] Based on the understanding of propargyl−allenyl isomerization and electrocyclization, it might be reasonably envisioned that the aza-electrocyclization of propargyl phenyl imines could undergo cycloaddition to give quinolines (Scheme 1).

Scheme 1

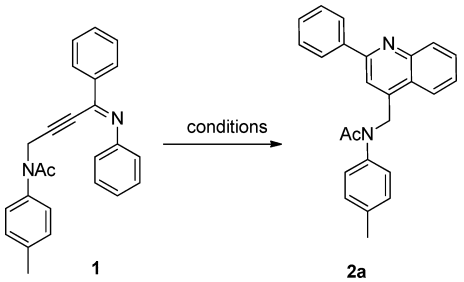


On the basis of this proposal, we chose *N*-(4-phenyl-4-(phenylimino)but-2-yn-1-yl)-*N*-(*p*-tolyl)acetamide (**1**) as the starting material, which could be prepared via the Sonogashira coupling of *N*-phenylbenzimidoyl chloride with *N*-(prop-2-yn-1-yl)-*N*-(*p*-tolyl)acetamide.[8] We initiated our study by testing the reaction of **1** in the presence of various bases and examining the solvent effects. DBU (1, 8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) could trigger the expected reaction and give *N*-((2-phenylquinolin-4-yl)methyl)-*N*-(*p*-tolyl)acetamide (**2a**) as the product (entries 6 and 7, Table 1). Further screening showed that acetonitrile was a suitable solvent (entry 7, Table 1). Interestingly, 0.3 equiv of DBU could offer better results than stoichiometric base, and **2a** was obtained in 65% yield (entry 19, Table 1).

Received: August 25, 2012
Published: September 24, 2012

dx.doi.org/10.1021/jo3018186 | J. Org. Chem. 2012, 77, 9418−9421

Table 1. Examination of Base and Solvent Effects



entry	base	solvent	yield of **2a** (%)
1	Et_3N (3 equiv)	MeCN	NR
2	K_2CO_3 (1 equiv)	MeCN	NR
3[a]	Cs_2CO_3 (1 equiv)	MeCN	7
4	EtONa (1 equiv)	EtOH	13
5	*t*-BuOK (1 equiv)	THF	0
6	DBN (1 equiv)	MeCN	42
7	DBU (1 equiv)	MeCN	45
8	DBU (1 equiv)	DMF	35
9	DBU (1 equiv)	DMSO	15
10	DBU (1 equiv)	acetone	18
11	DBU (1 equiv)	MeOH	25
12	DBU (1 equiv)	Et_2O	24
13	DBU (1 equiv)	THF	15
14	DBU (1 equiv)	benzene	32
15	DBU (1 equiv)	toluene	28
16	DBU (0.1 equiv)	MeCN	52
17	DBU (0.15 equiv)	MeCN	59
18	DBU (0.2 equiv)	MeCN	58
19	**DBU (0.3 equiv)**	**MeCN**	**65**
20	DBU (0.5 equiv)	MeCN	56
21	DBU (2 equiv)	MeCN	42

[a]Starting material was recovered in 45% yield.

With this result in hand, we examined the scope of the reaction and obtained polyfunctionalized quinolines in moderate to good yields under mild conditions (Table 2).

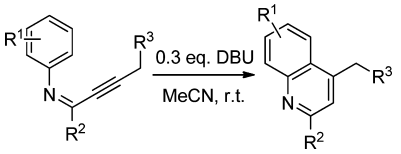
The *tert*-butyl carbamates, shown in Table 2, offered better yields than the acetamides (entries 3, 6, 8, 10, and 12, Table 2); on the other hand, *tert*-butyl carbamates afford a facile way to amines by the treatment of hydrochloric acid in THF. The corresponding quinolin-4-ylmethanamine may provide an access to 1,2-dihydropyrrolo[4,3,2-*de*]quinoline derivatives, which are known as an important class applied in pharmaceutical fields.[9] We treated **2l** with hydrochloric acid in THF then heated it at 90 °C with the catalysis of CuI/proline, and 6-methyl-1,4-diphenyl-1,2-dihydropyrrolo[4,3,2-*de*]quinoline (**3**) was isolated in 65% yield (Scheme 2).

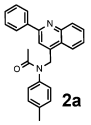
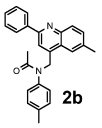
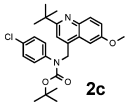
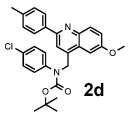
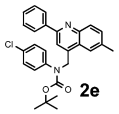
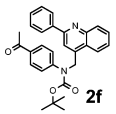
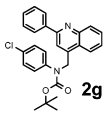
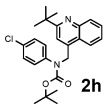
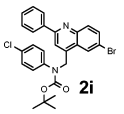
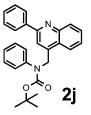
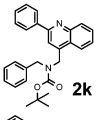
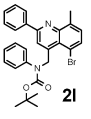
In summary, we have presented here a sequence of propargyl−allenyl isomerization and aza-electrocyclization for the facile synthesis of polyfunctionalized quinolines. This protocol, with the substrates having an amide group for promoting the reaction, may provide an efficient access to amines, which offer numerous choices for the functionalization of the products.

EXPERIMENTAL SECTION

Typical Procedure for the Synthesis of 2a. To a stirred solution of **1** (182 mg, 0.5 mmol) in 5 mL of dry acetonitrile was added DBU (22 mg, 0.15 mmol) by syringe at room temperature under N_2 atmosphere. Then the reaction mixture was allowed to stir for 6 h, diluted with 10 mL of water, and extracted with dichloromethane (2 × 15 mL). The extract was dried with anhydrous Na_2SO_4. After evaporation, chromatography on silica gel (hexane/ethyl acetate 5/1) of the reaction mixture afforded **2a**.

Table 2. Aza-electrocyclization via Propargyl−Allenyl Isomerization[a]

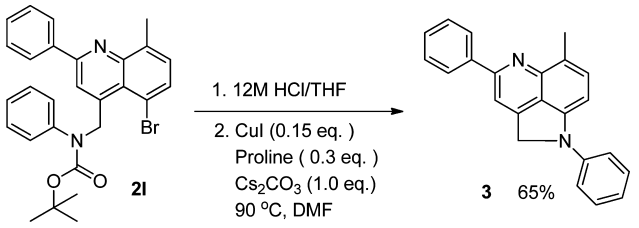


entry	time (h)	product	yield (%)
1	6	 **2a**	65
2	6	 **2b**	69
3	5	 **2c**	87
4	4	 **2d**	70
5	4	 **2e**	80
6	5	 **2f**	92
7	5	 **2g**	71
8	5	 **2h**	88
9	4	 **2i**	65
10	4	 **2j**	85
11	5	 **2k**	80
12	5	 **2l**	85

[a]All reactions were conducted in acetonitrile (5 mL) under N_2 atmosphere on a 0.5 mmol scale.

dx.doi.org/10.1021/jo3018186 | J. Org. Chem. 2012, 77, 9418−9421

Scheme 2



***N*-((2-Phenylquinolin-4-yl)methyl)-*N*-(*p*-tolyl)acetamide (2a):** yellow solid; mp = 52 − 54 °C; 119 mg, 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18−8.16 (d, J = 8.4 Hz, 1H), 8.11−8.09 (d, J = 8.4 Hz, 1H), 8.01−7.99 (d, J = 7.2 Hz, 2H), 7.73−7.70 (t, J = 15.6 Hz, 1H), 7.55−7.38 (m, 5H), 7.04−7.01 (d, J = 7.6 Hz, 2H), 6.82−6.80 (d, J = 8.4 Hz, 2H), 5.42 (s, 2H), 2.28 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 135.0, 134.1, 132.3, 130.8, 129.1, 128.8, 128.7, 127.6, 127.1, 126.9, 126.1, 125.5, 38.2, 19.9; IR (neat, cm^{-1}) 2924, 1856, 1601, 1551, 1511, 1388; HRMS (TOF) calcd for $C_{25}H_{22}N_2O$ 366.1732, found 366.1734.

***N*-((6-Methyl-2-phenylquinolin-4-yl)methyl)-*N*-(*p*-tolyl)-acetamide (2b):** amorphous solid; 131 mg, 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.07 (d, J = 8.4 Hz, 1H), 8.02−8.00 (d, J = 8.0 Hz, 2H), 7.80 (s, 1H), 7.57−7.44 (m, 5H), 7.09−7.07 (d, J = 7.6 Hz, 2H), 6.88−6.86 (d, J = 7.6 Hz, 2H), 5.40 (s, 2H), 2.53 (s, 3H), 2.30 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ170.5, 155.8, 146.8, 142.3, 139.5, 138.1, 136.3, 131.6, 130.1, 129.8, 129.0, 128.6, 127.7, 127.3, 125.6, 122.5, 119.6, 49.6, 22.7, 21.9, 20.9; IR (neat, cm^{-1}) 1655, 1509, 1444; HRMS (TOF) calcd for $C_{26}H_{24}N_2O$ 380.1889, found 380.1890.

***tert*-Butyl ((2-*tert*-Butyl-6-methoxyquinolin-4-yl)methyl)(4-chlorophenyl)carbamate (2c):** gum; 197 mg, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.22 (d, J = 8.4 Hz, 1H), 8.15−8.13 (d, J = 8.0 Hz, 2H), 7.77−7.72 (t, J = 15.6 Hz, 1H), 7.66 (s, 1H), 7.57−7.48 (m, 4H), 7.37−7.24 (m, 6H), 4.99 (s, 1H), 4.93 (s,1H), 4.61 (s, 1H), 4.44 (s, 1H), 1.58−1.48 (d, J = 36.8 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 157.4, 154.2, 143.4, 140.7, 140.3, 132.2, 132.1, 131.6, 131.4, 128.7, 128.5, 128.4, 127.8, 125.4, 121.2, 101.0, 81.1, 55.4, 51.1, 37.6, 29.9, 28.1; IR (neat, cm^{-1}) 1698, 1600, 1478, 1454, 1365; HRMS (TOF) calcd for $C_{26}H_{31}ClN_2O_3$ 454.2023, found 454.2024.

***tert*-Butyl (4-chlorophenyl)((6-methoxy-2-(*p*-tolyl)quinolin-4-yl)methyl)carbamate (2d):** yellow solid; mp = 48−51 °C; 171 mg, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.08 (d, J = 9.2 Hz, 1H), 7.93−7.91 (d, J = 7.6 Hz, 2H), 7.55 (s, 1H), 7.39−7.37 (d, J = 9.2 Hz, 1H), 7.30−7.19 (m, 3H), 7.20−7.18 (d, J = 8.4 Hz, 2H), 7.04 (s, 2H), 5.27 (s, 2H), 2.93 (s, 3H), 2.41 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ157.9, 154.3, 154.2, 132.0, 131.7, 129.0, 128.8, 128.7, 127.5, 127.1, 122.2, 101.1, 81.3, 55.5, 51.2, 29.6, 28.1; IR (neat, cm^{-1}) 1693, 1622, 1493, 1366; HRMS (TOF) calcd for $C_{29}H_{29}ClN_2O_3$ 488.1867, found 488.1868.

***tert*-Butyl (4-chlorophenyl)((6-methyl-2-phenylquinolin-4-yl)methyl)carbamate (2e):** gum; 183 mg, 80% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11−8.09 (d, J = 8.0 Hz, 1H), 8.07−8.05 (d, J = 7.2 Hz, 2H), 7.73 (s, 1H), 7.66 (s, 1H), 7.58−7.56 (d, J = 8.4 Hz, 1H), 7.51−7.47 (t, J = 14.8 Hz, 2H), 7.45−7.43 (d, J = 6.8 Hz, 2H), 7.22−7.20 (d, J = 8.8 Hz, 2H), 7.12 (s, 2H), 5.33 (s, 2H), 2.54 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ156.1, 154.3, 140.9, 136.5, 132.1, 131.8, 131.6, 130.2, 129.3, 128.9, 128.8, 127.4, 125.2, 121.8, 81.5, 51.2, 29.7, 28.2, 21.9; IR (neat, cm^{-1}) 1258, 1011, 789; HRMS (TOF) calcd for $C_{28}H_{27}ClN_2O_2$ 458.1761, found 458.1763.

***tert*-Butyl (4-acetylphenyl)((2-phenylquinolin-4-yl)methyl)-carbamate (2f):** yellow solid; mp = 62−65 °C; 208 mg, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.26 (d, J = 8.4 Hz, 1H), 8.12−8.10 (d, J = 7.2 Hz, 2H), 8.02−8.00 (d, J = 8.4 Hz, 2H), 7.91−7.89 (d, J = 8.8 Hz, 2H), 7.80−7.76 (t, J = 16.0 Hz, 2H), 7.61−7.58 (t, J = 14.8 Hz, 1H), 7.54−7.46 (m, 3H), 7.40−7.38 (d, J = 8.4 Hz, 2H), 5.48 (s, 2H), 2.56 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 156.9, 153.8, 148.3, 146.7, 143.6, 139.3, 134.0, 130.1, 129.6, 129.4, 129.0, 128.8, 127.3, 126.5, 125.0, 124.6, 122.3, 116.3, 81.9, 50.8, 28.1, 26.4; IR (neat, cm^{-1}) 1712, 1681, 1600, 1367; HRMS (TOF) calcd for $C_{29}H_{28}N_2O_3$ 452.2100, found 452.2103.

***tert*-Butyl (4-chlorophenyl)((2-phenylquinolin-4-yl)methyl)-carbamate (2g):** amorphous solid; 158 mg, 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27−8.24 (d, J = 8.4 Hz, 1H), 8.12−8.10 (d, J = 7.6 Hz, 2H), 8.02−8.00 (d, J = 7.6 Hz, 1H), 7.76−7.74 (t, J = 8.4 Hz, 2H), 7.57−7.48 (m, 4H), 7.28−7.23 (t, J = 17.2 Hz, 2H), 7.17 (s, 2H), 5.38 (s, 2H), 1.46 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 154.2, 148.3 139.4 130.5, 129.6, 129.4, 128.8, 127.4, 127.1,126.5, 125.1, 122.6, 81.494, 51.0, 28.1; IR (neat, cm^{-1}) 1697, 1602, 1493, 1367, 1318; HRMS (TOF) calcd for $C_{27}H_{25}ClN_2O_2$ 444.1605, found 444.1607.

***tert*-Butyl ((2-*tert*-Butylquinolin-4-yl)methyl)(4-chlorophenyl)carbamate (2h):** gum; 187 mg, 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.10 (d, J = 8.8 Hz, 1H), 7.97−7.95 (d, J = 8 Hz, H), 7.70−7.66 (t, J = 15.2 Hz, 1H), 7.53−7.49 (t, J = 14.8 Hz, 1H), 7.32 (s, 1H), 7.22−7.20 (d, J = 8.8 Hz, 2H), 7.09 (s, 2H), 5.29 (s, 2H), 1.44 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ168.7, 154.1, 147.5, 142.3, 140.7, 132.2, 132.1, 131.4, 130.1, 128.9, 128.7, 128.5, 128.4, 127.3, 125.8, 124.4, 122.3, 116.7, 81.3, 50.9, 38.0, 29.9, 28.1; IR (neat, cm^{-1}) 1696, 1560, 1493, 1366, 1321; HRMS (TOF) calcd for $C_{25}H_{29}ClN_2O_2$ 424.1918, found 424.1916.

***tert*-Butyl ((6-bromo-2-phenylquinolin-4-yl)methyl)(4-chlorophenyl)carbamate (2i):** yellow solid; mp = 50−53 °C; 170 mg, 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.08−8.06 (t, J = 11.2 Hz, 3H), 7.81−7.78 (m, 1H), 7.70 (s, 1H), 7.53−7.47 (m, 3H), 7.24−7.22 (d, J = 8.8 Hz, 2H), 7.10−7.09 (d, J = 6.8 Hz, 2H), 5.30 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ157.2, 154.1, 146.9, 142.9, 138.9, 133.0, 132.1, 131.8, 129.6, 128.9, 128.8, 127.3, 126.4, 125.4, 120.6, 81.7, 51.0, 28.2; IR (neat, cm^{-1})1705, 1600, 1492, 1369; HRMS (TOF) calcd for $C_{27}H_{24}BrClN_2O_2$ 522.0710, found 522.0715.

***tert*-Butyl phenyl((2-phenylquinolin-4-yl)methyl)carbamate (2j):** gum; 175 mg, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25−8.23 (d, J = 8.4 Hz, 1H), 8.11−8.10 (d, J = 6.8 Hz, 2H), 8.04−8.01 (d, J = 8.4 Hz, 1H), 7.78−7.77 (d, J = 2.8 Hz, 1H), 7.77−7.75 (d, J = 8.4 Hz, 1H), 7.56−7.46 (m, 4H), 7.28−7.27 (d, J = 2.4 Hz, 1H), 7.27−7.24 (d, J = 4.4 Hz, 1H), 7.24 (s,1H), 7.19−7.17 (t, J = 7.2 Hz, 1H), 5.41 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ157.0, 154.5, 148.2, 144.2, 142.3, 139.5, 130.4, 129.4, 129.3, 128.7, 127.4, 126.3, 126.0, 125.9, 125.2, 122.6, 120.5, 117.1, 81.1, 58.3, 51.1, 28.1, 18.3; IR (neat, cm^{-1}) 1689, 1600, 1494, 1478, 1407, 1366; HRMS (TOF) calcd for $C_{27}H_{26}N_2O_2$ 410.1994, found 410.1987.

***tert*-Butyl benzyl((2-phenylquinolin-4-yl)methyl)carbamate (2k):** gum; 170 mg, 80% yield; ^{1}H NMR (500 MHz, DMSO) δ 8.00−7.98 (m, 4H), 7.67−7.64 (t, J = 12.0 Hz, 1H), 7.57 (s, 1H), 7.48−7.41 (m, 3H), 7.39−7.37 (d, J = 5.6 Hz, 1H), 7.17−7.16 (m, 4 H), 7.12−7.09 (m, 1H), 4.89 (s, 2H), 4.43 (s, 2H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, DMSO) δ156.3, 155.7, 148.3, 139.4, 138.7, 130.3, 130.0, 129.9, 129.2, 128.8, 128.1, 127.5, 127.4, 126.8, 125.8, 123.7, 80.2, 51.2, 48.2, 28.5; IR (neat, cm^{-1})1698, 1600, 1478, 1454, 1365; HRMS calcd for $C_{28}H_{28}N_2O_2$ 424.2151, found 424.2150.

***tert*-Butyl ((5-bromo-8-methyl-2-phenylquinolin-4-yl)-methyl)(phenyl)carbamate (2l):** gum; 213 mg, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.27 (d, J = 7.2 Hz, 2H), 8.13 (s, 1H), 7.74−7.72 (d, J = 7.6 Hz, 1H), 7.56−7.48 (m, 3H), 7.41−7.31 (m, 5H), 7.19−7.16 (t, J = 14 Hz, 1H), 5.97 (s, 2H), 2.87 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ154.7, 154.4, 149.2, 145.6, 142.9, 138.7, 132.9, 129.6, 129.5, 128.8, 128.7, 127.2, 125.5, 125.1, 124.8, 116.1, 114.4, 55.2, 28.1, 19.0; IR (neat, cm^{-1}) 1697, 1593, 1493, 1370; HRMS (TOF) calcd for $C_{28}H_{27}BrN_2O_2$ 502.1256, found 502.1253.

6-Methyl-1,4-diphenyl-1,2-dihydropyrrolo[4,3,2-*de*]-quinoline (3). To a stirred solution of **2l** (202 mg, 0.5 mmol) in 5 mL of THF was added 0.5 mL of concentrated hydrochloric acid (12 M) at room temperature. After 12 h, the reaction mixture was diluted with 10 mL of NaOH (5%) and extracted with ethyl ether (3 × 30 mL). The extract was washed with water and dried over Na_2SO_4. After evaporation, the rescue was charged in a resealable Schlenk tube, and

dx.doi.org/10.1021/jo3018186 | J. Org. Chem. 2012, 77, 9418−9421

DMF (4 mL), CuI (14 mg, 0.073 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), L-(−)-proline(17 mg, 0.15 mmol) were added under nitrogen. The reaction mixture was stirred at 90 °C for 12 h and filtered through a plug silica gel (1 × 0.5 cm) eluting with ethyl acetate (50 mL). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate 10/1) to get **3** as a yellow solid: mp = 76−78 °C; 104 mg, 65% yield; ^{1}H′ NMR (400 MHz, $CDCl_3$) δ 8.18−8.16 (d, J = 8.0 Hz, 2H), 7.96 (s, 1H), 7.83 (s, 1H), 7.54 (s, 1H), 7.49−7.47 (m, 3H), 7.26 (s, 1H), 7.22−7.18 (t, J = 15.2 Hz, 2H), 6.79−6.78 (t, J = 14.4 Hz, 1H), 6.66−6.64 (d, J = 8.0 Hz, 2H), 4.74 (s, 2H), 2.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)155.2, 147.7, 144.8, 139.7, 138.4, 129.5. 129.3, 129.2, 128.6, 127.4, 126.0, 125.3, 120.4, 117.9, 116.5, 112.8, 45.6, 18.4; IR (neat, cm^{-1}) 1600, 1559, 1550, 1316; HRMS (TOF) calcd for $C_{23}H_{18}N_2$ 322.1470, found 322.1472.

■ ASSOCIATED CONTENT

Supporting Information

Proton and carbon NMRspectra of products and experimental procedures for the synthesis of the substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was received from the Natural Science Foundation of China (No. 20972134).

■ DEDICATION

Dedicated to the memory of Prof. Xian Huang.

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