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Synthesis of 1-Aminoisoquinolines by Gold(III)-Mediated Domino Reactions from 2-Alkynylbenzamides and Ammonium Acetate

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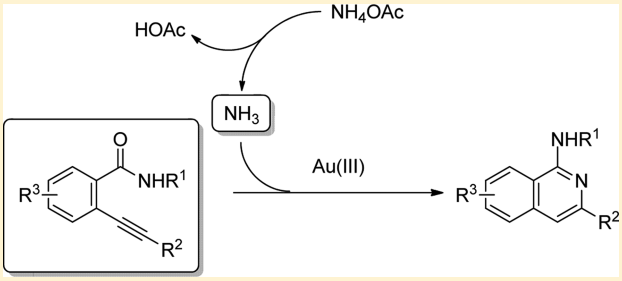
Supporting Information

ABSTRACT: A facile synthetic route toward pharmaceutically interesting 1-aminoisoquinoline derivatives by gold(III)-mediated domino reactions is described. This synthetic protocol starts from readily available 2-alkynylbenzamides and ammonium acetate and takes place under mild reaction conditions compatible with a variety of functional groups. A plausible mechanism for the domino process is proposed, supported by the reaction of a possible intermediate, *N*-(3-phenyl-1*H*-isochromen-1-ylidene)propan-1-amine.



INTRODUCTION

The synthesis of 1-aminoisoquinolines has recently attracted considerable attention from medicinal chemists due to the wide range of biological activities exhibited by their derivatives. These derivatives consist of known antitumor agents[1] and inhibitors of factor Xa,[2] thrombin,[3] and rho kinase-I.[4] They also display antimalarial activity[5] and are used for the treatment of diseases associated with inappropriate alk5.[6] While there is a high demand for 1-aminoisoquinoline derivatives in high-throughput drug screening, there are relatively few synthetic routes toward these compounds.

The most common method currently used by medicinal chemists to prepare 1-aminoisoquinolines involves the direct installation of an amino group in the 1-position of an existing isoquinoline by nucleophilic aromatic substitution (Scheme 1, path a).[1−6] One drawback to this method is that it involves harsh reaction conditions, including the use of strong bases, high reaction temperatures, or high pressure in the preparation of either the final products or the starting materials. Recently, Li et al. reported a synthetic pathway for the production of *N*-substituted 1-aminoisoquinolines through the Rh-catalyzed oxidative coupling of *N*-aryl- and *N*-alkylbenzamidines.[7] Additionally, a silver-catalyzed synthesis of 1-aminoisoquinolines from 2-alkynylbenzaldoximes has been reported by Wu et al.[8] It is important to note that, although both of these methods can be used to synthesize secondary amines, it is necessary to remove their alkyl and aryl groups in order to convert them into their more biologically important primary amine counterparts. Swager et al. have briefly reported the synthesis of 1-aminoisoquinolines by reacting isobenzopyrylium salts with anhydrous ammonia. However, only a few 1-aminoisoquinolines, formed in only moderate chemical yields, have been reported using this method.[9]

Gold, a soft Lewis acid with distinct carbophilic character, has been widely used in the catalysis of reactions of multiple carbon−carbon bonds. It is especially useful for activating carbon−carbon triple bonds during nucleophilic additions.[10] Gold-catalyzed intramolecular nucleophilic cyclizations have attracted particular interest due to their potential use in the synthesis of a wide variety of carbo- and heterocyclic compounds.[10,11]

Building on our previous success using ammonium acetate (NH_4OAc) in the synthesis of isoquinolines[12] and continuing our interest in developing new synthetic methods for the synthesis of biologically important molecules employing late-transition-metal catalysts,[12,13] we hereby report a facile synthesis of 1-aminoisoquinolines by gold(III)-mediated domino reactions from 2-alkynylbenzamides and ammonium acetate (Scheme 1, path b).

RESULTS AND DISCUSSION

The 2-alkynylbenzamide starting materials **3** were prepared by Sonogashira coupling[14] of 2-bromobenzamides (**2**) with terminal alkynes, except for compounds **3g,i,j,l** (Scheme 2). 2-Ethynylbenzamide (**3l**) was prepared from compound **3k** via a cesium fluoride mediated desilylation reaction. Compounds **3g,i,j** were prepared by Sonogashira coupling of **3l** with aryl iodides. 2-Bromobenzamides **2** were either commercially available or prepared from the corresponding 2-bromobenzoic acids **1** or 2-bromobenzoyl chloride, as shown in Scheme 2.

Our initial study focused on the reaction of the model substrate **3a** with 3 equiv of NH_4OAc in acetonitrile (CH_3CN) at 85 °C. In the absence of a catalyst, none of the desired 1-aminoisoquinoline **4a** was obtained after 20 h (Table 1, entry 1). In addition, no cyclization was observed in the presence of a Brønsted acid catalyst such as trifluoromethanesulfonic acid (TfOH) (Table 1, entry 2). Although no desired 1-amino-

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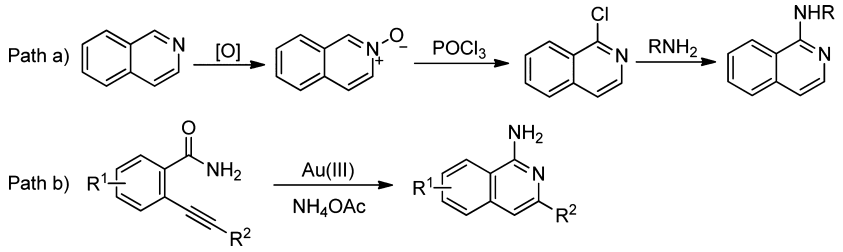
Scheme 1. Synthetic Routes toward 1-Aminoisoquinolines



Scheme 2. Preparation of 2-Alkynylbenzamides (3)

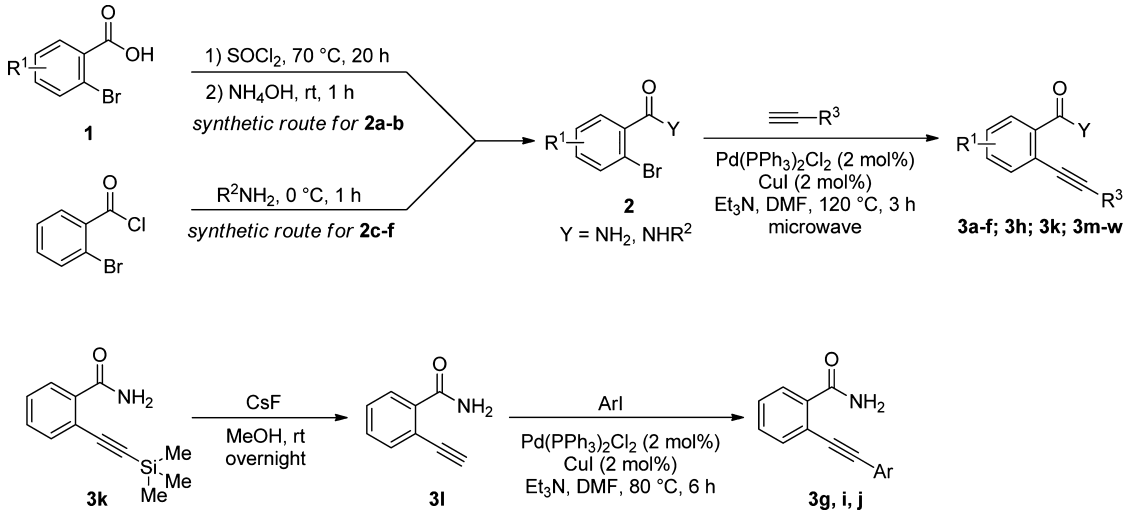
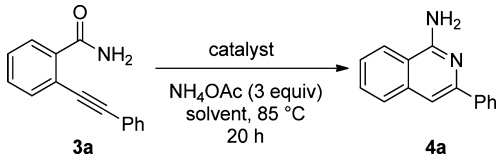


Table 1. Optimization of Reaction Conditions for the 1-Aminoisoquinoline Synthesis[a]



entry	catalyst (amt (mol %))	solvent	yield (%)[b]
1		CH_3CN	0
2	TfOH (6)	CH_3CN	0
3	CuI (6)	CH_3CN	0
4	$PtCl_2$ (6)	CH_3CN	0
5	$Pd(O_2CCF_3)_2$ (6)	CH_3CN	50
6	$Au(Ph_3P)Cl$ (6)	CH_3CN	28
7	$NaAuCl_4{\cdot}2H_2O$ (6)	CH_3CN	61
8	$NaAuCl_4{\cdot}2H_2O$ (12)	CH_3CN	72
9	$AgSbF_6$ (6)	CH_3CN	54
10	$AgSbF_6$ (12)	CH_3CN	73
11	$NaAuCl_4{\cdot}2H_2O/AgSbF_6$ (6/6)	CH_3CN	92
12	$NaAuCl_4{\cdot}2H_2O/AgSbF_6$ (6/6)	DCE	11
13	$NaAuCl_4{\cdot}2H_2O/AgSbF_6$ (6/6)	DME	34
14	$NaAuCl_4{\cdot}2H_2O/AgSbF_6$ (6/6)	THF	28
15[c]	$NaAuCl_4{\cdot}2H_2O/AgSbF_6$ (6/6)	CH_3CN	85
16[d]	$NaAuCl_4{\cdot}2H_2O/AgSbF_6$ (6/6)	CH_3CN	35
17	$NaAuCl_4{\cdot}2H_2O/AgSbF_6$ (3/3)	CH_3CN	45

[a]General procedure: In a 4 dram vial were added the catalyst, NH_4OAc (69.3 mg, 0.9 mmol), **3a** (66.3 mg, 0.3 mmol), and solvent (3 mL). The reaction mixture was stirred at 85 °C for 20 h. [b]Isolated yields after column chromatography. [c]Two equivalents of NH_4OAc was added. [d]The reaction mixture was heated at 50 °C for 20 h.

isoquinoline **4a** was obtained when a Lewis acid catalyst such as CuI or $PtCl_2$ was used (Table 1, entries 3 and 4), a moderate 50% chemical yield was obtained when a palladium(II) catalyst, $Pd(O_2CCF_3)_2$, was employed (Table 1, entry 5). While Au(I) catalysts such as $Au(Ph_3P)Cl$ only showed moderate catalytic activity (Table 1, entry 6), a 61% yield was obtained when the relatively more Lewis acidic Au(III) catalyst $NaAuCl_4{\cdot}2H_2O$ was used (Table 1, entry 7). The desired product **4a** was obtained in 54% yield when $AgSbF_6$ was employed as the catalyst (Table 1, entry 9). The chemical yields of **4a** were enhanced to more than 70% when the catalyst loading of either $NaAuCl_4{\cdot}2H_2O$ or $AgSbF_6$ was increased to 12 mol % (Table 1, entries 8 and 10). Further exploration showed that the yield of **4a** was significantly increased when $AgSbF_6$ was used as a cocatalyst with $NaAuCl_4{\cdot}2H_2O$, leading to a 92% yield (Table 1, entry 11).[15] Other solvents, such as 1,2-dichloroethane (DCE), 1,2-dimethoxyethane (DME), and tetrahydrofuran (THF), all showed inferior results in comparison with CH_3CN, and only low to moderate yields were obtained (Table 1, entries 12–14). Reducing the loading of NH_4OAc to 2 equiv resulted in a lower yield (Table 1, entry 15). The reaction parameters were then changed, by reducing the temperature to 50 °C. This resulted in a yield of only 35% (Table 1, entry 16). When the amount of gold catalyst was reduced to 3 mol %, a 45% yield was obtained (Table 1, entry 17). Taking these results into account, the conditions listed in entry 11 in Table 1 were chosen as the optimal reaction conditions.

A variety of 2-alkynylbenzamides, including those with aryl, heteroaryl, alkenyl, and alkyl groups at the distal position of the alkyne triple bond, were then subjected to these reaction conditions and found to be compatible (Table 2, entries 1–10).

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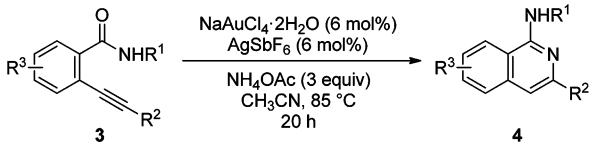
Table 2. Gold(III)-Mediated Synthesis of 1-Aminoisoquinolines[a]



3 4

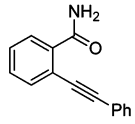
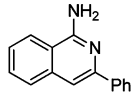
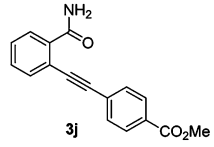
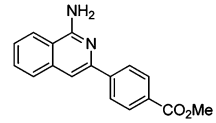
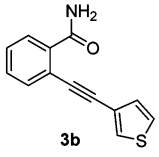
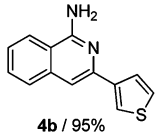
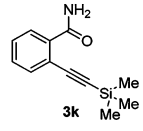
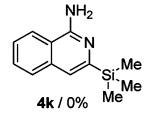
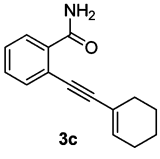
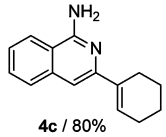
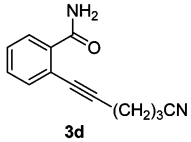
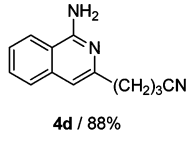
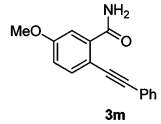
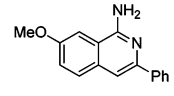
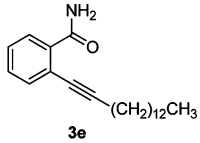
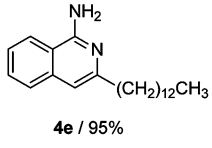
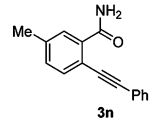
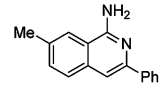
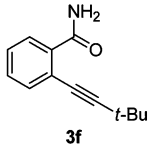
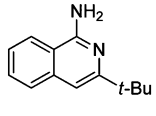
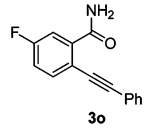
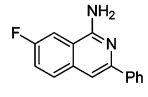
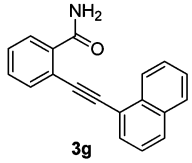
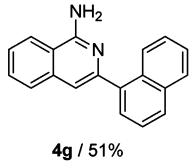
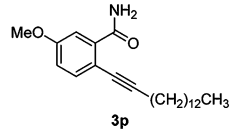
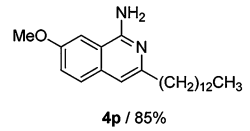
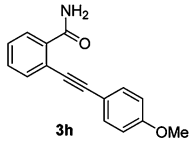
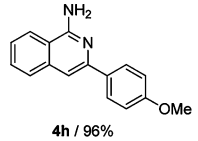
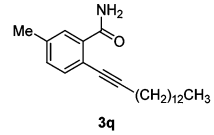
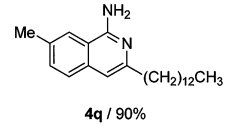
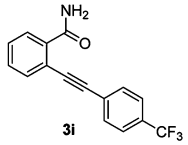
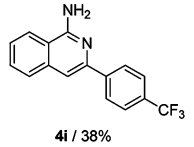
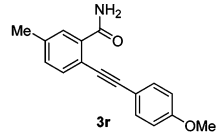
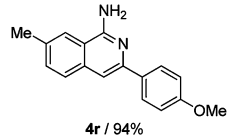
entry	substrate **3**	product **4** / yield[b]	entry	substrate **3**	product **4** / yield[b]
1	 **3a**	 **4a** / 92%	10	 **3j**	 **4j** / 54%
2	 **3b**	 **4b** / 95%	11	 **3k**	 **4k** / 0%
3	 **3c**	 **4c** / 80%	12	 **3l**	 **4l** / 0%
4	 **3d**	 **4d** / 88%	13	 **3m**	 **4m** / 74%
5	 **3e**	 **4e** / 95%	14	 **3n**	 **4n** / 80%
6	 **3f**	 **4f** / 85%	15	 **3o**	 **4o** / 85%
7[c]	 **3g**	 **4g** / 51%	16	 **3p**	 **4p** / 85%
8	 **3h**	 **4h** / 96%	17	 **3q**	 **4q** / 90%
9	 **3i**	 **4i** / 38%	18	 **3r**	 **4r** / 94%

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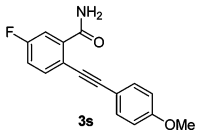
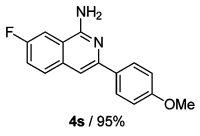
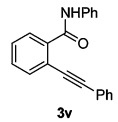
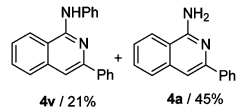
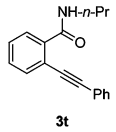
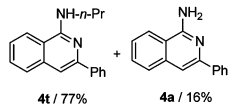
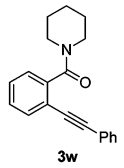
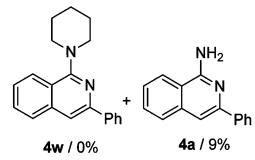
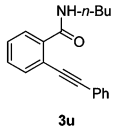
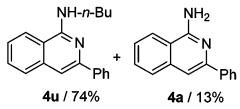
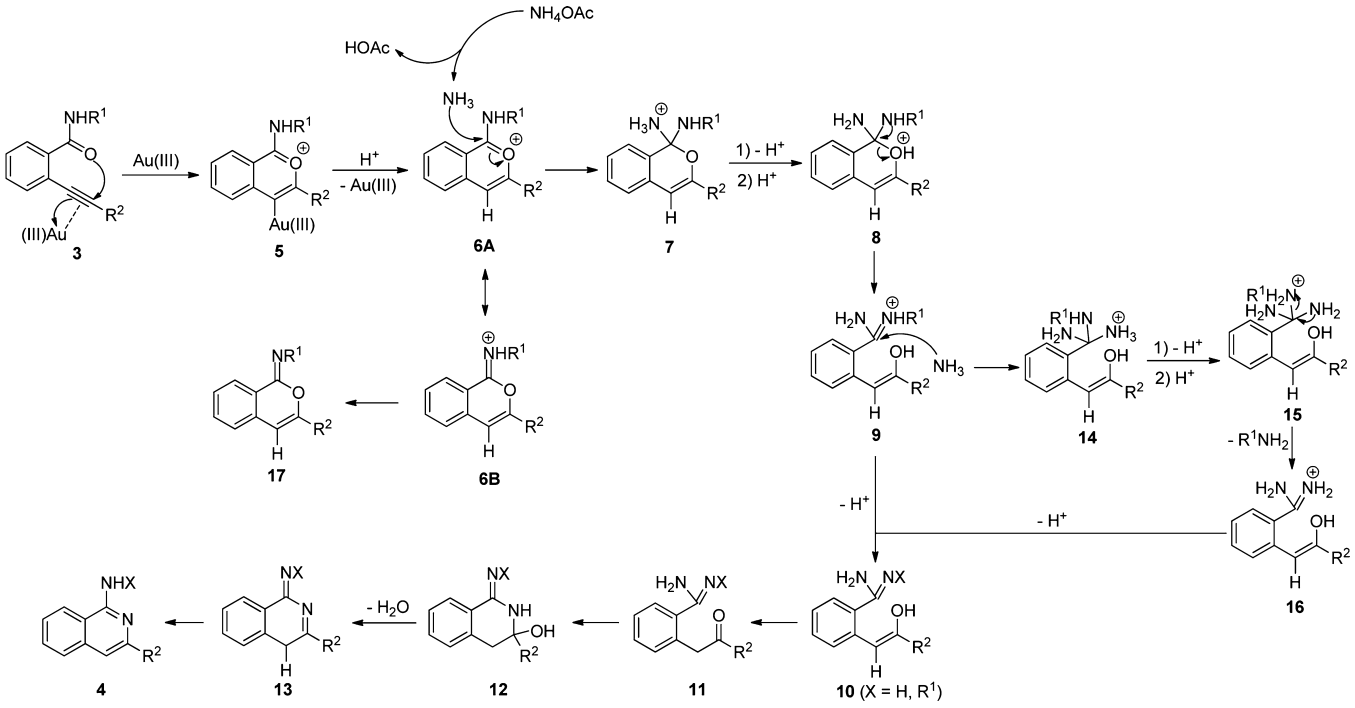
Table 2. continued

entry	substrate **3**	product **4** / yield[b]	entry	substrate **3**	product **4** / yield[b]
19	 **3s**	 **4s** / 95%	22[d]	 **3v**	 **4v** / 21% **4a** / 45%
20	 **3t**	 **4t** / 77% **4a** / 16%	23[e]	 **3w**	 **4w** / 0% **4a** / 9%
21	 **3u**	 **4u** / 74% **4a** / 13%			

[a]See the Experimental Section for the general procedure. [b]Isolated yields after column chromatography. [c]The starting material **3g** (40%) was recovered from the reaction mixture. [d]The starting material **3v** (12%) was recovered from the reaction mixture. [e]The starting material **3w** (82%) was recovered from the reaction mixture.

Scheme 3. Plausible Mechanism for Gold(III)-Mediated Synthesis of 1-Aminoisoquinolines (4) from 2-Alkynylbenzamides (3)



Although a sterically hindered alkyl group, *tert*-butyl, is well accommodated at the distal position of the alkyne triple bond, leading to an excellent 85% yield (Table 2, entry 6), a slower reaction was observed when a sterically hindered naphthyl group was introduced at the same position of the alkyne triple bond. In the latter case, only a moderate 51% yield was obtained after 20 h, along with 40% recovery of the starting material **3g** (Table 2, entry 7). While it was found that both electron-donating and electron-withdrawing groups were tolerated in the 2-alkynylbenzamide substrates, excellent chemical yields were only obtained when electron-donating groups were present (Table 2, entries 8, 13, 14, and 16−19). Only moderate chemical yields were obtained in the presence of strong electron-withdrawing groups (Table 2, entries 9 and 10). The current synthetic method is not applicable to either trimethylsilyl (TMS)-protected alkynes or terminal alkynes, as only an unidentifiable mixture was obtained under these reaction conditions (Table 2, entries 11 and 12). In addition to primary amides, the reactivities of secondary and tertiary amides have also been investigated in this reaction. While secondary amides with an aliphatic substituent on the nitrogen atom reacted appreciably (Table 2, entries 20 and 21), a low yield of the desired product **4v** was obtained, when an aryl substituent was present on the nitrogen atom (Table 2, entry 22). For each of the secondary amides, the side product 1-aminoisoquinoline **4a** was also observed (Table 2, entries 20−

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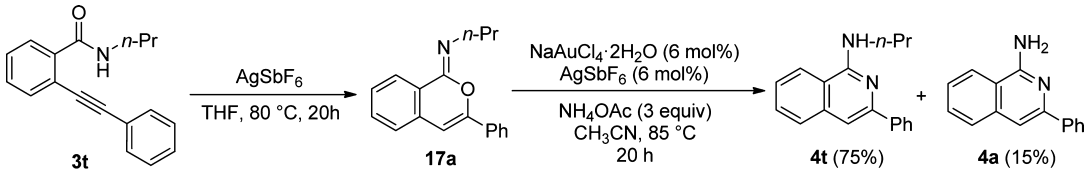
Scheme 4. Preparation and Gold(III)-Mediated Reaction of *N*-(3-Phenyl-1*H*-isochromen-1-ylidene)propan-1-amine (17a)



22). In contrast, none of the desired cyclization product **4w** was obtained when the *tert*-amide **3w** was subjected to these reaction conditions. Instead, the side product **4a** was obtained in 9% yield, along with the starting material **3w** recovered in 82% yield (Table 2, entry 23).

The current reaction presumably takes place by the Au(III)-catalyzed intramolecular 6-*endo*-*dig* cyclization of the 2-alkynylbenzamide **3** to the organogold intermediate **5**, which is converted to the isobenzopyrylium salt **6** after protonation. The nucleophilic addition of ammonia to isobenzopyrylium salt **6** leads to the isochromene intermediate **7**. After deprotonation of the ammonium nitrogen atom and protonation of the oxygen atom in isochromene **7**, isochromenylium **8** forms. The carbon−oxygen bond in **8** dissociates to form enol **9**, which subsequently converts to **10** after deprotonation and tautomerizes to ketone **11**. Intramolecular nucleophilic addition of the amino group to the ketone carbonyl group forms intermediate **12**. After subsequent dehydration and aromatization, the final product, 1-aminoisoquinoline **4**, is formed (Scheme 3). In the case when secondary and tertiary amides are employed, ammonia can substitute the primary or secondary amines in intermediate **9** through a sequential nucleophilic addition and elimination process, leading to intermediate **16**. The latter then undergoes a reaction mechanism similar to that for intermediate **9** to form a primary isoquinolin-1-amine. It is worth noting that the isobenzopyrylium salt **6** has a pair of resonance structures, **6A**,**B**. Deprotonation of the resonance structure **6B** could then give 1*H*-isochromen-1-imine **17**.

A possible intermediate, *N*-(3-phenyl-1*H*-isochromen-1-ylidene)propan-1-amine (**17a**), was therefore prepared from benzamide **3t**, according to a literature procedure (Scheme 4).[16] Compound **17a** was subjected to our optimal reaction conditions. After 20 h, 1-aminoisoquinolines **4t**,**a** were isolated from the reaction mixture in 75% and 15% yields, respectively. These results are comparable to the data shown in entry 20 of Table 2, providing evidence supporting the formation of isobenzopyrylium **6** in our proposed mechanism.

CONCLUSION

The synthesis of pharmaceutically interesting 1-aminoisoquinolines by gold(III)-mediated domino reactions is described. This synthetic route starts from readily available 2-alkynylbenzamides and ammonium acetate and takes place under mild reaction conditions. A variety of functional groups are compatible with the reaction conditions. A broad range of 2-alkynylbenzamides has been examined, leading to 1-aminoisoquinolines in moderate to excellent chemical yields. We expect that this facile synthetic route will soon find applications in high-throughput drug screening. The further exploration of new synthetic methods for biologically interesting heterocyclic and carbocyclic compounds by gold-mediated intramolecular cyclization is underway in our laboratory.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in sealed 4 dram vials unless otherwise indicated. All microwave irradiation reactions were carried out on a Biotage-EXP Microwave synthesis system, operating at a frequency of 2450 MHz with continuous irradiation power from 0 to 300 W. The microwave irradiation reactions were carried out in 20 mL oven-dried Biotage microwave vials sealed with an aluminum/Teflon crimp cap, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. An IR sensor was used to measure the reaction temperatures of the microwave irradiation reactions by measuring the temperature of the outer surface of the process vials. All commercially available chemicals were used as received without further purification unless otherwise noted. All products were purified by flash column chromatography on silica gel (230−400 mesh) unless otherwise noted. All ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, using $CDCl_3$ or DMSO-d_6 as the solvent. The chemical shifts of all ^{1}H and ^{13}C NMR spectra are referenced to the residual signal of $CDCl_3$ (δ 7.26 ppm for the ^{1}H NMR spectra and δ 77.23 ppm for the ^{13}C NMR spectra) or DMSO-d_6 (δ 2.54 ppm for the ^{1}H NMR spectra and δ 40.45 ppm for the ^{13}C NMR spectra). The high-resolution mass spectra were recorded on a double-focusing magnetic sector mass spectrometer using electrospray ionization. The melting points are uncorrected.

Synthesis of 2-Bromobenzamides (2a,b) from 2-Bromobenzoic Acids (1). A mixture of the appropriate benzoic acid (**1**, 12.0 mmol) and thionyl chloride (25 mL) was refluxed at 70 °C in a 50 mL round-bottomed flask equipped with a water condenser and a drying tube (filled with Drierite) for 20 h. The thionyl chloride was removed using a rotary evaporator under reduced pressure (20 mmHg). The residue was then dissolved in aqueous NH_4OH solution (25 mL, 5.0 N solution in water) and stirred for 1 h at room temperature. The reaction mixture was filtered, and the residue was dried under high-vacuum conditions to afford the desired amide.

*2-Bromo-5-methylbenzamide (**2a**).* This compound was obtained as a white solid (2.20 g, 86% yield): mp 195.8−196.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.49 (m, 2H), 7.11 (dd, J = 8.2, 2.1 Hz, 1H), 6.10 (s, 1H), 6.10 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 138.0, 136.2, 133.5, 132.8, 130.9, 115.9, 21.0; IR ($CHCl_3$, cm^{-1}) ν 3359, 3177, 1647; HRMS (ESI) calcd for C_8H_9BrNO $(M + H)^+$ 213.9862, found 213.9861.

*2-Bromo-5-fluorobenzamide (**2b**).* This compound was obtained as a white solid (1.80 g, 69% yield): mp 150.9−151.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57−7.60 (m, 1H), 7.40 (dd, J = 8.5, 3.1 Hz 1H), 7.03−7.07 (m, 1H), 6.18 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 161.9 (d, J_{C-F} = 247.8 Hz), 138.3 (d, J_{C-F} = 6.8 Hz), 135.4 (d, J_{C-F} = 7.6 Hz), 119.4 (d, J_{C-F} = 22.3 Hz), 117.6 (d, J_{C-F} = 24.4 Hz), 113.6 (d, J_{C-F} = 3.3 Hz); IR ($CHCl_3$, cm^{-1}) ν 3356, 3177, 1643; HRMS (ESI) calcd for C_7H_6BrFNO $(M + H)^+$ 217.9611, found 217.9611.

Synthesis of *N*-Substituted 2-Bromobenzamides (2c−f) from 2-Bromobenzoyl Chloride. The appropriate amine (5 mL) was added dropwise to 2-bromobenzoyl chloride (1.10 g, 5.0 mmol) at 0 °C. After the addition of amine, the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then poured into 30 mL of ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution (30 mL) and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator under reduced pressure (20 mmHg). This resulted in the formation of a

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solid, which was then dried under high-vacuum conditions to afford the desired amide.

*2-Bromo-N-propylbenzamide (**2c**).* This compound was obtained as a white solid (1.10 g, 91% yield): mp 83.5−84.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.0, 0.9 Hz, 1H), 7.53 (dd, J = 7.7, 1.7 Hz, 1H), 7.36 (dt, J = 7.5, 1.1 Hz, 1H), 7.26 (dt, J = 8.1, 1.8 Hz, 1H), 5.98 (s, 1H), 3.42−3.46 (m, 2H), 1.64−1.69 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 138.2, 133.5, 131.3, 129.7, 127.7, 119.3, 42.0, 22.9, 11.7; IR ($CHCl_3$, cm^{-1}) ν 3276, 1638; HRMS (ESI) calcd for $C_{10}H_{13}BrNO$ $(M + H)^+$ 242.0175, found 242.0177.

*2-Bromo-N-butylbenzamide (**2d**).* This compound was obtained as a white solid (1.27 g, 99% yield): mp 90.8−91.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.0, 0.8 Hz, 1H), 7.52 (dd, J = 7.6, 1.7 Hz, 1H), 7.35 (dt, J = 7.5, 0.9 Hz, 1H), 7.26 (dt, J = 7.8, 1.7 Hz, 1H), 5.99 (s, 1H), 3.44−3.48 (m, 2H), 1.59−1.65 (m, 2H), 1.42−1.46 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[17]

*2-Bromo-N-phenylbenzamide (**2e**).* This compound was obtained as a yellow solid (1.30 g, 94% yield): mp 119.1−120.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.62−7.65 (m, 4H), 7.37−7.42 (m, 3H), 7.30−7.34 (m, 1H), 7.16−7.19 (m, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[17]

*(2-Bromophenyl)(piperidin-1-yl)methanone (**2f**).* This compound was obtained as a yellow oil (1.29 g, 96% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 7.7 Hz, 1H), 7.33 (dt, J = 7.4, 1.0 Hz, 1H), 7.20−7.23 (m, 2H), 3.68−3.80 (m, 2H), 3.11−3.23 (m, 2H), 1.60−1.71 (m, 5H), 1.42−1.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 138.7, 132.9, 130.2, 127.8, 127.7, 119.3, 48.0, 42.7, 26.4, 25.6, 24.7; IR ($CHCl_3$, cm^{-1}) ν 1635; HRMS (ESI) calcd for $C_{12}H_{15}BrNO$ $(M + H)^+$ 268.0332, found 268.0334.

Synthesis of 2-Alkynylbenzamides 3 from 2-Bromobenzamides 2 and Terminal Alkynes. The following 2-alkynylbenzamides **3** were prepared via Sonogashira coupling reactions[18] of the corresponding 2-bromobenzamides **2** with terminal alkynes using microwave irradiation. An oven-dried 20 mL microwave vial was charged with a 2-bromobenzamide **2** (3.0 mmol), a terminal alkyne (3.3 mmol), $Pd(PPh_3)_2Cl_2$ (42.1 mg, 0.06 mmol), CuI (11.4 mg, 0.06 mmol), Et_3N (14 mL), and DMF (2 mL). The vial was flushed with nitrogen and sealed with an aluminum/Teflon crimp cap. The reaction mixture was stirred at 120 °C while undergoing microwave (300 W) irradiation for 3 h. This continued until the starting material disappeared, as monitored by thin-layer chromatography. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with brine (30 mL). The aqueous phase was extracted with ethyl acetate twice (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The residue was then purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate).

*2-(Phenylethynyl)benzamide (**3a**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a white solid (437.6 mg, 66% yield): mp 146.4−147.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 7.3 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.53−7.55 (m, 2H), 7.46−7.49 (m, 3H), 7.39−7.40 (m, 3H), 6.14 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[19]

*2-(Thiophen-3-ylethynyl)benzamide (**3b**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a light yellow solid (524.4 mg, 77% yield): mp 111.7−112.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (dd, J = 6.7, 1.0 Hz, 1H), 7.59−7.63 (m, 2H), 7.44−7.50 (m, 2H), 7.42 (s, 1H), 7.36−7.37 (m, 1H), 7.21 (d, J = 5.0 Hz, 1H), 5.90 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 134.6, 133.6, 131.2, 130.5, 129.9, 129.7, 129.0, 126.2, 121.2, 120.3, 91.2, 87.4; IR ($CHCl_3$, cm^{-1}) ν 3368, 3183, 1640; HRMS (ESI) calcd for $C_{13}H_{10}NOS$ $(M + H)^+$ 228.0478, found 228.0480.

*2-(Cyclohex-1-en-1-ylethynyl)benzamide (**3c**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a dark yellow solid (364.5 mg, 54% yield): mp 134.0−135.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, J = 7.5, 1.1 Hz, 1H), 7.60 (s, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.39−7.45 (m, 2H), 6.28 (s, 1H), 5.96 (s, 1H), 2.17−2.23 (m, 4H), 1.62−1.72 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 137.3, 133.9, 133.6, 131.2, 130.6, 128.5, 120.9, 120.2, 98.2, 85.5, 29.0, 26.0, 22.3, 21.5; IR ($CHCl_3$, cm^{-1}) ν 3382, 3179, 1657; HRMS (ESI) calcd for $C_{15}H_{16}NO$ $(M + H)^+$ 226.1226, found 226.1226.

*2-(5-Cyanopent-1-yn-1-yl)benzamide (**3d**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a light yellow solid (279.8 mg, 44% yield): mp 108.6−109.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96−7.98 (m, 1H), 7.48−7.50 (m, 1H), 7.38−7.44 (m, 2H), 7.15 (s, 1H), 6.44 (s, 1H), 2.68 (t, J = 6.8 Hz, 2H), 2.58 (t, J = 7.1 Hz, 2H), 1.96−2.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 135.2, 133.9, 131.1, 129.9, 128.7, 120.4, 119.2, 93.9, 81.2, 24.4, 18.9, 16.5; IR ($CHCl_3$, cm^{-1}) ν 3348, 3192, 2247, 1667; HRMS (ESI) calcd for $C_{13}H_{13}N_2O$ $(M + H)^+$ 213.1022, found 213.1025.

*2-(Pentadec-1-yn-1-yl)benzamide (**3e**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a light yellow solid (461.4 mg, 47% yield): mp 85.3−86.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12−8.14 (m, 1H), 7.72 (s, 1H), 7.49−7.50 (m, 1H), 7.38−7.44 (m, 2H), 6.03 (s, 1H), 2.49 (t, J = 7.2 Hz, 2H), 1.60−1.65 (m, 2H), 1.42−1.47 (m, 2H), 1.26−1.33 (m, 18H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 134.0, 131.2, 130.5, 128.3, 121.2, 98.2, 79.9, 32.1, 29.89, 29.86, 29.84, 29.7, 29.6, 29.3, 29.2, 28.6, 22.9, 19.8, 14.4 (fewer ^{13}C signals were observed due to signal overlapping); IR ($CHCl_3$, cm^{-1}) ν 3370, 3172, 1646; HRMS (ESI) calcd for $C_{22}H_{34}NO$ $(M + H)^+$ 328.2635, found 328.2635.

*2-(3,3-Dimethylbut-1-yn-1-yl)benzamide (**3f**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a white solid (319.6 mg, 53% yield): mp 96.4−96.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, J = 7.2, 2.5 Hz, 1H), 7.69 (s, 1H), 7.45−7.47 (m, 1H), 7.35−7.41 (m, 2H), 6.68 (s, 1H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 134.1, 133.7, 131.0, 130.4, 128.2, 120.9, 105.6, 78.5, 30.7, 28.5; IR ($CHCl_3$, cm^{-1}) ν 3439, 3179, 1670; HRMS (ESI) calcd for $C_{13}H_{16}NO$ $(M + H)^+$ 202.1226, found 202.1230.

*2-((4-Methoxyphenyl)ethynyl)benzamide (**3h**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a light yellow solid (466.9 mg, 62% yield): mp 123.7−124.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (dd, J = 7.7, 1.4 Hz, 1H), 7.60 (dd, J = 7.6, 1.4 Hz, 1H), 7.55 (s, 1H), 7.41−7.48 (m, 4H), 6.89 (d, J = 8.9 Hz, 2H), 6.30 (s, 1H), 3.83 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[19]

*2-((Trimethylsilyl)ethynyl)benzamide (**3k**).* Eluent of column chromatography: hexanes/ethyl acetate 4/1. This compound was obtained as a yellow solid (319.4 mg, 49% yield): mp 82.0−83.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15−8.17 (m, 1H), 7.76 (s, 1H), 7.55−7.58 (m, 1H), 7.43−7.47 (m, 2H), 5.82 (s, 1H), 0.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 134.7, 134.1, 131.1, 130.6, 129.3, 120.1, 104.0, 102.3, −0.2; IR ($CHCl_3$, cm^{-1}) ν 3444, 3180, 1656; HRMS (ESI) calcd for $C_{12}H_{16}NOSi$ $(M + H)^+$ 218.0996, found 218.1001.

*5-Methoxy-2-(phenylethynyl)benzamide (**3m**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a light yellow solid (369.1 mg, 49% yield): mp 162.5−163.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 2.7 Hz, 1H), 7.64 (s, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.50−7.52 (m, 2H), 7.36−7.39 (m, 3H), 7.02 (dd, J = 8.5, 2.8 Hz, 1H), 6.42 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 160.1, 136.1, 135.2, 131.6, 129.1, 128.8, 122.5, 118.5, 114.5, 112.4, 94.7, 87.9, 55.8; IR ($CHCl_3$, cm^{-1}) ν 3383, 3186, 1648; HRMS (ESI) calcd for $C_{16}H_{14}NO_2$ $(M + H)^+$ 252.1019, found 252.1021.

*5-Methyl-2-(phenylethynyl)benzamide (**3n**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a light yellow solid (324.4 mg, 46% yield): mp 168.3−169.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 0.6 Hz, 1H), 7.52−7.54 (m, 4H), 7.38−7.39 (m, 3H), 7.30 (dd, J = 7.8, 1.2 Hz, 1H), 6.19 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 139.6, 134.3, 133.7, 132.1, 131.7, 131.1, 129.3, 128.8, 122.4,

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113.3, 95.3, 88.0, 21.6; IR ($CHCl_3$, cm^{-1}) ν 3367, 3182, 1651; HRMS (ESI) calcd for $C_{16}H_{14}NO$ $(M + H)^+$ 236.1070, found 236.1070.

*5-Fluoro-2-(phenylethynyl)benzamide (**3o**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a white solid (358.6 mg, 50% yield): mp 160.3−161.2 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, J = 9.7, 2.8 Hz, 1H), 7.63 (dd, J = 8.5, 5.4 Hz, 1H), 7.58 (s, 1H), 7.52−7.54 (m, 2H), 7.39−7.41 (m, 3H), 7.20 (dt, J = 8.3, 2.8 Hz, 1H), 6.07 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 162.7 (d, J_{C-F} = 251.0 Hz), 137.0 (d, J_{C-F} = 7.1 Hz), 135.8 (d, J_{C-F} = 8.0 Hz), 131.7, 129.6, 128.9, 122.0, 118.8 (d, J_{C-F} = 22.0 Hz), 117.7 (d, J_{C-F} = 24.2 Hz), 116.5 (d, J_{C-F} = 3.5 Hz), 95.8, 86.8; IR ($CHCl_3$, cm^{-1}) ν 3364, 3177, 1649; HRMS (ESI) calcd for $C_{15}H_{11}FNO$ $(M + H)^+$ 240.0819, found 240.0823.

*5-Methoxy-2-(pentadec-1-yn-1-yl)benzamide (**3p**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a white solid (482.6 mg, 45% yield): mp 80.9−82.1 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.69 (d, J = 2.8 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 6.97 (dd, J = 8.6, 2.9 Hz, 1H), 6.01 (s, 1H), 3.86 (s, 3H), 2.46 (t, J = 7.2 Hz, 2H), 1.60−1.63 (m, 2H), 1.42−1.45 (m, 2H), 1.26 (s, 18H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 159.4, 135.4, 135.3, 118.6, 114.2, 113.4, 96.6, 79.7, 55.7, 32.1, 30.0, 29.9, 29.8, 29.7, 29.5, 29.3, 29.2, 28.7, 22.9, 19.8, 14.3 (fewer ^{13}C signals were observed due to signal overlapping); IR ($CHCl_3$, cm^{-1}) ν 3375, 3172, 1600; HRMS (ESI) calcd for $C_{23}H_{36}NO_2$ $(M + H)^+$ 358.2741, found 358.2740.

*5-Methyl-2-(pentadec-1-yn-1-yl)benzamide (**3q**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a light yellow solid (464.0 mg, 45% yield): mp 98.1−98.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 1.1 Hz, 1H), 7.76 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.23 (dd, J = 7.7, 1.3 Hz, 1H), 5.82 (s, 1H), 2.47 (t, J = 7.0 Hz, 2H), 2.38 (s, 3H), 1.59−1.65 (m, 2H), 1.41−1.47 (m, 2H), 1.26−1.34 (m, 18H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 138.6, 133.9, 133.6, 132.1, 131.1, 118.2, 97.3, 80.0, 32.1, 29.89, 29.87, 29.85, 29.7, 29.6, 29.3, 29.2, 28.7, 22.9, 21.5, 19.8, 14.4 (fewer ^{13}C signals were observed due to signal overlapping); IR ($CHCl_3$, cm^{-1}) ν 3368, 3178, 1648; HRMS (ESI) calcd for $C_{23}H_{36}NO$ $(M + H)^+$ 342.2791, found 342.2793.

*2-((4-Methoxyphenyl)ethynyl)-5-methylbenzamide (**3r**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a white solid (532.7 mg, 67% yield): mp 159.0−160.1 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.59 (s, 1H), 7.45−7.51 (m, 3H), 7.29 (dd, J = 9.0, 1.3 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 5.87 (s, 1H), 3.85 (s, 3H), 2.42 (s. 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 160.3, 139.1, 134.0, 133.5, 133.2, 132.1, 131.1, 117.7, 114.4, 95.5, 86.8, 55.5, 21.5 (fewer ^{13}C signals were observed due to signal overlapping); IR ($CHCl_3$, cm^{-1}) ν 3354, 3178, 1645; HRMS (ESI) calcd for $C_{17}H_{16}NO_2$ $(M + H)^+$ 266.1176, found 266.1178.

*5-Fluoro-2-((4-methoxyphenyl)ethynyl)benzamide (**3s**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a light yellow solid (363.6 mg, 45% yield): mp 164.7−165.3 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, J = 9.7, 2.7 Hz, 1H), 7.67 (s, 1H), 7.59−7.61 (m, 1H), 7.47 (d, J = 8.6 Hz, 2H), 7.19 (dt, J = 8.0, 2.8 Hz, 1H), 6.91 (d, J = 8.6 Hz, 2H), 6.05 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 162.5 (d, J_{C-F} = 249.4 Hz), 160.6, 136.6 (d, J_{C-F} = 7.1 Hz), 135.7 (d, J_{C-F} = 7.8 Hz), 133.2, 118.8 (d, J_{C-F} = 22.2 Hz), 117.8 (d, J_{C-F} = 24.3 Hz), 116.8 (d, J_{C-F} = 3.6 Hz), 114.5, 113.9, 96.1, 85.8, 55.6; IR ($CHCl_3$, cm^{-1}) ν 3372, 3190, 1651; HRMS (ESI) calcd for $C_{16}H_{13}FNO_2$ $(M + H)^+$ 270.0925, found 270.0926.

*2-(Phenylethynyl)-N-propylbenzamide (**3t**).* Eluent of column chromatography: hexanes/ethyl acetate 5/1. This compound was obtained as a white solid (426.5 mg, 54% yield): mp 97.8−98.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05−8.07 (m, 1H), 7.60−7.62 (m, 1H), 7.52−7.54 (m, 2H), 7.44−7.46 (m, 2H), 7.39−7.41 (m, 4H), 3.46−3.50 (m, 2H), 1.61−1.65 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H). The ^1H NMR spectral data are in good agreement with the literature data.[16]

*N-Butyl-2-(phenylethynyl)benzamide (**3u**).* Eluent of column chromatography: hexanes/ethyl acetate 5/1. This compound was obtained as a white solid (491.0 mg, 59% yield): mp 121.7−122.7 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05−8.07 (m, 1H), 7.59−7.61 (m, 1H), 7.52−7.54 (m, 2H), 7.43−7.46 (m, 2H), 7.39−7.40 (m, 3H), 7.34 (s, 1H), 3.49−3.53 (m, 2H), 1.55−1.59 (m, 2H), 1.35−1.42 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H). The ^1H NMR spectral data are in good agreement with the literature data.[20]

*N-Phenyl-2-(phenylethynyl)benzamide (**3v**).* Eluent of column chromatography: hexanes/ethyl acetate 5/1. This compound was obtained as a white solid (383.5 mg, 43% yield): mp 155.9−156.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.14−8.16 (m, 1H), 7.67 (d, J = 7.8 Hz, 3H), 7.49−7.52 (m, 4H), 7.33−7.40 (m, 5H), 7.14 (t, J = 7.4 Hz, 1H). The ^1H NMR spectral data are in good agreement with the literature data.[16]

*(2-(Phenylethynyl)phenyl)(piperidin-1-yl)methanone (**3w**).* Eluent of column chromatography: hexanes/ethyl acetate 5/1. This compound was obtained as a yellow oil (390.7 mg, 45% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 7.54−7.56 (m, 1H), 7.47−7.49 (m, 2H), 7.31−7.38 (m, 6H), 3.77−3.79 (m, 2H), 3.19−3.30 (m, 2H), 1.62−1.67 (m, 5H), 1.41−1.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 139.7, 132.1, 131.5, 128.7, 128.6, 128.4, 126.3, 122.9, 120.0, 92.7, 87.0, 48.1, 42.6, 26.4, 25.7, 24.5 (fewer ^{13}C signals were observed due to signal overlapping); IR ($CHCl_3$, cm^{-1}) ν 1632; HRMS (ESI) calcd for $C_{20}H_{20}NO$ $(M + H)^+$ 290.1539, found 290.1540.

Synthesis of 2-Ethynylbenzamide (3l). A 50 mL round-bottomed flask was charged with 2-((trimethylsilyl)ethynyl)benzamide (**3k**; 1.087 g, 5.0 mmol), CsF (1.139 g, 7.5 mmol), and methanol (25 mL). The reaction mixture was stirred overnight at room temperature until the starting material disappeared, as monitored by thin-layer chromatography. Methanol was removed using a rotary evaporator under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and washed with brine (30 mL). The aqueous phase was extracted with ethyl acetate (20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate 4/1), to afford a light yellow solid (688.8 mg, 95% yield): mp 117.3−118.2 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.45−7.50 (m, 2H), 7.36 (s, 1H), 5.95 (s, 1H), 3.53 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 135.5, 134.5, 131.2, 130.3, 129.6, 119.1, 84.2, 82.5; IR ($CHCl_3$, cm^{-1}) ν 3296, 3179, 1646; HRMS (ESI) calcd for C_9H_8NO $(M + H)^+$ 146.0600, found 146.0601.

Synthesis of 2-Alkynylbenzamides (3g,i,j) from 2-Ethynylbenzamide (3l) and Aryl Iodides. A 4 dram vial was charged with 2-ethynylbenzamide (**3l**; 145.2 mg, 1.0 mmol), an aryl iodide (1.0 mmol), $Pd(PPh_3)_2Cl_2$ (14.0 mg, 0.02 mmol), CuI (3.8 mg, 0.02 mmol), Et_3N (5 mL), and DMF (1 mL). The vial was flushed with nitrogen. The reaction mixture was stirred at 80 °C for 6 h until the starting material disappeared, as monitored by thin-layer chromatography. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with brine (20 mL). The aqueous phase was extracted with ethyl acetate (20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate).

*2-(Naphthalen-1-ylethynyl)benzamide (**3g**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a white solid (214.3 mg, 79% yield): mp 169.8−170.8 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 8.4 Hz, 1H), 8.13 (dd, J = 7.6, 1.4 Hz, 1H), 7.89 (t, J = 6.6 Hz, 2H), 7.76 (dt, J = 8.3, 1.1 Hz, 2H), 7.62 (dt, J = 6.9, 1.2 Hz, 1H), 7.48−7.58 (m, 5H), 6.26 (s, 1H). The ^1H NMR spectral data are in good agreement with the literature data.[19]

*2-((4-(Trifluoromethyl)phenyl)ethynyl)benzamide (**3i**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a light yellow solid (199.6 mg, 69% yield): mp 145.8−146.3 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 9.0 Hz, 1H), 7.63 (t, J = 9.4 Hz, 5H), 7.47−7.52 (m, 2H), 7.14 (s, 1H), 6.64 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 135.5, 133.8, 132.0, 130.9 (q, J_{C-F} = 32.5 Hz), 131.2, 130.1, 129.5, 126.1, 125.7 (q, J_{C-F} = 32.5 Hz), 123.9 (q, J_{C-F} = 270.7 Hz), 119.7, 94.0, 89.8; IR ($CHCl_3$, cm^{-1}) ν

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3362, 3191, 1655; HRMS (ESI) calcd for $C_{16}H_{11}F_3NO$ $(M + H)^+$ 290.0787, found 290.0787.

*Methyl 4-((2-Carbamoylphenyl)ethynyl)benzoate (**3j**).* Eluent of column chromatography: hexanes/ethyl acetate 3/1. This compound was obtained as a white solid (226.2 mg, 81% yield): mp 194.4−194.9 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04 (d, J = 8.4 Hz, 2H), 7.94 (s, 1H), 7.67−7.69 (m, 3H), 7.64 (s, 1H), 7.59−7.61 (m, 1H), 7.52−7.55 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.0, 166.6, 140.7, 133.7, 132.6, 130.7, 130.4, 130.3, 130.1, 128.7, 128.3, 120.2, 92.6, 92.1, 53.4; IR ($CHCl_3$, cm^{-1}) ν 3353, 3186, 1724, 1652; HRMS (ESI) calcd for $C_{17}H_{14}NO_3$ $(M + H)^+$ 280.0968, found 280.0971.

General Procedure for Gold-Catalyzed Synthesis of 1-Aminoisoquinolines (4). A 4 dram vial was charged with $NaAuCl_4{\cdot}2H_2O$ (7.2 mg, 0.018 mmol), $AgSbF_6$ (6.2 mg, 0.018 mmol), NH_4OAc (69.3 mg, 0.9 mmol), 2-alkynylbenzamide **3** (0.3 mmol), and acetonitrile (3 mL). The reaction mixture was stirred at 85 °C for 20 h. After it was cooled to room temperature, the resulting mixture was diluted with 15 mL of ethyl acetate and washed with brine (15 mL). The aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the corresponding 1-aminoisoquinoline product.

*3-Phenylisoquinolin-1-amine (**4a**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a light yellow solid (60.8 mg, 92% yield): mp 91.0−92.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 7.3 Hz, 2H), 7.77 (t, J = 9.0 Hz, 2H), 7.61 (m, 1H), 7.45−7.49 (m, 4H), 7.39 (d, J = 7.6 Hz, 1H), 5.30 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 149.6, 139.9, 138.4, 130.5, 128.8, 128.4, 127.8, 127.0, 126.2, 122.8, 117.1, 109.1; IR ($CHCl_3$, cm^{-1}) ν 3347, 3205; HRMS (ESI) calcd for $C_{15}H_{13}N_2$ $(M + H)^+$ 221.1073, found 221.1076.

*3-(Thiophen-3-yl)isoquinolin-1-amine (**4b**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a brown solid (64.5 mg, 95% yield): mp 108.6−109.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 4.8 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.37−7.39 (m, 2H) 5.27 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 145.8, 142.7, 138.4, 130.5, 127.6, 126.2, 126.1, 125.9, 123.0, 122.8, 117.1, 108.5; IR ($CHCl_3$, cm^{-1}) ν 3384, 3187; HRMS (ESI) calcd for $C_{13}H_{11}N_2S$ $(M + H)^+$ 227.0637, found 227.0638.

*3-(Cyclohex-1-en-1-yl)isoquinolin-1-amine (**4c**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a light yellow oil (54.0 mg, 80% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.54 (dt, J = 7.0, 0.9 Hz, 1H), 7.37 (dt, J = 8.1, 1.1 Hz, 1H), 7.04 (s, 1H), 6.94−6.96 (m, 1H), 5.15 (s, 2H), 2.51−2.54 (m, 2H), 2.28−2.31 (m, 2H), 1.79−1.84 (m, 2H), 1.67−1.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 150.6, 138.3, 135.7, 130.1, 127.7, 127.5, 125.5, 122.7, 117.2, 107.0, 26.1, 26.0, 23.1, 22.4; IR ($CHCl_3$, cm^{-1}) ν 3378, 3213, 1621; HRMS (ESI) calcd for $C_{15}H_{17}N_2$ $(M + H)^+$ 225.1386, found 225.1388.

*4-(1-Aminoisoquinolin-3-yl)butanenitrile (**4d**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a white solid (55.8 mg, 88% yield): mp 106.2−107.2 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.58 (dt, J = 8.0, 0.9 Hz, 1H), 7.40 (dt, J = 8.1, 1.2 Hz, 1H), 6.84 (s, 2H), 6.77 (s, 1H), 2.68 (t, J = 7.3 Hz, 2H), 2.50−2.52 (m, 2H), 1.96−2.00 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.1, 152.8, 138.6, 130.9, 127.0, 125.7, 124.9, 121.7, 117.0, 108.4, 37.0, 25.7, 16.9; IR ($CHCl_3$, cm^{-1}) ν 3365, 3180, 2361; HRMS (ESI) calcd for $C_{13}H_{14}N_3$ $(M + H)^+$ 212.1182, found 212.1185.

*3-Tridecylisoquinolin-1-amine (**4e**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a yellow solid (93.2 mg, 95% yield): mp 87.2−87.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.58 (dt, J = 6.9, 0.8 Hz, 1H), 7.40−7.43 (m, 1H), 6.88 (s, 1H), 5.13 (s, 2H), 2.70 (t, J = 7.7 Hz, 2H), 1.72−1.75 (m, 4H), 1.25−1.38 (m, 18H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 154.1, 138.3, 130.3, 126.9, 125.4, 122.7, 116.4, 110.1, 38.2, 32.1, 29.93, 29.91, 29.90, 29.87, 29.84, 29.80, 29.7, 29.6, 22.9, 14.4 (fewer ^{13}C signals were observed due to signal overlapping); IR ($CHCl_3$, cm^{-1}) ν 3301, 3115; HRMS (ESI) calcd for $C_{22}H_{35}N_2$ $(M + H)^+$ 327.2795, found 327.2794.

*3-(tert-Butyl)isoquinolin-1-amine (**4f**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a yellow oil (51.0 mg, 85% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.55−7.58 (m, 1H), 7.39−7.42 (m, 1H), 7.02 (s, 1H), 5.13 (s, 2H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 155.2, 138.3, 129.9, 127.4, 125.4, 122.6, 116.3, 106.5, 36.9, 30.2; IR ($CHCl_3$, cm^{-1}) ν 3383, 3217; HRMS (ESI) calcd for $C_{13}H_{17}N_2$ $(M + H)^+$ 201.1386, found 201.1389.

*3-(Naphthalen-1-yl)isoquinolin-1-amine (**4g**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a light yellow solid (41.4 mg, 51% yield): mp 168.3−168.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 1H), 7.91 (t, J = 7.0 Hz, 2 H), 7.83 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.66 (m, 2H), 7.45−7.58 (m, 4H), 7.31 (s, 1H), 5.37 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 151.2, 139.1, 138.1, 134.1, 131.1, 130.6, 128.5, 128.4, 127.6, 127.4, 126.37, 126.35, 126.3, 125.9, 125.5, 122.8, 116.8, 113.5; IR ($CHCl_3$, cm^{-1}) ν 3306, 3174; HRMS (ESI) calcd for $C_{19}H_{15}N_2$ $(M + H)^+$ 271.1230, found 271.1233.

*3-(4-Methoxyphenyl)isoquinolin-1-amine (**4h**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a white solid (72.1 mg, 96% yield): mp 137.4−138.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00−8.03 (m, 2H), 7.77 (d, J = 8.6 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.60 (dt, J = 8.1, 1.0 Hz, 1H), 7.41−7.44 (m, 2H), 7.01−6.98 (m, 2H), 5.24 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 156.0, 149.5, 138.5, 132.7, 130.4, 128.2, 127.6, 125.7, 122.8, 116.8, 114.1, 108.0, 55.5; IR ($CHCl_3$, cm^{-1}) ν 3289, 3130; HRMS (ESI) calcd for $C_{16}H_{15}N_2O$ $(M + H)^+$ 251.1179, found 251.1183.

*3-(4-(Trifluoromethyl)phenyl)isoquinolin-1-amine (**4i**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a light yellow solid (32.9 mg, 38% yield): mp 135.9−137.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 8.2 Hz, 2H), 7.78−7.82 (m, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.65 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 7.3 Hz, 2H), 5.28 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 148.1, 143.4, 138.2, 130.7, 130.1 (q, J_{C-F} = 32.2 Hz), 127.9, 127.2, 126.7, 125.7 (q, J_{C-F} = 3.8 Hz), 123.6 (q, J_{C-F} = 184.4 Hz), 122.8, 117.5, 109.8; IR ($CHCl_3$, cm^{-1}) ν 3314, 3111; HRMS (ESI) calcd for $C_{16}H_{12}F_3N_2$ $(M + H)^+$ 289.0947, found 289.0949.

*Methyl 4-(1-Aminoisoquinolin-3-yl)benzoate (**4j**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a light yellow solid (45.1 mg, 54% yield): mp 175.2−176.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12−8.16 (m, 4H), 7.79−7.83 (m, 2H), 7.65 (dt, J = 7.0, 0.9 Hz, 1H), 7.57 (s, 1H), 7.50−7.53 (m, 1H), 5.29 (s, 2H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 156.2, 148.4, 144.3, 138.2, 130.7, 130.1, 129.7, 128.0, 126.8, 126.7, 122.8, 117.5, 110.1, 52.4; IR ($CHCl_3$, cm^{-1}) ν 3375, 3220, 1716; HRMS (ESI) calcd for $C_{17}H_{15}N_2O_2$ $(M + H)^+$ 279.1128, found 279.1130.

*7-Methoxy-3-phenylisoquinolin-1-amine (**4m**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a beige solid (56.0 mg, 74% yield): mp 126.1−126.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 7.7 Hz, 2H), 7.68 (d, J = 8.9 Hz, 1H), 7.45−7.47 (m, 3H), 7.34−7.37 (m, 1H), 7.29 (d, J = 8.7 Hz, 1H), 7.05 (s, 1H), 5.25 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 155.2, 147.4, 139.9, 133.5, 129.3, 128.8, 128.1, 126.8, 122.5, 117.9, 109.2, 101.9, 55.7; IR ($CHCl_3$, cm^{-1}) ν 3373, 3201; HRMS (ESI) calcd for $C_{16}H_{15}N_2O$ $(M + H)^+$ 251.1179, found 251.1182.

*7-Methyl-3-phenylisoquinolin-1-amine (**4n**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a light yellow oil (57.0 mg, 80% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04−8.06 (m, 2H), 7.67 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 0.4 Hz, 1H), 7.45−7.48 (m, 4H), 7.35−7.39 (m, 1H), 5.23 (s, 2H),

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2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 148.8, 140.1, 136.4, 136.0, 132.5, 128.7, 128.2, 127.6, 126.9, 122.0, 113.2, 109.0, 22.1; IR ($CHCl_3$, cm^{-1}) ν 3315, 3178; HRMS (ESI) calcd for $C_{16}H_{15}N_2$ $(M + H)^+$ 235.1230, found 235.1232.

*7-Fluoro-3-phenylisoquinolin-1-amine (**4o**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a yellow solid (61.0 mg, 85% yield): mp 112.8−113.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, J = 8.0, 0.5 Hz, 2H), 7.76−7.79 (m, 1H), 7.37−7.50 (m, 6H), 5.13 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6 (d, J_{C-F} = 248.4 Hz), 155.6 (d, J_{C-F} = 4.9 Hz), 149.2 (d, J_{C-F} = 2.7 Hz), 139.7, 135.4, 130.2 (d, J_{C-F} = 8.0 Hz), 128.8, 128.5, 126.9, 120.6 (d, J_{C-F} = 24.7 Hz), 117.5 (d, J_{C-F} = 7.2 Hz), 108.8, 107.1 (d, J_{C-F} = 21.5 Hz); IR ($CHCl_3$, cm^{-1}) ν 3378, 3197; HRMS (ESI) calcd for $C_{15}H_{12}FN_2$ $(M + H)^+$ 239.0979, found 239.0981.

*7-Methoxy-3-tridecylisoquinolin-1-amine (**4p**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a light yellow oil (90.9 mg, 85% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 9.1 Hz, 1H), 7.29−7.27 (m, 2H), 6.78 (s, 1H), 6.21 (s, 2H), 3.92 (s, 3H), 2.70 (t, J = 7.6 Hz, 2H), 1.74−1.70 (m, 2H), 1.24−1.36 (m, 20H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 154.9, 133.2, 128.4, 123.5, 117.2, 109.7, 102.6, 56.0, 36.6, 32.1, 29.89, 29.86, 29.80, 29.7, 29.62, 29.57, 22.9, 14.3 (fewer ^{13}C signals were observed due to signal overlapping); IR ($CHCl_3$, cm^{-1}) ν 3335, 3149; HRMS (ESI) calcd for $C_{23}H_{37}N_2O$ $(M + H)^+$ 357.2900, found 357.2902.

*7-Methyl-3-tridecylisoquinolin-1-amine (**4q**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a light yellow oil (91.5 mg, 90% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.54 (m, 2H), 7.40 (dd, J = 8.4, 1.4 Hz, 1H), 6.84 (s, 1H), 5.17 (s, 2H), 2.69 (t, J = 7.7 Hz, 2H), 2.49 (s, 3H), 1.70−1.76 (m, 2H), 1.25−1.37 (m, 20H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 153.1, 136.4, 135.1, 132.3, 126.7, 121.9, 116.5, 109.9, 38.1, 32.1, 29.93, 29.90, 29.89, 29.87, 29.83, 29.80, 29.7, 29.6, 22.9, 22.0, 14.4 (fewer ^{13}C signals were observed due to signal overlapping); IR ($CHCl_3$, cm^{-1}) ν 3303, 3128; HRMS (ESI) calcd for $C_{23}H_{37}N_2$ $(M + H)^+$ 341.2951, found 341.2951.

*3-(4-Methoxyphenyl)-7-methylisoquinolin-1-amine (**4r**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a green solid (74.9 mg, 94% yield): mp 166.9−167.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00−8.01 (m, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.54 (s, 1H), 7.42 (dd, J = 8.3, 1.3 Hz, 1H), 7.38 (s, 1H), 6.98−7.01 (m, 2H), 5.25 (s, 2H), 3.86 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 155.6, 148.5, 136.6, 135.6, 132.7, 132.4, 128.1, 127.4, 122.0, 116.9, 114.1, 107.9, 55.5, 22.0; IR ($CHCl_3$, cm^{-1}) ν 3354, 3170; HRMS (ESI) calcd for $C_{17}H_{17}N_2O$ $(M + H)^+$ 265.1335, found 265.1337.

*7-Fluoro-3-(4-methoxyphenyl)isoquinolin-1-amine (**4s**).* Eluent of column chromatography: hexanes/ethyl acetate 2/1. This compound was obtained as a yellow solid (76.5 mg, 95% yield): mp 180.5−181.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.4 Hz, 2H), 7.76−7.73 (m, 1H), 7.42−7.37 (m, 3H), 7.00 (d, J = 8.3 Hz, 2H), 5.11 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3 (d, J_{C-F} = 245.5 Hz), 160.1, 155.5 (d, J_{C-F} = 4.8 Hz), 149.0, 135.5, 132.4, 130.1 (d, J_{C-F} = 8.3 Hz), 128.1, 120.5 (d, J_{C-F} = 24.4 Hz), 117.2 (d, J_{C-F} = 7.1 Hz), 114.2, 107.7, 107.1 (d, J_{C-F} = 21.4 Hz), 55.6; IR ($CHCl_3$, cm^{-1}) ν 3241, 3111; HRMS (ESI) calcd for $C_{16}H_{14}FN_2O$ $(M + H)^+$ 269.1085, found 269.1086.

*3-Phenyl-N-propylisoquinolin-1-amine (**4t**).* Eluent of column chromatography: hexanes/ethyl acetate 5/1. This compound was obtained as a yellow solid (60.6 mg, 77% yield): mp 47.8−48.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 7.6 Hz, 2H), 7.74 (t, J = 7.7 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.40−7.45 (m, 3H), 5.29 (s, 1H), 3.73−3.77 (m, 2H), 1.80−1.88 (m, 2H), 1.11 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 149.1, 140.4, 138.1, 129.7, 128.6, 128.2, 127.8, 126.8, 125.6, 121.4, 117.5, 106.6, 43.7, 23.0, 12.0; IR ($CHCl_3$, cm^{-1}) ν 3458; HRMS (ESI) calcd for $C_{18}H_{19}N_2$ $(M + H)^+$ 263.1543, found 263.1545.

*N-Butyl-3-phenylisoquinolin-1-amine (**4u**).* Eluent of column chromatography: hexanes/ethyl acetate 5/1. This compound was obtained as a light yellow oil (61.4 mg, 74% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 8.0 Hz, 2H), 7.74 (t, J = 8.0 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.39−7.45 (m, 3H), 5.26 (s, 1H), 3.77−3.81 (m, 2H), 1.77−1.83 (m, 2H), 1.52−1.59 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 149.1, 140.4, 138.1, 129.8, 128.6, 128.2, 127.8, 126.8, 125.6, 121.4, 117.5, 106.6, 41.7, 32.0, 20.7, 14.3; IR ($CHCl_3$, cm^{-1}) ν 3452; HRMS (ESI) calcd for $C_{19}H_{21}N_2$ $(M + H)^+$ 277.1699, found 277.1699.

*N,3-Diphenylisoquinolin-1-amine (**4v**).* Eluent of column chromatography: hexanes/ethyl acetate 5/1. This compound was obtained as a brown solid (19.0 mg, 21% yield): mp 89.2−90.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 7.2 Hz, 2H), 7.95 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.83 (d, J = 8.1 Hz, 1H), 7.64−7.67 (m, 2H), 7.54 (dt, J = 8.2, 1.1 Hz, 1H) 7.49 (t, J = 7.9 Hz, 2H), 7.37−7.43 (m, 3H), 7.24 (s, 1H), 7.09 (t, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 149.0, 140.7, 139.9, 138.5, 130.2, 129.1, 128.8, 128.5, 128.2, 126.9, 126.5, 122.6, 121.5, 120.0, 118.1, 109.4; IR ($CHCl_3$, cm^{-1}) ν 3446; HRMS (ESI) calcd for $C_{21}H_{17}N_2$ $(M + H)^+$ 297.1386, found 297.1390.

Synthesis of *N*-(3-Phenyl-*1H*-isochromen-1-ylidene)propan-1-amine (17a). Eluent of column chromatography: hexanes/ethyl acetate 5/1. This compound was synthesized from 2-(phenylethynyl)-*N*-propylbenzamide (**3t**) on a 0.5 mmol scale according to a procedure in the literature.[16] The compound was obtained as a colorless oil (56.7 mg, 43% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 7.9 Hz, 1H), 7.80 (dd, J = 8.4, 0.8 Hz, 2H), 7.45−7.48 (m, 3H), 7.40−7.42 (m, 1H), 7.33 (dt, J = 7.6, 1.2 Hz, 1H), 7.26 (d, J = 7.7 Hz, 1H), 6.63 (s, 1H), 3.62 (t, J = 7.1 Hz, 2H), 1.77−1.81 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[16]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^{1}H and ^{13}C NMR spectra for the new compounds. 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.

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■ REFERENCES

(1) Smith, A. L.; De Morin, F. F.; Paras, N. A.; Huang, Q.; Petkus, J. K.; Doherty, E. M.; Nixey, T.; Kim, J. L.; Whittington, D. A.; Epstein, L. F.; Lee, M. R.; Rose, M. J.; Babij, C.; Fernando, M.; Hess, K.; Le, Q.; Beltran, P.; Carnahan, J. *J. Med. Chem.* **2009**, *52*, 6189.

(2) Song, Y.; Clizbe, L.; Bhakta, C.; Teng, W.; Li, W.; Wong, P.; Huang, B.; Sinha, U.; Park, G.; Reed, A.; Scarborough, R. M.; Zhu, B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2043.

(3) Rewinkel, J. B. M.; Lucas, H.; van Galen, P. J. M.; Noach, A. B. J.; van Dinther, T. G.; Rood, A. M. M.; Jenneboer, A. J. S. M.; van Boeckel, C. A. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 685.

(4) Ray, P.; Wright, J.; Adam, J.; Bennett, J.; Boucharens, S.; Black, D.; Cook, A.; Brown, A. R.; Epemolu, O.; Fletcher, D.; Haunso, A.; Huggett, M.; Jones, P.; Laats, S.; Lyons, A.; Mestres, J.; De Man, J.; Morphy, R.; Rankovic, Z.; Sherborne, B.; Sherry, L.; van Straten, N.; Westwood, P.; Zaman, G. Z. R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 97.

(5) Gutteridge, C. E.; Hoffman, M. M.; Bhattacharjee, A. K.; Milhous, W. K.; Gerena, L. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 786.
(6) Washio, Y. PCT Int. Appl. WO 2005049577 A1 20050602, 2005.
(7) Wei, X.; Zhao, M.; Du, Z.; Li, X. *Org. Lett.* **2011**, *13*, 4636.
(8) (a) Zheng, D.; Chen, Z.; Liu, J.; Wu, J. *Org. Biomol. Chem.* **2011**, *9*, 4763. (b) Chen, Z.; Yu, X.; Su, M.; Yang, X.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 2702.
(9) Tovar, J. D.; Swager, T. M. *J. Org. Chem.* **1999**, *64*, 6499.
(10) For selected reviews, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Fuerstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (e) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (f) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. (g) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994.
(11) For selected work on cyclization reactions of γ-carbonylalkynes, see: (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (b) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028. (c) Yue, D.; Della Ca, N.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581. (d) Asao, N.; Sato, K. *Org. Lett.* **2006**, *8*, 5361. (e) Tang, J.; Liu, T.; Liu, R. *J. Org. Chem.* **2008**, *73*, 8479. (f) Gou, F.; Huo, P.; Bi, H.; Guan, Z.; Liang, Y. *Org. Lett.* **2009**, *11*, 3418. (g) Liu, L.; Hammond, G. B. *Org. Lett.* **2010**, *12*, 4640.
(12) Yang, D.; Burugupalli, S.; Daniel, D.; Chen, Y. *J. Org. Chem.* **2012**, *77*, 4466.
(13) She, Z.; Niu, D.; Chen, L.; Gunawan, M. A.; Shanja, X.; Hersh, W. H.; Chen, Y. *J. Org. Chem.* **2012**, *77*, 3627.
(14) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; p 203.
(15) For a discussion of silver effects on gold catalysis, see: Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012.
(16) Liu, G.; Zhou, Y.; Ye, D.; Zhang, D.; Ding, X.; Jiang, H.; Liu, H. *Adv. Synth. Catal.* **2009**, *351*, 2605.
(17) Hellal, M.; Cuny, G. D. *Tetrahedron Lett.* **2011**, *52*, 5508.
(18) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
(19) Zhang, S.-W.; Kaneko, T.; Yoneda, E.; Sugioka, T.; Takahashi, S. *Inorg. Chim. Acta* **1999**, *296*, 195.
(20) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145.