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Synthesis of Substituted 1,2-Dihydroisoquinolines by Palladium-Catalyzed Cascade Cyclization–Coupling of Trisubstituted Allenamides with Arylboronic Acids

Masahiro Yoshida*, Ryunosuke Imaji and Shinya Shiomi

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, 180 Nishihamabouji, Yamashiro-cho, Tokushima 770-8514, Japan

* Correspondence: yoshida@ph.bunri-u.ac.jp

Abstract: 1,2-Dihydroisoquinolines are important compounds due to their biological and medicinal activities, and numerous approaches to their synthesis have been reported. In this study, a palladium-catalyzed cascade cyclization-coupling of trisubstituted allenamides containing a bromoaryl moiety with arylboronic acids is described. The reaction proceeds via intramolecular cyclization, followed by transmetallation with the arylboronic acid of the resulting allylpalladium intermediate. A variety of substituted 1,2-dihydroisoquinolines were concisely obtained using this methodology because the allenamides, as reaction substrates, were prepared from readily available propargylamines in one step.

Keywords: allenamide; cascade reaction; palladium catalyst; cyclization; coupling; organoboronic compound; 1,2-dihydroisoquinoline

1. Introduction

Isoquinolines and their derivatives, especially 1,2-dihydroisoquinolines, are among the important structure classes of chemical substances. A wide variety of natural products and biologically active pharmacophores have been reported [1-8] such as acetoneberberine IK-2 (**I**) [5], cribrostatin 4 (**II**) [6], *N*-carboxymethyl compound **III** for a carrier for brain-specific delivery [7], and nitro-substituted 1,2-dihydroisoquinoline **IV** as a HIV-1 inhibitor [8]. For this reason, numerous approaches to the synthesis of 1,2-dihydroisoquinolines have been developed (Figure 1) [9-22].

Allenamides are powerful and versatile synthetic building blocks in organic synthesis, extensively utilized as reaction substrates to produce a variety of synthetically useful organic molecules [23,24]. Among them, palladium-catalyzed cascade cyclization of ortho-haloaryl-substituted allenamides provides efficient approaches for the synthesis of *N*-heterocyclic compounds (Scheme 1, eq 1) [25-37]. The key intermediate in this strategy is the π-allylpalladium species, which is generated by an oxidative addition and allene insertion sequence. Diverse nucleophiles or organic main group element compounds are applied to undergo subsequent allylic substitution reactions, yielding a variety of substituted heterocycles. Considerable effort has been devoted to developing methods for the synthesis of various *N*-heterocyclic compounds, but few examples using polysubstituted allenamides have been reported, presumably due to the difficulty in synthesizing polysubstituted allenamides. Recently, we reported a facile synthesis of trisubstituted allenamides via *N*-acetylation followed by DBU-promoted isomerization, where various substituted allenamides can be conveniently synthesized from readily available propargylamines with high efficiency (Scheme 1, eq 2) [38]. In light of this research background, we focused on the utility of this methodology for the synthesis of substituted 1,2-dihydroisoquinolines. Herein, we describe a palladium-catalyzed cascade cyclization-coupling of trisubstituted allenamides containing a bromoaryl moiety with arylboronic acids, concisely yielding a variety of substituted 1,2-dihydroisoquinolines (Scheme 1, eq 3).

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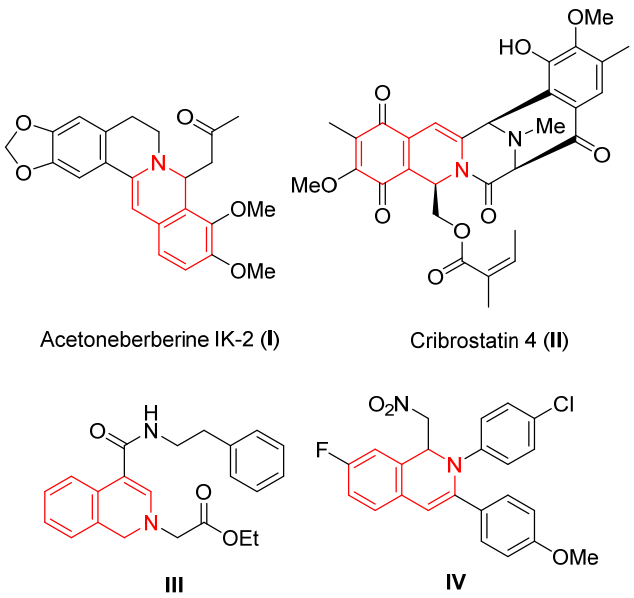
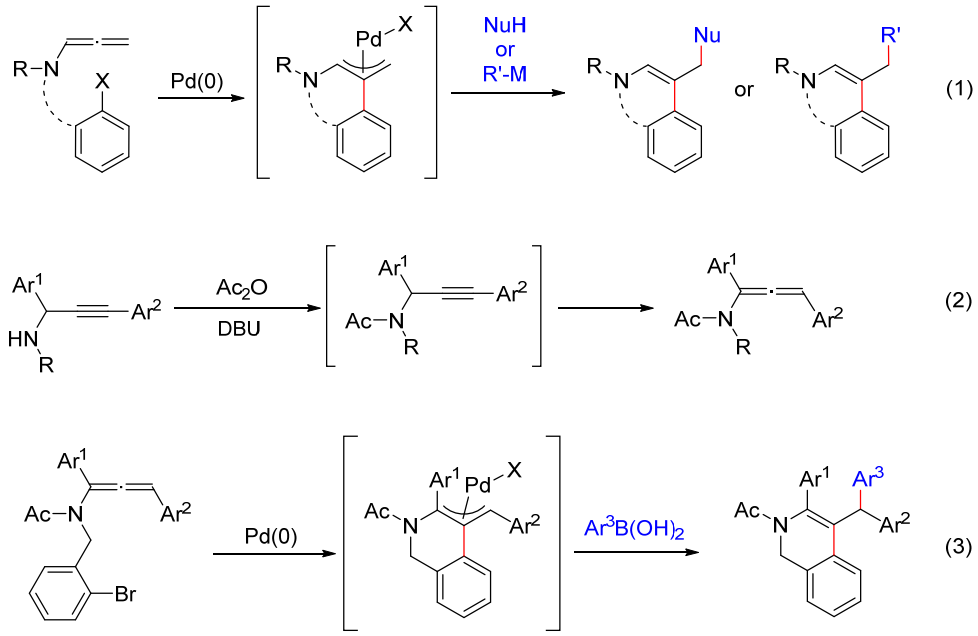


Figure 1. Structure of biologically active molecules containing 1,2-dihydroisoquinoline moiety.



Scheme 1. Palladium-catalyzed cyclization of allenamides and synthesis of allenamides.

2. Results and Discussion

Trisubstituted allenamides for the palladium-catalyzed cascade cyclization were prepared as shown in Scheme 2. The three-component reaction of arylaldehyde, monosubstituted alkyne and *o*-bromobenzyl amine gave the propargylamines **1a–1e**, which were subjected to the reaction with acetic anhydride and DBU [38], according to our procedure, to afford the corresponding trisubstituted allenamides **2a–2e** in moderate to good yields, respectively.

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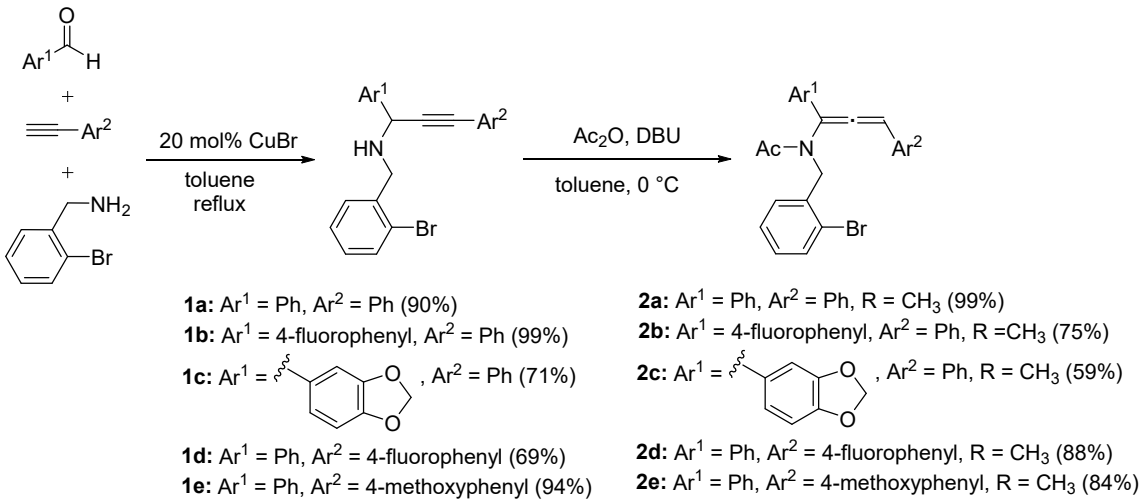
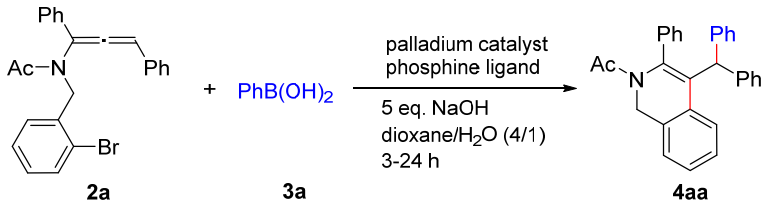


Scheme 2. Synthesis of trisubstituted allenamides.

The initial attempts for the palladium-catalyzed cascade reaction were carried out using the *N*-acetyl diphenyl-substituted trisubstituted allenamide **2a** with phenylboronic acid (**3a**) (Table 1). When **2a** and **3a** were treated with 5 mol% of $Pd(OAc)_2$, 10 mol% of P(*o*-tolyl)$_3$, and 5 equivalents of NaOH in dioxane/H_2O (4/1) at 80 °C, the expected reaction proceeded, affording a substituted 1,2-dihydroisoquinoline **4aa** in 78% yield (entry 1). Upon examining the catalyst amounts (entries 2 and 3), it was found that increasing the amounts to 10 mol% of $Pd(OAc)_2$ and 20 mol% of P(o-tolyl)$_3$ increased the yield to 88% (entry 3). Reaction temperatures were then investigated (entries 4–6). The yield of **4aa** was 86% when the reaction was carried out at 50 °C (entry 4), but a significant decrease in yield was observed when the temperature was lowered to 25 °C (entry 5). The product was obtained in 76% yield when the reaction temperature was raised to 100 ºC (entry 6). The product was produced in 70% yield when PPh_3 was used (entry 7), but the yield decreased to 19% when PCy_3 was used (entry 8). The reactions using bidentate ligands such as DPPE and DPPF also proceeded, giving **4aa** in 47% and 70% yields, respectively (entries 9 and 10).

Table 1. Initial attempts using allenamide **2a** with phenylboronic acid (**3a**).



Entry	Palladium Catalyst	Phosphine Ligand	Temperature	Yield (%)
1	$Pd(OAc)_2$ (5 mol%)	P(*o*-tolyl)$_3$ (10 mol%)	80	78
2	$Pd(OAc)_2$ (5 mol%)	P(*o*-tolyl)$_3$ (20 mol%)	80	85
3	$Pd(OAc)_2$ (10 mol%)	P(*o*-tolyl)$_3$ (20 mol%)	80	88
4	$Pd(OAc)_2$ (10 mol%)	P(*o*-tolyl)$_3$ (20 mol%)	50	86
5	$Pd(OAc)_2$ (10 mol%)	P(*o*-tolyl)$_3$ (20 mol%)	25	30
6	$Pd(OAc)_2$ (10 mol%)	P(*o*-tolyl)$_3$ (20 mol%)	100	75
7	$Pd(OAc)_2$ (10 mol%)	PPh_3 (20 mol%)	80	70
8	$Pd(OAc)_2$ (10 mol%)	PCy_3 (20 mol%)	80	19
9	$Pd(OAc)_2$ (10 mol%)	DPPE (10 mol%)	80	47

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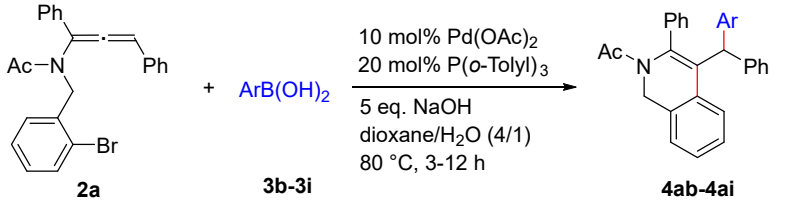
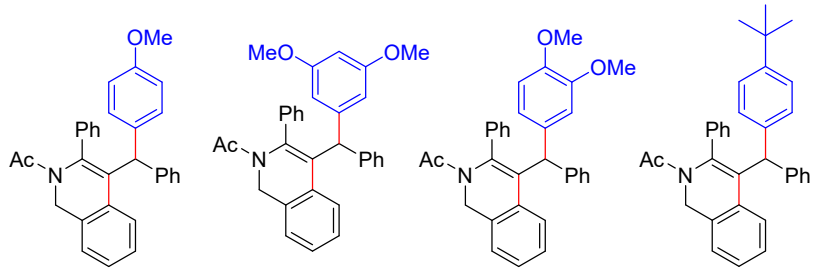
10	$Pd(OAc)_2$ (10 mol%)	DPPF (10 mol%)	80	70

We next carried out a study on the substrate scope using various arylboronic acids **3b–3i** with **2a** (Table 2). When 4-methoxyphenylboronic acid (**3b**) was subjected to the reaction, the corresponding 1,2-dihydroisoquinoline **4ab** was obtained in 82% yield. Arylboronic acids **3c** and **3d** having dimethoxyphenyl groups reacted with **2a** to produce the products **4ac** and **4ad** in 98% and 86% yields, respectively. The reaction of **3e**, having a *tert*-butyl group, also proceeded to give the product **4ae** in 92% yield. The corresponding products **4af** and **4ag** were obtained in good yields from the reactions using 4-chloro- and 4-fluorophenyl boronic acids **3f** and **3g**, respectively. The reaction using 4-acetylphenylboronic acid (**3h**) afforded the product **4ah** in 85% yield. When 1-naphtylboronic acid (**3i**) was subjected to the reaction, the corresponding 1,2-dihydroisoquinoline **4ai** was produced in 67% yield.

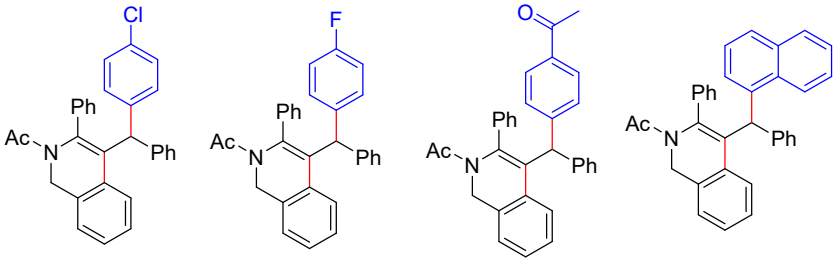
Table 2. Reactions using allenamide **2a** with various arylboronic acids **3**.



2a **3b-3i** **4ab-4ai**



4ab 82% **4ac** 98% **4ad** 86% **4ae** 92%



4af 96% **4ag** 81% **4ah** 85% **4ai** 67%

Table 2. b–2e with various substituents and phenylboronic acid (**3a**) are summarized in Table 3. When the substrate **2b**, having a 4-fluorophenyl group at the 1-position, was subjected to the reaction, the corresponding 1,2-dihydroisoquinoline **4ba** was obtained in 55% yield. The reaction of allenamide **2c**, which have a 1,3-benzodioxole moiety, proceeded to afford the cyclized product **4ca** in 80% yield. The substrates **2d** and **2e**, containing a 4-fluoro- and 4-methoxyphenyl group at the 3-posion, also reacted with **3a** to produce the corresponding substituted products **4da** (**4ag**) and **4ea** (**4ab**) in 66% and 72% yields, respectively.

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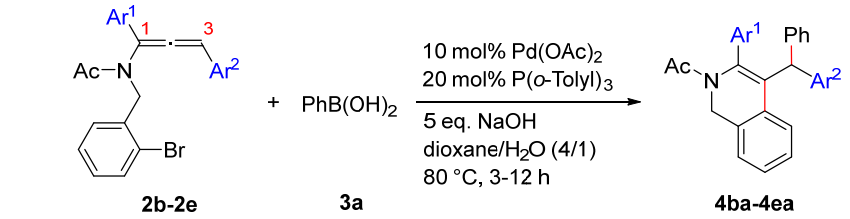
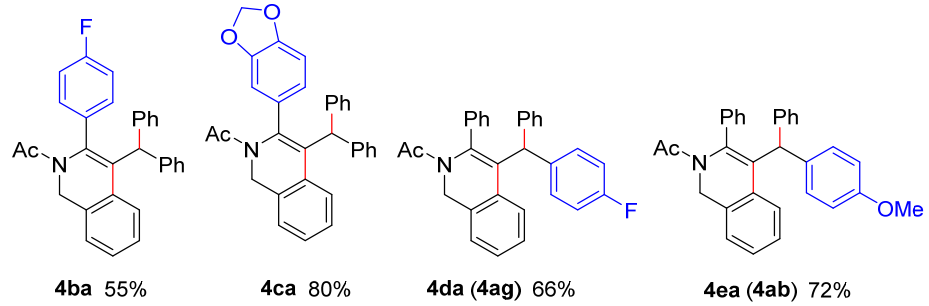
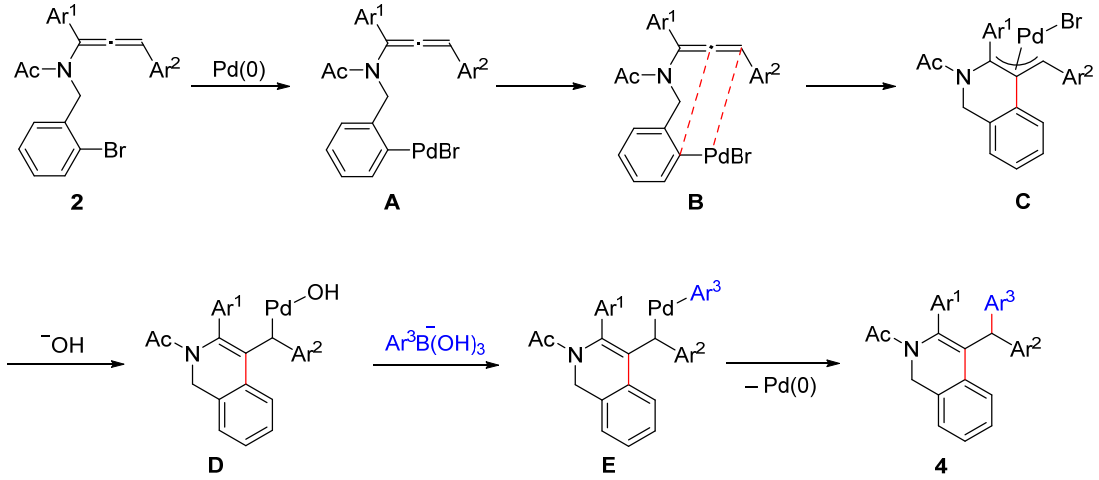
Table 3. Reactions using various allenamides **2** with phenylboronic acid (**3a**).





A plausible mechanism for the cyclization process is shown in Scheme 3. The reaction was initiated with the oxidative addition of the aryl bromide moiety of the allenamide **2** to palladium, generating arylpalladium intermediate **A**. This is followed by an intramolecular allene insertion process (**B**) to generate the π-allyl-palladium intermediate **C** [25-37]. Then ligand exchange of palladium complex **C** with hydroxide ion occurs, forming hydroxypalladium species **D** [39]. This species undergoes transmetallation with the arylborate complex via intermediate **E** to produce the substituted 1,2-dihydroisoquinoline **4**.



Scheme 3. Proposed mechanism for the production of 1,2-dihydroisoquinoline **4**.

3. Materials and Methods

All commercially available reagents were used without further purification. All reactions were performed in glassware equipped with a septum under the positive pressure of argon. The reaction mixture was magnetically stirred. Concentration was performed under reduced pressure. The heating experiments were conducted under an oil bath as a heat source. The reactions were monitored by TLC. TLC was performed on pre-coated plates (0.25 mm, silica gel Merck $60F_{245}$). Spots were visualized by exposure to UV light, or by immersion into a solution of 10% phosphomolybdic acid in ethanol, followed by heating at ca. 200 °C. Column chromatography was performed on silica gel (40–50 µm, Kanto Chemical Co., Inc.). NMR spectra were recorded on Bruker AVANCED III HD-500 (^{1}H:

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500 MHz, ^{13}C: 125 MHz) spectrometer using tetramethylsilane (^{1}H NMR at 0.00 ppm) and $CDCl_3$ (^{13}C NMR at 77.16) as a reference standard. Chemical sifts were reported in ppm. The following abbreviations were used to denote peak multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sept, septet; m, multiplet; br, broadened. Mass spectra and high-resolution mass spectra were recorded on JEOL JMS-700 mass spectrometers (double-focusing magnetic sector).

3.1. General procedure for the three-component reaction of arylaldehyde, alkyne and amine in Scheme 2. Synthesis of propargylamine 1a

To a solution of benzaldehyde (531 mg, 5.00 mmol) in toluene (6 mL) was added phenylacetylene (766 mg, 7.50 mmol), 2-bromobenzylamine (1.40 g, 7.50 mmol) and CuBr (143 mg, 1.00 mmol) at rt under argon atmosphere. The reaction mixture was then stirred under reflux condition for 2 h. The reaction was quenched with sat. NH_4Cl. The aq. mixture was extracted with AcOEt. The organic layer was washed brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (hexane/AcOEt = 30/1 to 10/1) to afford propargylamine **1a** (1.71 g, 4.54 mmol, 90%).

3.2. N-(2-Bromobenzyl)-1,3-diphenylprop-2-yn-1-amine (1a)

Yield 90%; yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.62 (d, 2H, *J* = 7.5 Hz), 7.53 (d, 1H, *J* = 7.5 Hz), 7.52–7.46 (m, 4H), 7.38–7.29 (m, 7H), 4.82 (s, 1H), 4.06 (d, 1H, *J* = 6.6 Hz), 4.04 (d, 1H, *J* = 6.6 Hz), 1.92 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 140.2, 138.9, 132.9, 131.8 (2C), 130.6, 128.8, 128.6 (2C), 128.3 (2C), 128.2, 127.9, 127.8 (2C), 127.5, 124.3, 123.2, 89.0, 85.9, 54.0, 51.3; HRMS (EI) *m/z* calcd for $C_{22}H_{18}NBr$ $[M]^+$ 375.0623, found 375.0626.

3.3. N-(2-Bromobenzyl)-1-(4-fluorophenyl)-3-phenylprop-2-yn-1-amine (1b)

Yield 99%; yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.58 (dd, 1H, *J* = 9.0 and 5.5 Hz), 7.52–7.46 (m, 4H), 7.43 (d, 1H, *J* = 7.5 Hz), 7.31–7.25 (m, 3H), 7.23 (t, 1H, *J* = 7.5 Hz), 7.06–6.99 (m, 3H), 4.77 (s, 1H), 4.03 (d, 1H, *J* = 6.6 Hz), 4.01 (d, 1H, *J* = 6.6 Hz), 1.91 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 162.3 (d, *J* = 244 Hz), 138.7, 135.9, 132.8. 131.7 (2C), 130.5, 129.4, 129.3 (2C, d, *J* = 7.9 Hz), 128.7, 128.3 (2C), 127.4, 124.1, 122.9, 115.3 (2C, d, *J* = 21.6 Hz), 88.7, 86.1, 53.2, 51.1; HRMS (EI) *m/z* calcd for $C_{22}H_{17}NBrF$ $[M]^+$ 393.0528, found 393.0534.

3.4 1-(Benzo[d][1,3]dioxol-5-yl)-N-(2-bromobenzyl)-3-phenylprop-2-yn-1-amine (1c)

Yield 71%; colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.55 (d, 1H, *J* = 8.0 Hz), 7.49–7.46 (m, 3H), 7.33–7.27 (m, 4H), 7.15–7.11 (m, 2H), 7.07 (d, 1H, *J* = 8.0 Hz), 6.79 (d, 1H, *J* = 8.0 Hz), 5.96 (s, 2H), 4.74 (s, 1H), 4.07 (d, 1H, *J* = 6.6 Hz), 4.03 (d, 1H, *J* = 6.6 Hz), 1.60 (brs, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 147.9, 147.3, 138.9, 134.3, 132.9, 131.8 (2C), 130.7, 128.8, 128.4 (2C), 128.3, 128.2, 127.6, 124.3, 123.1, 121.1, 108.4, 108.1, 89.0, 85.9, 53.8, 51.3; HRMS (EI) *m/z* calcd for $C_{23}H_{18}NO_2Br$ $[M]^+$ 419.0521, found 419.0524.

3.5. N-(2-Bromobenzyl)-3-(4-fluorophenyl)-1-phenylprop-2-yn-1-amine (1d)

Yield 69%; yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.59 (d, 2H, *J* = 7.5 Hz), 7.48 (d, 1H, *J* = 8.0 Hz), 7.43–7.39 (m, 3H), 7.33 (t, 2H, *J* = 7.5 Hz), 7.25 (t, 1H, *J* = 7.5 Hz), 7.20 (t, 1H, *J* = 7.5 Hz), 7.03 (dt, 1H, *J* = 7.5 and 8.0 Hz), 6.96–9.91 (m, 2H), 4.78 (s, 1H), 4.04 (d, 1H, *J* = 6.6 Hz), 4.00 (d, 1H, *J* = 6.6 Hz), 1.93 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 162.3 (d, *J* = 247 Hz), 140.0, 138.8, 133.5 (2C, d, *J* = 8.8 Hz), 132.7, 130.4, 128.6, 128.5 (2C), 127.8, 127.6 (2C), 127.4, 124.1, 119.1, 115.5 (2C, d, *J* = 21.6 Hz), 88.7, 84.7, 53.9, 51.2; HRMS (EI) *m/z* calcd for $C_{22}H_{17}NBrF$ $[M]^+$ 393.0528, found 393.0524.

3.6. N-(2-bromobenzyl)-3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-amine (1e)

Yield 94%; yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.61 (d, 2H, *J* = 7.0 Hz), 7.51 (d, 1H, *J* = 8.0 Hz), 7.45 (d, 1H, *J* = 8.0 Hz), 7.42 (d, 2H, *J* = 9.0 Hz),7.33 (t, 2H, *J* = 7.0 Hz), 7.28–7.22 (m, 2H), 7.07 (t,

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1H, *J* = 8.0 Hz), 6.81 (d, 2H, *J* = 9.0 Hz), 4.80 (s, 1H), 4.06 (d, 1H, *J* = 6.6 Hz), 4.04 (d, 1H, *J* = 6.6 Hz), 3.73 (s, 3H)1.92 (brs, 1H); 159.5, 140.3, 138.9, 133.1 (2C), 132.8, 130.5, 128.7, 128.5 (2C), 127.8, 127.7 (2C), 127.4, 124.1, 115.2, 113.9 (2C), 87.5, 85.8, 55.2, 54.0, 51.2; HRMS (EI) *m*/*z* calcd for $C_{23}H_{20}NOBr$ $[M]^+$ 405.0728, found 405.0725.

3.7. General procedure for the one-pot synthesis of trisubstituted allenamide in Scheme 2. Synthesis of allenamide 2a.

To a solution of propargylamine **1a** (314 mg, 0.835 mmol) in toluene (7 mL) were added Ac_2O (0.40 mL, 4.18 mmol) and DBU (0.62 mL, 4.18 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at same temperature for 24 h. The reaction was quenched with 1 M HCl. The aq. mixture was extracted with AcOEt. The organic layer was washed brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (hexane/AcOEt = 8/1) to afford the allnenamide **2a** (349 mg, 0.834 mmol, 99%).

3.8. N-(2-Bromobenzyl)-N-(1,3-diphenylpropa-1,2-dien-1-yl)acetamide (2a)

Yield 99%; yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.46 (d, 1H, *J* = 7.9 Hz), 7.40–7.31 (m, 4H), 7.26–7.20 (m, 5H), 7.07 (t, 1H, *J* = 7.6 Hz), 7.03–7.00 (m, 3H), 6.62 (s, 1H), 5.23 (d, 1H, *J* = 15.3 Hz), 4.72 (d, 1H, *J* = 15.3 Hz), 2.23 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 206.9, 171.5, 136.3, 132.7, 132.6, 131.9, 130.0, 129.1 (2C), 128.8 (2C), 128.7, 128.6, 128.3, 127.7 (2C), 127.5, 125.5 (2C), 123.8, 115.8, 101.9, 49.6, 22.2; HRMS (EI) *m*/*z* calcd for $C_{24}H_{20}BrNO$ $[M]^+$ 417.0728, found 417.0730.

3.9. N-(2-Bromobenzyl)-N-(1-(4-fluorophenyl)-3-phenylpropa-1,2-dien-1-yl)acetamide (2b)

Yield 75%; yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.46 (d, 1H, *J* = 7.9 Hz), 7.32–7.29 (m, 2H), 7.26–7.22 (m, 4H), 7.09–6.98 (m, 6H), 6.61 (s, 1H), 5.23 (d, 1H, *J* = 15.5 Hz), 4.68 (d, 1H, *J* = 15.5 Hz), 2.24 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 206.6, 171.4, 162.9 (d, *J* = 247 Hz), 136.2, 132.7, 130.2, 128.9 (2C), 128.8, 128.7, 128.5, 128.4, 127.7 (2C), 127.6, 127.4 (2C, d, *J* = 8.8 Hz), 123.9, 116.3 (2C, d, *J* = 21.6 Hz), 115.0, 102.1, 49.4, 22.2; HRMS (EI) *m*/*z* calcd for $C_{24}H_{19}NOBrF$ $[M]^+$ 435.0634, found 435.0632.

3.10. N-(1-(Benzo[d][1,3]dioxol-5-yl)-3-phenylpropa-1,2-dien-1-yl)-N-(2-bromobenzyl)acetamide (2c)

Yield 59%; yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.46 (d, 1H, *J* = 8.0 Hz), 7.26–7.21 (m, 4H), 7.08–6.98 (m, 4H), 6.84–6.80 (m, 3H), 6.58 (s, 1H), 5.97 (s, 2H), 5.21 (d, 1H, *J* = 15.5 Hz), 4.71 (d, 1H, *J* = 15.5 Hz), 2.24 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 206.4, 171.4, 148.6, 148.2, 136.3, 132.7, 132.0, 130.0, 128.9, 128.8 (2C), 128.3, 127.6 (2C), 127.5, 126.6, 123.8, 119.2, 115.7, 108.8, 106.0, 101.9, 101.5, 49.5, 22.1; HRMS (EI) *m*/*z* calcd for $C_{25}H_{20}NO_3Br$ $[M]^+$ 461.0627, found 461.0622.

3.11. N-(2-Bromobenzyl)-N-(3-(4-fluorophenyl)-1-phenylpropa-1,2-dien-1-yl)acetamide (2d)

Yield 88%; yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45 (d, 1H, *J* = 8.0 Hz), 7.40–7.37 (m, 2H), 7.34–7.31 (m, 1H), 7.24 (d, 1H, *J* = 8.0 Hz), 7.07–7.00 (m, 2H), 6.95–6.87 (m, 6H), 6.60 (s, 1H), 5.31 (d, 1H, *J* = 15.5 Hz), 4.64 (d, 1H, *J* = 15.5 Hz), 2.24 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 206.6, 171.5, 162.6 (d, *J* = 247 Hz), 136.3, 132.7, 132.5, 130.0, 129.3, 129.2 (3C), 128.8 (2C, d, *J* = 8.8 Hz), 128.0, 127.9, 127.6, 125.6 (2C), 123.9, 115.9 (2C, d, *J* = 21.6 Hz), 100.8, 49.5, 22.2; HRMS (EI) *m*/*z* calcd for $C_{24}H_{19}NOBrF$ $[M]^+$ 435.0634, found 435.0638.

3.12. N-(2-Bromobenzyl)-N-(3-(4-methoxyphenyl)-1-phenylpropa-1,2-dien-1-yl)acetamide (2e)

Yield 84%; white solid; mp 123.5–157.2 °C ($CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.45 (d, 1H, *J* = 7.5 Hz), 7.38–7.28 (m, 6H), 7.08–7.00 (m, 2H), 6.93 (d, 2H, *J* = 9.0 Hz), 6.75 (d, 2H, *J* = 9.0 Hz), 6.59 (s, 1H), 5.23 (d, 1H, *J* = 15.5 Hz), 4.69 (d, 1H, *J* = 15.5 Hz), 3.78 (s, 3H), 2.25 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 206.1, 171.6, 159.7, 136.3, 132.9, 132.6, 129.9, 129.1 (2C), 128.9 (2C), 128.7, 128.5, 127.5, 125.5 (2C), 124.1, 123.8, 115.5, 114.3 (2C), 101.4, 55.4, 49.6, 22.2; HRMS (EI) *m*/*z* calcd for $C_{25}H_{22}NO_2Br$ $[M]^+$ 447.0834, found 447.0830.

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3.13. General procedure for the palladium-catalyzed cascade reaction of allenamide with arylboronic acid. Synthesis of 1,2-dihydroisoquinoline 4aa.

To a stirred solution of allenamide **2a** (60.1 mg, 0.144 mmol) in 1,4-dioxane (2.4 mL) and H_2O (0.6 mL) were added phenylboronic acid (**3a**) (26.3 mg, 0.216 mmol), $Pd(OAc)_2$ (3.2 mg, 0.0144 mmol), P(*o*-tolyl)$_3$ (8.7 mg, 0.0287 mmol) and NaOH (28.8 mg, 0.720 mmol) at rt under argon atmosphere. The reaction mixture was stirred for 3 h at 80 °C. The reaction mixture was added water and extracted with AcOEt. The organic layer was washed brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (hexane/AcOEt = 7/1) to afford the 1,2-dihydroisoquinoline **4aa** (53.2 mg, 88%).

3.14 1-(4-Benzhydryl-3-phenylisoquinolin-2(1H)-yl)ethan-1-one (4aa)

Yield 88%; colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.33–7.31 (m, 5H), 7.26–7.15 (m, 12H), 7.06 (t, 1H, *J* = 7.5 Hz), 6.94 (t, 1H, *J* = 7.5 Hz), 5.76 (s, 1H), 4.99 (s, 2H), 1.56 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.3, 142.6 (2C), 138.5, 137.7, 135.3, 132.2, 129.7, 129.4 (3C), 129.3, 129.0, 128.9, 128.7, 128.4, 128.3 (3C), 127.6, 127.2, 126.5 (3C), 126.4, 125.1, 51.4, 46.5, 24.4; HRMS (EI) *m*/*z* calcd for $C_{30}H_{25}NO$ $[M]^+$ 415.1936, found 415.1935.

3.15 1-(4-((4-Methoxyphenyl)(phenyl)methyl)-3-phenylisoquinolin-2(1H)-yl)ethan-1-one (4ab/4ea)

Yield 82% from **2a** with **3b**, and yield 72% from **2e** with **3a**; colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35–7.28 (m, 6H), 7.24–7.20 (m, 4H), 7.18–7.14 (m, 4H), 7.06 (t, 1H, *J* = 7.5 Hz), 6.95 (t, 1H, *J* = 7.5 Hz), 6.80 (d, 2H, *J* = 8.5 Hz), 5.71 (s, 1H), 5.02–4.93 (m, 2H), 3.78 (s, 3H), 1.51 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.3, 158.1, 142.9, 138.3, 137.7, 135.3, 134.5, 132.3, 130.4 (2C), 129.7, 129.3 (3C), 129.2, 128.8, 128.7, 128.3 (3C), 127.6, 127.2, 126.4, 126.3, 125.1, 113.7 (2C), 55.3, 50.6, 46.5, 24.4; HRMS (EI) *m*/*z* calcd for $C_{31}H_{27}NO_2$ $[M]^+$ 445.2042, found 445.2041.

3.16 1-(4-((3,5-Dimethoxyphenyl)(phenyl)methyl)-3-phenylisoquinolin-2(1H)-yl)ethan-1-one (4ac)

Yield 98%; colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36–7.31 (m, 5H), 7.27–7.22 (m, 5H), 7.18–7.15 (m, 2H), 7.07 (t, 1H, *J* = 7.5 Hz), 6.97 (t, 1H, *J* = 7.5 Hz), 6.42 (s, 2H), 6.31 (s, 1H), 5.68 (s, 1H), 5.03 (d, 1H, *J* = 13.5 Hz), 4.93 (d, 1H, *J* = 13.5 Hz), 3.68 (s, 6H), 1.56 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.3, 160.7, 145.0, 142.3, 138.5, 137.7, 135.3, 132.2, 129.7 (2C), 129.4 (2C), 129.0, 128.9, 128.7 (2C), 128.3 (2C), 127.6 (2C), 127.2, 126.4 (2C), 125.0, 107.9 (2C), 98.1, 55.3 (2C), 51.5, 46.5, 24.4; HRMS (EI) *m*/*z* calcd for $C_{32}H_{29}NO_3$ $[M]^+$ 475.2147, found 475.2148.

3.17 1-(4-((3,4-Dimethoxyphenyl)(phenyl)methyl)-3-phenylisoquinolin-2(1H)-yl)ethan-1-one (4ad)

Yield 86%; colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36–7.30 (m, 4H), 7.26–7.21 (m, 7H), 7.18–7.14 (m, 1H), 7.07 (t, 1H, *J* = 8.0 Hz), 6.96 (t, 1H, *J* = 7.5 Hz), 6.83 (d, 1H, *J* = 8.5 Hz), 6.78 (d, 1H, *J* = 8.5 Hz), 6.73 (s, 1H), 5.69 (s, 1H), 5.04 (d, 1H, *J* = 13.5 Hz), 4.90 (d, 1H, *J* = 13.5 Hz), 3.86 (s, 3H), 3.69 (s, 3H), 1.55 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.3, 148.7, 147.6, 142.8, 138.3, 137.7, 135.4, 134.9, 132.3, 129.6 (2C), 129.2 (2C), 128.9, 128.7 (2C), 128.3 (2C), 127.6 (2C), 127.2, 126.5, 126.4, 125.1, 121.7, 112.8, 110.9, 56.0, 55.9, 51.0, 46.5, 24.4; HRMS (EI) *m*/*z* calcd for $C_{32}H_{29}NO_3$ $[M]^+$ 475.2147, found 475.2148.

3.18 1-(4-((4-(tert-Butyl)phenyl)(phenyl)methyl)-3-phenylisoquinolin-2(1H)-yl)ethan-1-one (4ae)

Yield 92%; colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.34–7.30 (m, 5H), 7.28–7.24 (m, 2H), 7.22–7.20 (m, 5H), 7.16 (d, 4H, *J* = 8.5 Hz), 7.06 (t, 1H, *J* = 7.5 Hz), 6.95 (t, 1H, *J* = 7.5 Hz), 5.73 (s, 1H), 5.09 (d, 1H, *J* = 14.0 Hz), 4.88 (d, 1H, *J* = 14.0 Hz), 1.52 (s, 3H), 1.30 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.3, 149.2, 142.9, 139.2, 138.3, 137.8, 135.3, 132.3, 129.7 (2C), 129.3 (2C), 129.2, 129.0 (2C), 128.8, 128.7 (2C), 128.2 (2C), 127.7, 127.1, 126.5, 126.3, 125.2 (2C), 125.0, 50.9, 46.5, 34.5, 31.5 (3C), 24.4; HRMS (EI) *m*/*z* calcd for $C_{34}H_{33}NO$ $[M]^+$ 471.2562, found 471.2559.

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3.19 1-(4-((4-Chlorophenyl)(phenyl)methyl)-3-phenylisoquinolin-2(1H)-yl)ethan-1-one (4af)

Yield 96%; white solid; mp 205.5–233.9 °C ($CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.33–7.31 (m, 5H), 7.27–7.20 (m, 7H), 7.17–7.14 (m, 4H), 7.08 (t, 1H, *J* = 8.0 Hz), 6.96 (t, 1H, *J* = 8.0 Hz), 5.71 (s, 1H), 5.05 (d, 1H, *J* = 14.0 Hz), 4.90 (d, 1H, *J* = 14.0 Hz), 1.50 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.26, 142.1, 141.2, 137.5, 135.3, 132.2, 131.9, 130.7 (2C), 129.6, 129.2 (2C), 129.0, 128.8, 128.6 (2C), 128.5 (2C), 128.4, 127.4, 127.3 (2C), 126.7 (2C), 126.5, 125.2, 50.9, 46.5, 24.4; HRMS (EI) *m*/*z* calcd for $C_{30}H_{24}NOCl$ $[M]^+$ 449.1546, found 449.1546.

3.20 1-(4-((4-Fluorophenyl)(phenyl)methyl)-3-phenylisoquinolin-2(1H)-yl)ethan-1-one (4ag/4da)

Yield 81% from **2a** with **3g**, and yield 66% from **2d** with **3a**; white solid; mp 154.9–200.0 °C ($CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35–7.31 (m, 5H), 7.28–7.24 (m, 3H), 7.22–7.16 (m, 5H), 7.07 (t, 1H, *J* = 7.5 Hz), 6.98–6.96 (m, 4H), 5.72 (s, 1H), 5.07 (d, 1H, *J* = 14.0 Hz), 4.89 (d, 1H, *J* = 14.0 Hz), 1.51 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.2, 161.3 (d, *J* = 244 Hz), 142.4, 138.6, 138.3, 137.6, 135.3, 132.0, 130.8 (2C, d, *J* = 7.9 Hz), 129.6, 129.2 (2C), 129.0, 128.8, 128.7, 128.5 (2C), 127.4 (2C), 127.3, 126.6 (2C), 126.5, 125.2, 115.1 (2C, d, *J* = 21.7 Hz), 50.7, 46.5, 24.4; HRMS (EI) *m*/*z* calcd for $C_{30}H_{24}NOF$ $[M]^+$ 433.1842, found 433.1846.

3.21 1-(4-((2-Acetyl-3-phenyl-1,2-dihydroisoquinolin-4-yl)(phenyl)methyl)phenyl)ethan-1-one (4ah)

Yield 85%; white solid; mp 205.9–220.7 °C ($CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.83 (d, 3H, *J* = 8.5 Hz), 7.33–7.29 (m, 11H), 7.16 (t, 2H, *J* = 7.0 Hz), 7.07 (t, 1H, *J* = 7.5 Hz), 6.95 (t, 1H, *J* = 7.5 Hz), 5.79 (s, 1H), 5.10 (d, 1H, *J* = 14.0 Hz), 4.88 (d, 1H, *J* = 14.0 Hz), 2.55 (s, 3H), 1.51 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 197.8, 171.2, 148.4, 141.7, 139.0, 137.5, 135.5, 135.3, 131.9, 129.7, 129.6 (2C), 129.4 (2C), 129.3, 129.2, 129.1, 128.8, 128.6 (2C), 128.4 (2C), 128.2, 127.4, 127.2, 126.8, 126.6, 125.2, 51.5, 46.5, 26.7, 24.4; HRMS (EI) *m*/*z* calcd for $C_{32}H_{27}NO_2$ $[M]^+$ 457.2042, found 457.2037.

3.22 1-(4-(Naphthalen-1-yl(phenyl)methyl)-3-phenylisoquinolin-2(1H)-yl)ethan-1-one (4ai)

Yield 67%; colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.81 (d, 2H, *J* = 8.0 Hz), 7.72 (d, 2H, *J* = 8.0 Hz), 7.54–7.51 (m, 4H), 7.41–7.37 (m, 4H), 7.28–7.17 (m, 3H), 7.10 (d, 2H, *J* = 7.0 Hz), 7.01 (t, 2H, *J* = 7.5 Hz), 6.92 (t, 2H, *J* = 7.0 Hz), 6.18 (s, 1H), 5.00 (d, 1H, *J* = 13.0 Hz), 4.89 (d, 1H, *J* = 13.0 Hz), 1.50 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.3, 143.5, 139.1, 138.3, 137.8, 135.4, 133.9, 132.5, 132.1, 129.7, 129.6 (2C), 129.5, 129.0, 128.9 (2C), 128.7 (2C), 128.5, 128.4, 127.9, 127.8, 127.1, 126.4 (2C), 125.8, 125.5, 125.2 (2C), 125.0, 124.5, 49.5, 46.4, 24.3; HRMS (EI) *m*/*z* calcd for $C_{34}H_{27}NO$ $[M]^+$ 465.2093, found 465.2096

3.23 1-(4-Benzhydryl-3-(4-fluorophenyl)isoquinolin-2(1H)-yl)ethan-1-one (4ba)

Yield 55%; white solid; mp 211.4–229.1 °C ($CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.32–7.29 (m, 2H), 7.27–7.22 (m, 9H), 7.20–7.14 (m, 3H), 7.06 (t, 1H, *J* = 7.5 Hz), 7.00 (t, 2H, *J* = 8.0 Hz), 6.95 (t, 1H, *J* = 7.5 Hz), 5.69 (s, 1H), 4.97 (s, 2H), 1.53 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.2, 162.8 (d, *J* = 250 Hz), 142.4 (2C), 137.4, 135.3, 133.7, 132.1, 131.5 (2C), 129.3 (3C), 129.2 (2C, d, *J* = 7.9 Hz), 128.4 (3C), 127.6 (2C), 127.3, 126.6 (3C), 125.1, 115.9 (2C, d, *J* = 21.6 Hz), 51.4, 46.5, 24.5; HRMS (EI) *m*/*z* calcd for $C_{30}H_{24}NOF$ $[M]^+$ 433.1842, found 433.1843.

3.24 1-(4-Benzhydryl-3-(benzo[d][1,3]dioxol-5-yl)isoquinolin-2(1H)-yl)ethan-1-one (4ca)

Yield 80%; white solid; mp 183.1–250.2 °C ($CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.26–7.24 (m, 8H), 7.19–7.16 (m, 3H), 7.13 (d, 1H, *J* = 7.0 Hz), 7.03 (t, 1H, *J* = 7.0 Hz), 6.93 (t, 1H, *J* = 7.0 Hz), 6.83–6.80 (m, 2H), 6.71 (d, 1H, *J* = 8.0 Hz), 5.95 (s, 2H), 5.79 (s, 1H), 4.94 (s, 2H), 1.60 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.4, 148.1, 147.9, 142.5 (2C), 138.0, 135.2, 132.3, 131.7, 131.4 (2C), 129.4 (3C), 128.3 (3C), 127.5 (2C), 127.1, 126.4 (3C), 125.0, 123.8, 109.8, 108.4, 101.5, 51.5, 46.5, 24.4; HRMS (EI) *m*/*z* calcd for $C_{31}H_{25}NO_3$ $[M]^+$ 459.1834, found 459.1835.

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4. Conclusions

The studies described above have resulted in the synthesis of substituted 1,2-dihydroisoquinolines through a palladium-catalyzed cascade cyclization-coupling of trisubstituted allenamides containing a bromoaryl moiety with arylboronic acids. A variety of substituted 1,2-dihydroisoquinolines were concisely obtained using this methodology because the allenamides, as reaction substrates, were prepared from readily available propargylamines in one step.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/xxx/s1, Copies of the ^{1}H NMR and ^{13}C NMR spectra for all new compounds.

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