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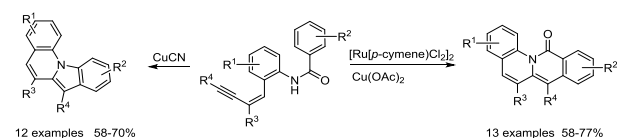
Synthesis of Fused Tetracyclic Compounds *via* Oxidative Annulation: Access to Copper-Catalyzed Indolo[1,2-*a*]Quinolines and to Ruthenium-Catalyzed Isoquinolin-1[2H]-ones

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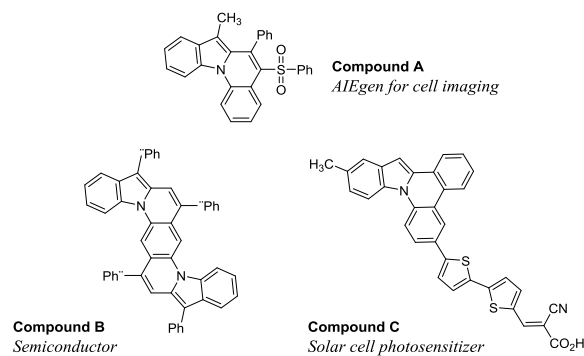


ABSTRACT: A facile double oxidative annulation of (en-3-yn-1-yl)phenylbenzamides was developed allowing us to synthesize fused tetracyclic compounds. Under copper catalysis, the reaction proceeds with high efficiency and leads to new indolo[1,2-*a*]quinolines *via* a decarbonylative double oxidative annulation. On the other hand, under ruthenium catalysis, new isoquinolin-1[2H]-ones were obtained *via* a double oxidative annulation.

INTRODUCTION

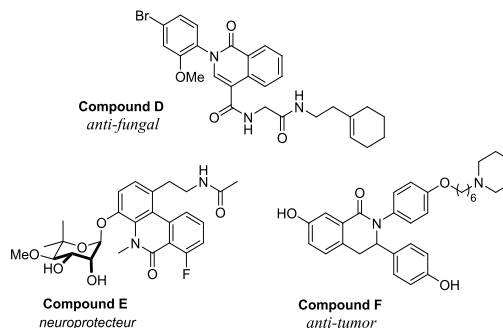
Polycyclic heteroaromatic compounds often exhibit interesting biological and physical properties, as in pharmaceuticals, biologically active products, fluorescent bioimaging probes and optoelectronic materials.¹ Therefore, particular attention has been devoted to design efficient catalytic routes to synthesize these compounds.² Among them, indolo[1,2-*a*]quinoline unit is an important scaffold found in many organic compounds such as functional materials (Figure 1).³ For instance, compound **A** is suitable for applications of one-photon/two-photon targeted imaging in live cell.⁴ compound **B** is an organic semiconductor⁵ and compound **C** a solar cell photosensitizer⁶.

Figure 1. Examples of Indolo[1,2-*a*]quinolines with Application in the Field of Organic Functional Materials.



On the other hand, isoquinolin-1(2H)-ones have attracted considerable attention as a privileged structure present in various biologically active and/or natural products (Figure 2).⁷⁻⁸ For instance, compound **D** is a potent enhancer of anti-fungal activity of fluconazole against *Candida Albicans*.⁹ Compound **E** exhibits neuroprotective activity.¹⁰ While compound **F** shows anti-breast cancer activity.¹¹

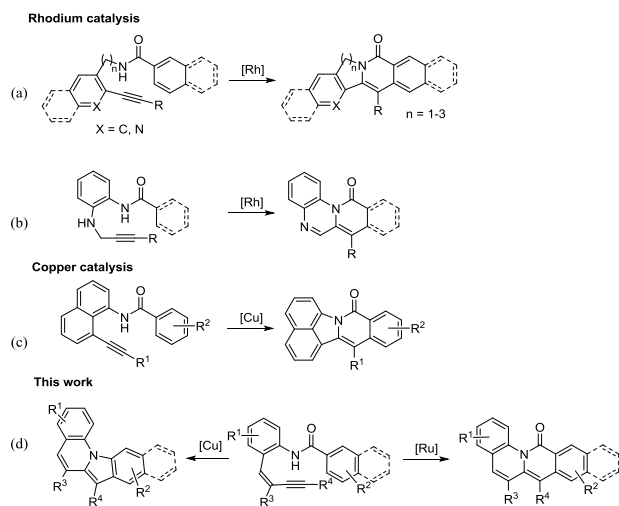
Figure 2. Examples of Bioactive Compounds Containing Isoquinolin-1(2H)-one Scaffolds.



To synthesize such molecules, oxidative addition of benzamides with alkynes has drawn lot of attention as it does not require prefunctionalization of the substrates while affording multi-substituted adducts.¹² In particular, alkynyl-tethered amides, are well-recognized as versatile building blocks towards *N*-containing cyclic architectures, proved to be efficient in intramolecular oxidative annulations, leading to isoquinolinone fused tricyclic com-

pounds.¹³ However, only few examples of access to tetracyclic adducts have been described.¹⁴⁻¹⁶ The group of Song developed a rhodium(III)-catalyzed intramolecular annulation triggered by C-H activation (Scheme 1a).¹⁴ The group of Reddy also used rhodium catalyst to successfully annulate propargyl amino phenyl benzamides to access isoquinolino quinoxalinones (Scheme 1b).¹⁵ More recently, the group of Zhou reported an efficient copper-catalyzed preparation of benzo[3,4]indolo[1,2-*b*]isoquinoline-8-ones (Scheme 1c).¹⁶

Scheme 1. Intramolecular Oxidative Annulation of Alkynyl-tethered Amides



In connection with our research interest focused on the use of organo bis-boranes as versatile intermediates in heterocyclic chemistry,¹⁷ we herein report the synthesis of (*en*-3-*yn*-1-*yl*)phenylbenzamides and their conversion to fused tetra-, and pentacyclic compounds through intramolecular double oxidative annulation (Scheme 1d). Surprisingly, copper catalysis allowed us to obtain new indolo[1,2-*a*]quinolines **5** via a decarbonylative double oxidative annulation. A simple change of the catalytic system to ruthenium opened the way to hitherto unreported isoquinolin-1[2H]-ones **6** via a double oxidative annulation.

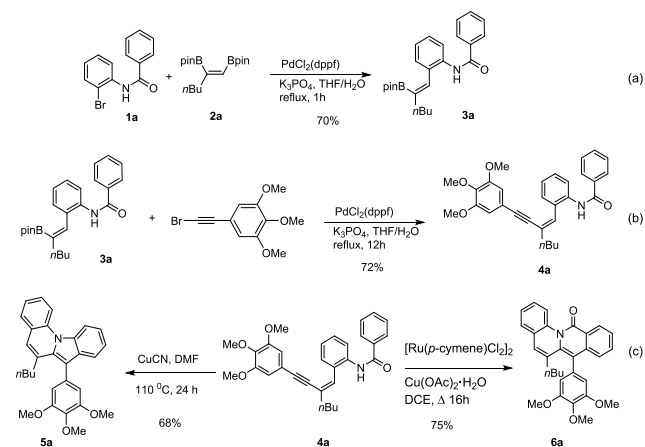
RESULTS AND DISCUSSION

Initially, benzamide **1a** and bispinacol boronate **2a** were selected as model substrates and the alkenylbenzamide **3a**, was obtained in 70% yield, in presence of [1,1'-bis(diphenylphosphino) ferrocene]dichloro palladium(II) and potassium phosphate tribasic monohydrate in THF/H₂O at reflux for 1 hour, via a Suzuki-Miyaura cross-coupling reaction.¹⁸ As previously reported, this reaction occurred regioselectively at the terminal C-B bond with the formation of a single (*E*)-stereomer (Scheme 2a).^{17d,e} Compound **3a** was then engaged in a second Suzuki-Miyaura cross-coupling reaction with 5-(bromoethynyl)-1,2,3-trimethoxybenzene, using the same conditions, heating at reflux 12 hours. The desired alkynyl-tethered benzamide **4a** could be obtained in good yield (Scheme 2b). In order to perform the oxidative annulation

on compound **4a**, we used the conditions described by Zhou,¹⁶ *i.e.* catalysis with CuCN in dimethylformamide (DMF) at 110 °C for one day under air. Surprisingly, it did not result in the expected adduct **6a**, but instead the indolo[1,2-*a*]quinoline **5a**, without carbonyl function, was formed (Scheme 2c, Table 1, entry 1). The structure of this adduct was later confirmed by X-Ray diffraction crystallography (Scheme 4). This interesting result could be a new method to synthesize substituted indolo[1,2-*a*]quinolines.

However, changing the conditions, isoquinolin-1(2H)-one **6a** could be obtained using 2.2 equivalents of copper acetate monohydrate and dichloro(*p*-cymene)ruthenium(II) dimer as catalyst, at reflux of dichloroethane (DCE) for 16h under air (Scheme 2c).¹⁵

Scheme 2. Synthesis of Indolo[1,2-*a*]quinoline **5a** and Isoquinolin-1(2H)-one **6a**



Some other conditions were tested to optimize the yields of **5a**. Changing the solvent to toluene, dichloroethane or *tert*-amyl alcohol did not improve the yields (Table 1, entries 2-4). By changing the catalyst to copper, compound **5a** was obtained in very low yield (Table 1, entry 6).¹⁹ The effect of radical scavengers such as butylated hydroxytoluene (BHT) or 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was also investigated. The desired compound **5a** was obtained in around 50% yield adding 2 equivalents of BHT or TEMPO (Table 1, entries 5 and 6). This result may help us to discard the idea of a radical pathway for its formation.

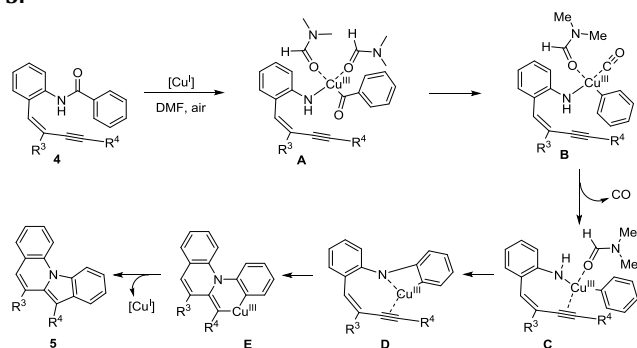
Table 1. Synthesis of Indolo[1,2-*a*]quinolines. Optimization of the Reaction Conditions^a

Entry	Cat.	Additive	Solvent	Yield 5a ^b
1	CuCN		DMF	68
2	CuCN		Tol	12
3	CuCN		<i>t</i> AmOH	29
4	CuCN		DCE ^c	0
5	CuCN	BHT ^c	DMF	49
6	CuCN	TEMPO ^d	DMF	51

^a Reaction conditions: **4a** (0.1 mmol), CuCN (0.02 mmol), solvent (2 mL), under air, 110 °C, 24 h. ^b Yields of isolated products. ^c Radical scavenger butylated hydroxytoluene (44 mg, 0.2 mmol). ^d ^e Radical scavenger 2,2,6,6-tetramethylpiperidine 1-oxyl (31 mg, 0.2 mmol). ^e **4a** (0.1 mmol), Cu (0.01 mmol), DMSO (1 mL), under air, 100 °C, 24 h.

Based on these experimental results and literature,^{16,19} the proposed mechanism for transformation of **4** to **5** is shown in Scheme 3. The formation of the intermediate **A** probably occurred by an oxidative addition under air atmosphere, through a sequential DMF-aided Cu insertion into the amide C-N bond. Decarbonylation assisted by solvent would, then, proceed with the formation of the intermediate **B**.¹⁹ Further support for the proposed mechanism is derived from the fact that replacing of DMF with dichloroethane inhibits the reaction (Table 1, entry 4). The next step would afford the seven-membered ring intermediate **C** with coordination of the alkyne to the metal after elimination of CO. Copper-catalyzed C-H activation would then afford the intermediate **D**. An intramolecular *N*-attacked cis-addition would then occur leading to polycyclic copper species **E**. Finally, this intermediate **E** would undergo a reductive elimination to provide final product **5** with regeneration of Cu^I.¹⁶

Scheme 3. Proposed Reaction Mechanism of Formation of **5**.



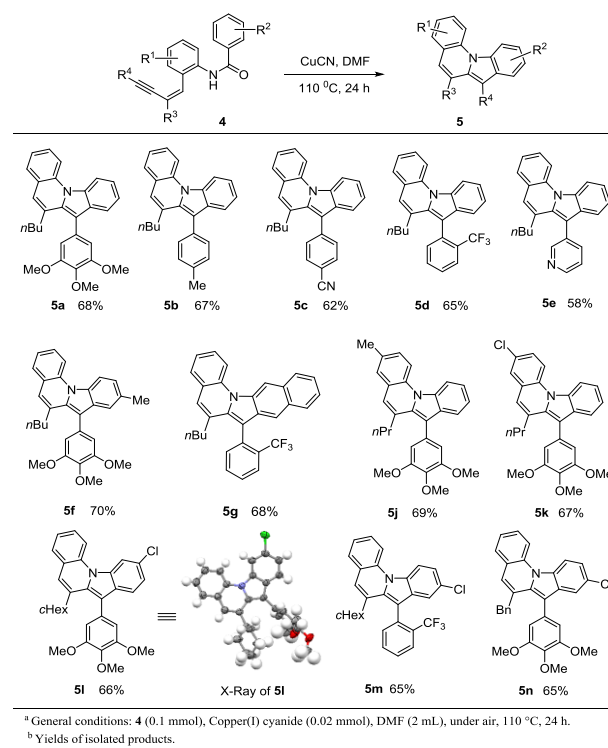
In order to explore the generality of the decarbonylative double oxidative annulation into indolo[1,2-*a*]quinolines **5** as well as the potential of these three steps sequences, we extended these results to various benzamides **1**²⁰ and bispinacol boronates **2**²¹. New (*Z*)-*N*-(2-(2-(pinacolylvinyl)phenyl)benzamide) **3** with methyl or chlorine on aromatic rings could be obtained *via* a Suzuki-Miyaura cross-coupling reaction, in good yields (61-70%) (See SI). Compounds **3** were further engaged in a Suzuki-Miyaura cross-coupling reaction with different (bromoethynyl)benzene derivatives to lead to various (en-3-yn-1-yl)phenylbenzamides **4** in 60% to 72% yields (See SI).

With diversified alkyne-amides in hand, we decided to investigate the scope of the decarbonylative double oxidative annulation with copper cyanide as catalyst.¹⁶ A large variety of indolo[1,2-*a*]quinolines **5** could be prepared by this protocol in good yields (58-70%) (Scheme 4). The indolo[1,2-*a*]quinolines **5** were then fully characterized by

¹H, ¹³C, ¹⁹F NMR and mass spectrometry (see SI). As previously stated, a single crystal of compound **5l** was grown by slow evaporation of a methylene chloride solution and the structure was further ascertained by X-ray diffraction crystallography (Scheme 4).²² It proved that this double oxidative annulation occurred with loss of the carbonyl group.

Exploring the effect of substituents on amide unit, we found that electron-donating methyl substituent (**4f**) was tolerated in *para* to the carbonyl with no loss of reactivity. Incorporation of halogen such as Cl at the same position was also successful giving products **5m** and **5n** in comparable yields. Similarly, annulation reaction tolerated both electron-donating and electron-withdrawing groups in the phenyl substituent of the alkyne like methyl, trimethoxy, cyano and trifluoromethyl groups. It is noteworthy that the reaction of compound **4e** having a pyridine afforded product **5e** in a 58% yield. Moreover, the reaction was proven to be scalable (3.2 mmol) with (*E*)-cyclohexylethenyl-1,2-bis(boronate) **2c** as model substrate, delivering the desired product **5l** in 27% isolated yield over three steps by obtention of intermediates **3h** and **4l** with respectively 62% and 67% yields (see SI for more details). When we extended the study of these oxidative annulation to naphthyl amide, compound **4g** gave access to the indolo[1,2-*a*]quinoline **5g** with fused pentacycles. Unfortunately, under the same conditions, no reaction occurred with compound **4h**, having a thiophenyl group, and the expected product could not be synthesized.

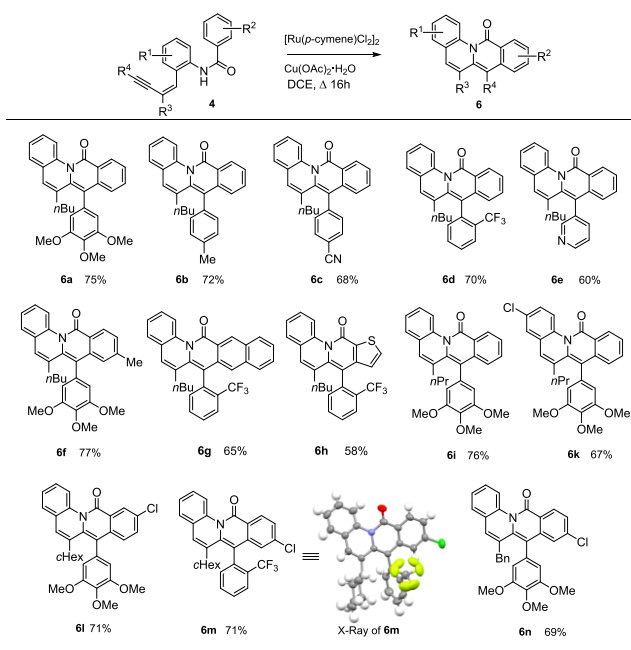
Scheme 4. Scope of Indolo[1,2-*a*]Quinolines **5a,b**



We, then, explored the scope of the double oxidative annulation, this time, with [Ru(*p*-cymene)Cl₂]₂ as catalyst in presence of copper acetate monohydrate.^{15,23} This pro-

vided us a large variety of isoquinolin-1(2H)-ones **6** with good yields (58-77%) (Scheme 5). As observed, for the synthesis of compounds **5**, no significant influence was noticed on changing substituents. The indolo[1,2-*a*]quinolines **6** were, likewise, fully characterized by ^1H , ^{13}C , ^{19}F NMR and mass spectrometry (see SI). ^{13}C NMR spectra display a signal in the 160-165 ppm region that confirms the presence of the carbonyl group of the amide function. The structure of compound **6m** was ascertained by X-ray diffraction crystallography (Scheme 5).²⁴ The synthesis of **6l** could be performed on 1 mmole scale from **3h** without a significant loss of yield (see SI). Isoquinolin-1(2H)-ones **6g** and **6h**, with naphthyl and thiophenyl group respectively, could be obtained in 65% and 58%, giving a fused pentacyclic compound in the case of naphthyl derivative.

Scheme 5. Scope of Isoquinolin-1(2H)-ones 6^{a,b}



^a General conditions: **4** (0.1 mmol), Copper(II) acetate monohydrate (0.22 mmol), $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (0.0025 mmol), DCE (2 mL), under air, reflux, 16 h. ^b Yields of isolated products.

CONCLUSION

In this article, we have developed a simple and efficient route to a large range of fused tetra- and pentacyclic indolo[1,2-*a*]quinoline and isoquinolin-1(2H)-one derivatives through a double oxidative annulation starting from the same enynylphenylbenzamides. It is noticed that the formation of the indolo[1,2-*a*]quinolines occurred with a decarbonylation. A detailed investigation is undertaken on the scope of the reaction to show an excellent functional-group tolerance. These fused compounds may find important applications in the area of biology, as well as in material science and research in these directions is ongoing in our groups.

EXPERIMENTAL SECTION

General Information All solvents and all commercially available chemicals were used without further purification. ^1H

NMR (400 or 500 MHz), ^{13}C NMR (101 or 126 MHz) and ^{19}F (376 MHz) spectra were recorded on Bruker AC 400 and AC 500 spectrometers. Chemical shifts δ are given in ppm, and coupling constants *J* in hertz. Multiplicities are presented as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hex = hexuplet, m = multiplet, ttd = triplet of triplet of doublets. High-resolution mass spectrometry (HRMS) (ESI⁺) was performed using Xevo G2-XS QToF double-focusing mass spectrometer. Purifications by silica gel chromatography were carried out on silica 0.060-0.200 mm, 60 Å. Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 plates. Melting points were measured on a melting-point apparatus Stuart SMP10 and are uncorrected. For the synthesis of compounds **3** and **4** see SI.

Synthesis of Indolo[1,2-*a*]Quinolines 5. In a round bottom flask, were placed compound **4** (0.10 mmol) and CuCN (2 mg, 0.02 mmol) in DMF (2 mL). The resulting suspension was stirred at 110 °C using an oil bath, under air, for 24 h. The reaction mixture was then cooled to room temperature, diluted with water and extracted with ethyl acetate (2 x 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered and evaporated under vacuum. The residue was purified by column chromatography (230-400 mesh Silica gel, EtOAc in Hexane) to give the corresponding cyclized products **5**. The reaction was also carried out on a 0.66 mmol scale for **5l**.

6-Butyl-7-(3,4,5-trimethoxyphenyl)indolo[1,2-*a*]quinolone 5a. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 30 mg (68%). White solid, mp = 190-193 °C. *R*_f = 0.60 (Hexane/EtOAc: 80/20). ^1H NMR (500 MHz, CDCl₃) δ 8.61 (d, *J* = 8.4 Hz, 1H), 8.51 (d, *J* = 8.6 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.57 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 7.45 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.36 (ddd, *J* = 7.8, 7.0, 0.7 Hz, 1H), 7.32 (td, *J* = 7.5, 0.9 Hz, 1H), 6.96 (s, 1H), 6.73 (s, 2H), 3.96 (s, 3H), 3.86 (s, 6H), 2.56-2.52 (m, 2H), 1.46-1.39 (m, 2H), 1.04 (hex, *J* = 7.4 Hz, 2H), 0.74 (t, *J* = 7.4 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) δ 152.9, 138.8, 137.5, 135.2, 132.8, 131.8, 131.4, 129.8, 128.2, 127.9, 127.8, 124.5, 123.3, 122.5, 120.7, 120.3, 115.2, 113.9, 111.3, 108.7, 61.1, 56.2 (2C), 38.0, 33.7, 26.8, 26.0. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ (C₂₉H₃₀NO₃): 440.2226, found 440.2220.

6-Butyl-7-(*p*-tolyl)indolo[1,2-*a*]quinolone 5b. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 24 mg (67%). White solid, mp = 183-187 °C. *R*_f = 0.60 (Hexane/EtOAc: 90/10). ^1H NMR (400 MHz, CDCl₃) δ 8.60 (d, *J* = 8.4 Hz, 1H), 8.50 (d, *J* = 8.6 Hz, 1H), 7.60 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.58-7.53 (m, 2H), 7.43 (ddd, *J* = 8.5, 7.0, 1.3 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.34-7.27 (m, 4H), 6.92 (s, 1H), 2.51-2.46 (m, 2H), 2.47 (s, 3H), 1.38-1.29 (m, 2H), 0.97 (hex, *J* = 7.5 Hz, 2H), 0.69 (t, *J* = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) δ 136.6, 135.9, 133.7, 132.8, 132.4, 132.0, 131.6, 131.5, 128.5, 127.8, 127.6, 124.4, 122.7, 122.4, 122.1, 121.6, 120.0, 115.3, 114.0, 111.8, 33.0, 31.7, 22.3, 21.3, 13.6. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ (C₂₇H₂₆N): 364.2065, found 364.2035.

4-(6-Butylindolo[1,2-*a*]quinolin-7-yl)benzotrionitrile 5c. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 23 mg (62%). Yellow solid, mp = 192-197 °C. *R*_f = 0.50 (Hexane/EtOAc: 90/10). ^1H NMR (400 MHz, CDCl₃) δ 8.63 (d, *J* = 8.5 Hz, 1H), 8.53 (d, *J* = 8.6 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.68-7.55 (m, 4H), 7.49-7.45 (m, 2H), 7.39-7.32 (m, 2H), 7.02 (s, 1H), 2.44 (dd, *J* = 8.0, 7.3 Hz, 2H), 1.36-1.29 (m, 2H), 0.97 (hex, *J* = 7.2 Hz, 2H), 0.70 (t, *J* = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl₃) δ 141.8, 135.6, 132.7, 132.6, 132.5, 132.2, 131.6, 130.6, 128.1, 124.3, 123.6, 123.2, 122.6, 122.3, 119.3, 119.2,

115.5, 114.3, 110.7, 109.7, 33.2, 31.4, 22.3, 13.7. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₇H₂₃N₂): 375.1861, found 375.1838.

6-Butyl-7-(2-(trifluoromethyl)phenyl)indolo[1,2-a]quinolone 5d. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 27 mg (65%). Yellow solid, mp = 197-199 °C. R_f = 0.60 (Hexane/EtOAc: 90/10). ¹H NMR (500 MHz, CDCl₃) δ 8.65 (d, J = 8.4 Hz, 1H), 8.54 (d, J = 8.7 Hz, 1H), 7.88 (dd, J = 7.7, 1.5 Hz, 1H), 7.67-7.52 (m, 5H), 7.46 (ddd, J = 8.5, 6.1, 2.2 Hz, 1H), 7.38-7.29 (m, 3H), 6.97 (s, 1H), 2.42-2.14 (m, 2H), 1.57-1.39 (m, 2H), 1.07 (hex, J = 7.4 Hz, 1H), 0.96 (hex, J = 7.4 Hz, 1H), 0.75 (t, J = 7.4 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 135.9, 135.4, 134.5, 133.5, 133.2, 132.0, 131.5 (q, J = 29.3 Hz), 131.1, 128.1, 128.0, 127.9, 126.2 (q, J = 5.2 Hz), 124.5, 124.2 (q, J = 27.4 Hz), 123.0, 122.7, 122.2, 122.0, 120.1, 115.5, 114.2, 107.6, 32.1, 31.5, 22.6, 13.8. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -59.0. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₇H₂₃F₃N): 418.1783, found 418.1772.

6-Butyl-7-(pyridin-3-yl)indolo[1,2-a]quinolone 5e. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 20 mg (58%). Yellow solid, mp = 201-203 °C. R_f = 0.50 (Hexane/EtOAc: 90/10). ¹H NMR (400 MHz, CDCl₃) δ 8.79 (s, 1H), 8.70 (d, J = 4.1 Hz, 1H), 8.61 (d, J = 8.5 Hz, 1H), 8.52 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.49 (t, J = 7.9 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 6.99 (s, 1H), 2.44 (dd, J = 7.9, 7.9 Hz, 2H), 1.40-1.29 (m, 2H), 1.03-0.93 (m, 2H), 0.71 (t, J = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 151.7, 147.7, 139.4, 135.7, 133.2, 132.6, 132.3, 131.1, 128.15, 128.09, 124.3, 123.4, 123.1, 123, 122.6, 122.3, 119.3, 115.4, 114.3, 107.2, 33.2, 31.4, 22.4, 13.7. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₅H₂₃N₂): 351.1861, found 351.1854.

6-Butyl-9-methyl-7-(3,4,5-trimethoxyphenyl)indolo[1,2-a]quinoline 5f. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 32 mg (70%). White solid, mp = 187-191 °C. R_f = 0.60 (Hexane/EtOAc: 90/10). ¹H NMR (400 MHz, CDCl₃) δ 8.59 (d, J = 8.4 Hz, 1H), 8.36-8.25 (m, 1H), 7.61-7.53 (m, 2H), 7.50 (d, J = 8.1 Hz, 1H), 7.30 (td, J = 7.4, 1.0 Hz, 1H), 7.20 (dd, J = 8.1, 1.3 Hz, 1H), 6.90 (s, 1H), 6.72 (s, 2H), 3.95 (s, 3H), 3.86 (s, 6H), 2.67 (s, 3H), 2.57-2.49 (m, 2H), 1.49-1.37 (m, 2H), 1.04 (hex, J = 7.4 Hz, 2H), 0.73 (t, J = 7.4 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 152.8, 137.3, 135.9, 133.8, 132.5, 132.4, 132.1, 131.8, 129.4, 127.9, 127.7, 124.6, 123.8, 122.8, 122.3, 119.8, 115.5, 114.2, 111.7, 109.1, 61.1, 56.3 (2C), 33.1, 32.4, 22.7, 22.6, 13.9. HRMS (ESI⁺) calculated for [M+H]⁺ (C₃₀H₃₂NO₃): 454.2382, found 454.2381.

6-Butyl-7-(2-(trifluoromethyl)phenyl)benzo[5,6]indolo[1,2-a]quinoline 5g. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 32 mg (68%). White solid, mp = 205-208 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.74 (d, J = 8.5 Hz, 1H), 8.68 (d, J = 9.3 Hz, 1H), 8.04-7.91 (m, 2H), 7.78 (d, J = 9.3 Hz, 1H), 7.74-7.65 (m, 4H), 7.60 (ddd, J = 8.7, 7.3, 1.6 Hz, 1H), 7.44-7.36 (m, 2H), 7.23-7.15 (m, 2H), 6.98 (s, 1H), 2.31-2.13 (m, 2H), 1.46 (quint, J = 7.6 Hz, 2H), 1.07 (hex, J = 7.4 Hz, 1H), 0.96 (hex, J = 7.2 Hz, 1H), 0.75 (t, J = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 137.8, 134.9, 134.4, 133.4, 132.3, 131.8, 131.5 (q, J = 29.3 Hz), 130.6, 129.3, 128.5, 128.43, 128.37, 128.1, 127.5, 126.6 (q, J = 5.3 Hz), 125.6, 125.1, 124.9, 124.3, 124.2 (q, J = 27.5 Hz), 123.9, 123.6, 123.3, 121.6, 116.4, 114.8, 109.4, 31.8, 31.8, 22.7, 13.9. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -60.6. HRMS (ESI⁺) calculated for [M+H]⁺ (C₃₁H₂₅F₃N): 468.1939, found 468.1918.

3-Methyl-6-propyl-7-(3,4,5-trimethoxyphenyl)indolo[1,2-a]quinolone 5j. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 30 mg (69%). White solid, mp = 186-189 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz,

CDCl₃) δ 8.53 (d, J = 8.5 Hz, 1H), 8.44 (s, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.93 (s, 1H), 6.74 (s, 2H), 3.98 (s, 3H), 3.87 (s, 6H), 2.62 (s, 3H), 2.52-2.44 (m, 2H), 1.47 (hex, J = 7.3 Hz, 2H), 0.68 (t, J = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 152.7, 138.1, 137.3, 135.9, 132.8, 132.2, 132.0, 131.7, 131.4, 127.8, 124.0, 123.0, 122.12, 122.08, 121.9, 120.0, 115.8, 114.2, 111.5, 109.1, 61.2, 56.3 (2C), 35.2, 23.6, 22.4, 13.9. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₉H₃₀NO₃): 440.2226, found 440.2220.

3-Chloro-6-propyl-7-(3,4,5-trimethoxyphenyl)indolo[1,2-a]quinolone 5k. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 29 mg (67%). White solid, mp = 193-197 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (500 MHz, CDCl₃) δ 8.49 (d, J = 8.9 Hz, 1H), 8.41 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.48 (dd, J = 8.9, 2.5 Hz, 1H), 7.46 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 6.85 (s, 1H), 6.72 (s, 2H), 3.97 (s, 3H), 3.87 (s, 6H), 2.51-2.47 (m, 2H), 1.48 (hex, J = 7.5 Hz, 2H), 0.68 (t, J = 7.3 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 152.8, 137.4, 134.9, 134.2, 132.1, 131.9, 131.3, 131.2, 127.9, 127.5, 127.1, 125.9, 122.8, 122.2, 121.7, 120.3, 116.5, 113.9, 112.4, 109.1, 61.1, 56.3 (2C), 35.1, 23.5, 13.9. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₈H₂₇ClNO₃): 460.1679, found 460.1674.

10-Chloro-6-cyclohexyl-7-(3,4,5-trimethoxyphenyl)indolo[1,2-a]quinolone 5l. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 33 mg (66%), 211 mg (64%) on a 0.66 mmol scale. White solid, mp = 194-198 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.49 (d, J = 1.6 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H), 7.62 (dd, J = 7.7, 1.4 Hz, 1H), 7.58 (ddd, J = 8.7, 7.4, 1.6 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.33 (td, J = 7.5, 0.8 Hz, 1H), 7.31 (dd, J = 8.5, 1.7 Hz, 1H), 7.00 (s, 1H), 6.69 (s, 2H), 3.96 (s, 3H), 3.85 (s, 6H), 2.72 (tt, J = 11.6, 2.7 Hz, 1H), 1.82 (d, J = 12.4 Hz, 1H), 1.75-1.51 (m, 4H), 1.34 (tdd, J = 12.8, 12.8, 3.3 Hz, 2H), 1.14 (ttd, J = 13.1, 13.1, 3.7 Hz, 1H), 0.98-0.72 (m, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 153.0, 139.0, 137.7, 135.3, 133.0, 132.0, 131.5, 129.9, 128.3, 128.1, 128.0, 124.7, 123.4, 122.6, 120.9, 120.4, 115.3, 114.1, 111.4, 108.9, 61.2, 56.4 (2C), 38.2, 33.9, 26.9, 26.2. HRMS (ESI⁺) calculated for [M+H]⁺ (C₃₁H₃₁ClNO₃): 500.1992, found 500.1987.

9-Chloro-6-cyclohexyl-7-(2-(trifluoromethyl)phenyl)indolo[1,2-a]quinoline 5m. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 31 mg (65%). White solid, mp = 190-195 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (400 MHz, CDCl₃) δ 8.51 (d, J = 1.4 Hz, 1H), 8.49 (s, 1H), 7.92-7.85 (m, 1H), 7.72-7.55 (m, 4H), 7.48 (dd, J = 6.9, 1.6 Hz, 1H), 7.34 (td, J = 7.5, 0.8 Hz, 1H), 7.28 (dd, J = 8.6, 1.7 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.01 (s, 1H), 2.26 (tt, J = 11.8, 2.7 Hz, 1H), 1.81-1.65 (m, 3H), 1.55-1.46 (m, 3H), 1.20-1.01 (m, 2H), 0.80 (ttd, J = 13.3, 13.3, 3.8 Hz, 1H), 0.36 (ttd, J = 13.1, 12.8, 3.4 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 138.7, 135.3, 135.1, 133.9, 133.8, 132.1, 131.5, 131.4 (q, J = 29.3 Hz), 130.3, 128.4, 128.2, 128.1, 127.9, 126.3 (q, J = 5.3 Hz), 124.7, 124.2 (q, J = 27.4 Hz), 123.4, 122.7, 121.1, 120.8, 115.4, 114.1, 107.1, 38.2, 35.2, 31.7, 26.9, 26.6, 26.1. ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ -59.9. HRMS (ESI⁺) calculated for [M+H]⁺ (C₂₉H₂₄ClF₃N): 478.1549, found 478.1532.

6-Benzyl-9-chloro-7-(3,4,5-trimethoxyphenyl)indolo[1,2-a]quinolone 5n. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 33 mg (65%). White solid, mp = 201-204 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ¹H NMR (500 MHz, CDCl₃) δ 8.51 (d, J = 1.5 Hz, 1H), 8.51 (d, J = 8.3 Hz, 1H), 7.68-7.58 (m, 2H), 7.44 (d, J = 8.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.30 (dd, J = 8.5, 1.6 Hz, 1H), 7.16-7.11 (m, 3H), 6.91 (s, 1H),

6.83-6.80 (m, 2H), 6.38 (s, 2H), 3.97 (s, 2H), 3.95 (s, 3H), 3.68 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 152.5, 139.2, 137.2, 135.6, 132.7, 131.9, 130.3, 130.2, 129.7, 128.5, 128.3, 128.2, 128.1, 125.9, 125.7, 124.1, 123.3, 122.5, 120.8, 115.2, 113.9, 112.3, 108.7, 60.9, 55.9, 39.0. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{32}\text{H}_{27}\text{ClNO}_3$): 508.1679, found 508.1674.

Synthesis of Isoquinolones 6. In a round bottom flask, were placed compound **4** (0.10 mmol) in DCE (2 mL), $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ (1.5 mg, 0.0025 mmol) and $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ (44 mg, 0.22 mmol) were then added. The resulting suspension was stirred at reflux, using an oil bath, under air, for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by column chromatography (230-400 mesh Silica gel, EtOAc in Hexane) to give the corresponding cyclized products **6**. The reaction was also carried out on a 0.66 mmol scale for **6l**.

6-Butyl-7-(3,4,5-trimethoxyphenyl)-12H-isoquinolino[2,3-a]quinolin-12-one 6a. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 35 mg (75%). White solid, mp = 168-172 °C. R_f = 0.50 (Hexane/EtOAc: 80/20). ^1H NMR (500 MHz, CDCl_3) δ 8.56 (d, J = 8.9 Hz, 1H), 7.91 (s, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.36-7.31 (m, 2H), 7.27-7.23 (m, 2H), 6.85 (s, 1H), 4.06 (s, 3H), 3.91 (s, 3H), 3.11 (s, 3H), 1.55-1.50 (m, 2H), 1.12-1.05 (m, 2H), 0.90 (hex, J = 7.4 Hz, 2H), 0.69 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 163.7, 153.5, 138.2, 136.6, 135.8, 135.1, 134.0, 133.5, 132.6, 128.5, 128.3, 127.2, 126.7, 126.4, 125.5, 125.4, 125.3, 125.1, 120.4, 117.6, 109.2, 61.3, 56.4 (2C), 35.2, 32.7, 22.5, 13.9. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{30}\text{H}_{30}\text{NO}_4$): 468.2175, found 468.2169.

6-Butyl-7-(p-tolyl)-12H-isoquinolino[2,3-a]quinolin-12-one 6b. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 28 mg (72%). White solid, mp = 175-178 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ^1H NMR (400 MHz, CDCl_3) δ 8.76 (s, 1H), 8.74-8.73 (m, 1H), 8.65-8.58 (m, 1H), 7.62-7.48 (m, 2H), 7.36-7.31 (m, 2H), 7.31-7.20 (m, 5H), 6.85 (d, J = 0.9 Hz, 1H), 2.47 (s, 3H), 1.81-1.74 (m, 2H), 1.21-1.13 (m, 2H), 0.94 (hex, J = 7.3 Hz, 2H), 0.70 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 163.7, 138.1, 136.8, 136.0, 135.2, 135.0, 134.1, 132.5, 132.0, 129.4, 128.2, 127.1, 126.6, 126.3, 125.5, 125.3, 125.2, 120.4, 117.9, 35.4, 31.9, 22.3, 21.5, 13.9. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{28}\text{H}_{26}\text{NO}$): 392.2014, found 392.1998.

4-(6-Butyl-12-oxo-12H-isoquinolino[2,3-a]quinolin-7-yl)benzonitrile 6c. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 27 mg (68%). Yellow solid, mp = 178-182 °C. R_f = 0.60 (Hexane/EtOAc: 80/20). ^1H NMR (400 MHz, CDCl_3) δ 8.11 (d, J = 8.1 Hz, 1H), 7.93 (s, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.63-7.59 (m, 1H), 7.59-7.56 (m, 1H), 7.51 (dd, J = 5.0, 1.1 Hz, 1H), 7.42 (d, J = 7.0 Hz, 1H), 7.39-7.32 (m, 3H), 7.20 (td, J = 7.6, 1.1 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 6.74 (s, 1H), 2.51-2.45 (m, 2H), 1.76-1.67 (m, 2H), 1.44 (hex, J = 7.4 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 163.4, 143.6, 135.5, 134.8, 134.2, 133.0, 132.8, 132.3, 131.0, 129.3, 128.4, 127.5, 126.9, 126.4, 125.5, 125.0, 124.8, 124.4, 120.2, 118.6, 115.4, 112.0, 35.5, 31.6, 22.1, 13.7. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{28}\text{H}_{23}\text{N}_2\text{O}$): 403.1810, found 403.1799.

6-Butyl-7-(2-(trifluoromethyl)phenyl)-12H-isoquinolino[2,3-a]quinolin-12-one 6d. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 31 mg (70%). Yellow solid, mp = 179-182 °C. R_f = 0.70 (Hexane/EtOAc: 80/20). ^1H NMR (400

MHz, CDCl_3) δ 8.65-8.63 (m, 1H), 8.52-8.50 (m, 1H), 7.75 (dd, J = 7.6, 1.5 Hz, 1H), 7.58-7.51 (m, 2H), 7.46-7.39 (m, 2H), 7.37-7.35 (m, 1H), 7.29-7.25 (m, 1H), 7.24 (s, 1H), 7.19-7.15 (m, 1H), 6.79 (s, 1H), 6.69-6.66 (m, 1H), 1.78-1.70 (m, 1H), 1.56-1.48 (m, 1H), 1.21-1.13 (m, 2H), 0.95-0.79 (m, 2H), 0.64 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 164.3, 137.5, 137.1, 135.0, 134.9, 134.8, 134.4, 132.5, 131.7, 131.4 (q, J = 29.8 Hz), 128.7, 128.2, 127.9, 127.1, 126.8 (q, J = 4.9 Hz), 126.6, 126.4, 125.4, 125.3, 124.95, 124.89, 123.9 (q, J = 274.4 Hz), 120.6, 113.0, 34.7, 31.8, 22.3, 13.8. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3) δ -60.0. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{28}\text{H}_{23}\text{F}_3\text{NO}$): 446.1732, found 446.1713.

6-Butyl-7-(pyridin-3-yl)-12H-isoquinolino[2,3-a]quinolin-12-one 6e. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 23 mg (60%). Yellow solid, mp = 186-189 °C. R_f = 0.40 (Hexane/EtOAc: 80/20). ^1H NMR (400 MHz, CDCl_3) δ 8.80 (s, 1H), 8.77-8.70 (m, 1H), 8.68-8.61 (m, 1H), 8.01 (d, J = 7.1 Hz, 1H), 7.69 (s, 1H), 7.63 (t, J = 6.9 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.42-7.37 (m, 2H), 7.30 (td, J = 7.6, 1.1 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 7.00 (s, 1H), 1.80-1.73 (m, 1H), 1.65-1.58 (m, 1H), 1.24-1.15 (m, 2H), 0.96 (hex, J = 7.2 Hz, 2H), 0.71 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 163.5, 150.7, 147.5, 141.4, 135.9, 135.6, 135.0, 133.9, 133.1, 129.9, 128.7, 127.7, 127.1, 126.7, 125.7, 125.2, 124.9, 124.3, 120.3, 112.6, 36.0, 31.4, 22.2, 13.9. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{26}\text{H}_{23}\text{N}_2\text{O}$): 379.1805, found 379.1788.

6-Butyl-9-methyl-7-(3,4,5-trimethoxyphenyl)-12H-isoquinolino[2,3-a]quinolin-12-one 6f. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 37 mg (77%). White solid, mp = 165-169 °C. R_f = 0.50 (Hexane/EtOAc: 80/20). ^1H NMR (400 MHz, CDCl_3) δ 8.73 (d, J = 8.8 Hz, 1H), 8.51 (d, J = 8.2 Hz, 1H), 7.39-7.31 (m, 3H), 7.27-7.23 (m, 1H), 7.08 (s, 1H), 6.86 (s, 1H), 6.58 (s, 2H), 3.97 (s, 3H), 3.83 (s, 6H), 2.42 (s, 3H), 1.86-1.82 (m, 2H), 1.23-1.18 (m, 2H), 0.99 (hex, J = 7.4 Hz, 2H), 0.73 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 163.5, 153.4, 143.2, 138.1, 136.6, 135.8, 135.1, 134.1, 133.4, 128.3, 128.2, 127, 126.2, 125.2, 125.1, 124.9, 122.9, 120.4, 117.4, 109.1, 61.2, 56.3 (2C), 35.1, 32.6, 22.4, 22.3, 13.8. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{31}\text{H}_{32}\text{NO}_4$): 482.2331, found 482.2307.

6-Butyl-7-(2-(trifluoromethyl)phenyl)-14H-benzo[6,7]isoquinolino[2,3-a]quinolin-14-one 6g. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 32 mg (65%). Yellow solid, mp = 177-180 °C. R_f = 0.50 (Hexane/EtOAc: 90/10). ^1H NMR (400 MHz, CDCl_3) δ 10.19 (d, J = 8.6 Hz, 1H), 8.78 (d, J = 8.4 Hz, 1H), 7.91-7.84 (m, 3H), 7.84 (d, J = 9.0 Hz, 1H), 7.82-7.78 (m, 1H), 7.70-7.65 (m, 2H), 7.63 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 7.53-7.44 (m, 1H), 7.44-7.37 (m, 2H), 7.30 (td, J = 7.4, 1.0 Hz, 1H), 7.26 (s, 1H), 7.02 (s, 1H), 6.78 (d, J = 9.0 Hz, 1H), 1.94-1.84 (m, 1H), 1.71-1.60 (m, 1H), 1.37-1.26 (m, 2H), 1.00 (hex, J = 7.4 Hz, 1H), 0.93 (hex, J = 7.2 Hz, 1H), 0.73 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 165.3, 138.3, 138.1, 135.9, 135.0, 134.7, 134.6, 133.6, 132.0, 131.9, 131.7 (q, J = 29.7 Hz), 131.4, 128.9, 128.8, 128.7, 128.5, 127.3, 127.1, 126.9 (q, J = 5.0 Hz), 126.6, 126.5, 125.5, 124.9, 124.3 (q, J = 274.5 Hz), 123.4, 120.4, 118.0, 112.5, 34.5, 32.0, 22.4, 13.9. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3) δ -59.6. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{32}\text{H}_{25}\text{F}_3\text{NO}$): 496.1883, found 496.1862.

6-Butyl-7-(2-(trifluoromethyl)phenyl)-11H-thieno[3',2':4,5]pyrido[1,2-a]quinolin-11-one 6h. Purified by flash column chromatography (EtOAc/Hexane = 1/9); 26 mg (58%). Yellow solid, mp = 186-189 °C. R_f = 0.60 (Hexane/EtOAc: 90/10). ^1H NMR (400 MHz, CDCl_3) δ 9.11 (d, J = 9.1 Hz, 1H), 7.82 (dd, J = 7.8, 1.4 Hz, 1H), 7.65 (dtd, J = 7.4, 7.5, 1.4 Hz, 1H), 7.64-7.57 (m, 2H), 7.52 (d, J = 7.2 Hz, 1H), 7.43-7.39

(m, 2H), 7.33 (ddd, $J = 7.3, 7.3, 1.0$ Hz, 1H), 6.99 (s, 1H), 6.48 (d, $J = 5.3$ Hz, 1H), 2.04-1.88 (m, 1H), 1.80-1.72 (m, 1H), 1.34-1.26 (m, 2H), 0.99 (hex, $J = 7.7$ Hz, 1H), 0.90 (hex, $J = 6.7$ Hz, 1H), 0.72 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 160.2, 145.6, 138.1, 136.7, 135.0, 134.7, 133.7, 133.4, 131.7, 130.5 (q, $J = 29.6$ Hz), 128.7, 128.2, 127.7, 126.8 (q, $J = 4.9$ Hz), 126.4, 125.8, 125.3, 124.9, 123.5 (q, $J = 275.1$ Hz), 121.4, 111.7, 34.8, 31.9, 22.3, 13.8. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3) δ -59.9. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{26}\text{H}_{21}\text{F}_3\text{NOS}$): 452.1296, found 452.1282.

6-Propyl-7-(3,4,5-trimethoxyphenyl)-12H-isoquinolino[2,3-a]quinolin-12-one 6i. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 36 mg (76%). White solid, mp = 161-164 °C. $R_f = 0.50$ (Hexane/EtOAc: 80/20). ^1H NMR (400 MHz, CDCl_3) δ 8.74 (d, $J = 8.6$ Hz, 1H), 8.61 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.62 (ddd, $J = 8.3, 7.1, 1.5$ Hz, 1H), 7.54 (ddd, $J = 8.1, 7.1, 1.2$ Hz, 1H), 7.39-7.28 (m, 3H), 7.31-7.22 (m, 1H), 6.88 (s, 1H), 6.59 (s, 2H), 3.96 (s, 3H), 3.83 (s, 6H), 1.94-1.78 (m, 2H), 1.27 (hex, $J = 7.3$ Hz, 2H), 0.62 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 163.7, 153.5, 138.3, 136.6, 135.7, 135.2, 133.9, 133.4, 132.6, 128.7, 128.3, 127.2, 126.7, 126.4, 125.5, 125.4, 125.2, 125.1, 120.5, 117.6, 109.1, 61.4, 56.4 (2C), 37.5, 23.7, 13.7. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{29}\text{H}_{28}\text{NO}_4$): 454.2013, found 454.1996.

3-Chloro-6-propyl-7-(3,4,5-trimethoxyphenyl)-12H-isoquinolino[2,3-a]quinolin-12-one 6k. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 33 mg (67%). White solid, mp = 172-175 °C. $R_f = 0.60$ (Hexane/EtOAc: 80/20). ^1H NMR (400 MHz, CDCl_3) δ 8.70 (d, $J = 9.1$ Hz, 1H), 8.59 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.63 (ddd, $J = 8.4, 7.1, 1.5$ Hz, 1H), 7.55 (ddd, $J = 8.0, 6.9, 1.0$ Hz, 1H), 7.32 (d, $J = 7.9$ Hz, 1H), 7.31 (d, $J = 2.5$ Hz, 1H), 7.27 (dd, $J = 9.5, 2.5$ Hz, 1H), 6.79 (s, 1H), 6.58 (s, 2H), 3.96 (s, 3H), 3.83 (s, 6H), 1.86-1.78 (m, 2H), 1.26 (hex, $J = 7.3$ Hz, 2H), 0.62 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 163.5, 153.6, 138.4, 137.2, 136.5, 133.5, 133.3, 133.1, 132.8, 130.4, 128.2, 127.5, 127.0, 126.9, 126.8, 125.6, 125.5, 125.0, 122.0, 118.3, 109.0, 61.3, 56.4 (2C), 37.5, 23.6, 13.7. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{29}\text{H}_{27}\text{ClNO}_4$): 488.1629, found 488.1607.

9-Chloro-6-cyclohexyl-7-(3,4,5-trimethoxyphenyl)-12H-isoquinolino[2,3-a]quinolin-12-one 6l. Purified by flash column chromatography (EtOAc/Hexane = 2/8); 37 mg (71%), 240 mg (69%) on a 0.66 mmol scale. White solid, mp = 178-181 °C. $R_f = 0.60$ (Hexane/EtOAc: 80/20). ^1H NMR (500 MHz, CDCl_3) δ 8.69 (d, $J = 8.5$ Hz, 1H), 8.53 (d, $J = 8.6$ Hz, 1H), 7.47 (dd, $J = 8.6, 2.0$ Hz, 1H), 7.38 (dd, $J = 7.5, 1.6$ Hz, 1H), 7.37-7.33 (m, 2H), 7.28 (td, $J = 7.4, 1.0$ Hz, 1H), 6.99 (s, 1H), 6.57 (s, 1H), 3.97 (s, 3H), 3.84 (s, 6H), 1.86 (tt, $J = 11.5, 2.9$ Hz, 1H), 1.66-1.50 (m, 4H), 1.13 (tdd, $J = 12.7, 12.7, 2.8$ Hz, 2H), 1.09-0.97 (m, 2H), 0.76 (ttd, $J = 12.4, 12.4, 3.4$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 163.1, 153.9, 140.7, 139.3, 138.5, 137.8, 135.3, 134.7, 133.2, 130.1, 127.4, 127.1, 126.74, 126.66, 125.5, 125.1, 124.7, 123.4, 120.0, 116.4, 108.8, 61.4, 56.5 (2C), 39.4, 34.1, 27.0, 26.2. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{32}\text{H}_{31}\text{ClO}_4\text{N}$): 528.1942, found 528.1918.

9-Chloro-6-cyclohexyl-7-(2-(trifluoromethyl)phenyl)-12H-isoquinolino[2,3-a]quinolin-12-one 6m. Purified by flash column chromatography EtOAc/Hexane = 1/9); 36 mg (71%). Yellow solid, mp = 170-173 °C. $R_f = 0.60$ (Hexane/EtOAc: 90/10). ^1H NMR (400 MHz, CDCl_3) δ 8.67 (d, $J = 8.3$ Hz, 1H), 8.51 (d, $J = 8.6$ Hz, 1H), 7.89 (dd, $J = 7.6, 1.5$ Hz, 1H), 7.78-7.63 (m, 2H), 7.44 (dd, $J = 8.6, 1.9$ Hz, 1H), 7.42 (d, $J = 8.5$ Hz, 1H), 7.39-7.32 (m, 2H), 7.30-7.24 (m, 1H), 7.01 (s, 1H), 6.71 (d, $J = 1.9$ Hz, 1H), 1.75 (tt, $J = 11.4, 2.7$ Hz, 1H), 1.66-1.47 (m, 5H), 1.32 (tdd, $J = 12.0, 11.9, 2.8$ Hz, 1H), 1.11-0.91 (m, 2H), 0.64

(ttd, $J = 12.5, 12.5, 3.9$ Hz, 1H), 0.50 (ttd, $J = 12.9, 12.7, 3.9$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 163.8, 140.2, 139.1, 138.3, 137.0, 135.9, 134.6, 133.9, 132.6, 131.2 (q, $J = 29.8$ Hz), 129.8, 129.0, 127.4, 127.4 (q, $J = 4.4$ Hz), 127.3, 127.0, 126.7, 125.6, 124.9, 124.6, 123.9 (q, $J = 274.4$ Hz), 123.1, 120.2, 111.8, 39.1, 34.8, 32.9, 26.8, 26.4, 25.9. $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3) δ -60.6. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{30}\text{H}_{24}\text{ClF}_3\text{NO}$): 506.1499, found 506.1492.

6-Benzyl-9-chloro-7-(3,4,5-trimethoxyphenyl)-12H-isoquinolino[2,3-a]quinolin-12-one 6n. Purified by flash column chromatography EtOAc/Hexane = 2/8); 37 mg (69%). White solid, mp = 182-186 °C. $R_f = 0.60$ (Hexane/EtOAc: 80/20). ^1H NMR (400 MHz, CDCl_3) δ 8.56 (d, $J = 8.5$ Hz, 1H), 7.66-7.57 (m, 4H), 7.38 (td, $J = 7.4, 7.2, 0.9$ Hz, 1H), 7.32 (d, $J = 8.6$ Hz, 1H), 7.12 (s, 1H), 7.05-7.01 (m, 3H), 6.95 (dd, $J = 7.1, 2.4$ Hz, 2H), 6.49 (s, 1H), 4.06 (s, 2H), 4.02 (s, 3H), 3.67 (s, 3H), 3.60 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 192.4, 151.3, 141.7, 139.9, 139.1, 138.3, 138.2, 137.9, 134.1, 131.5, 130.4, 129.4, 128.7, 128.4, 128.1, 127.9, 127.4, 127.2, 126.4, 124.3, 123.8, 120.6, 120.5, 110.9, 97.0, 62.2, 61.8, 56.1, 39.8. HRMS (ESI⁺) calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{33}\text{H}_{27}\text{ClNO}_4$): 536.1629, found 536.1616.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information Statement

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data of compounds **3** and **4**, ^1H , ^{13}C , ^{11}B and ^{19}F NMR spectra for new compounds **3-6**, X-ray crystallography data of compounds **5I** and **6m** (file type, i.e., PDF)

Accession Codes

CCDC 2205942 and **2205943** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Singh, R.; Kumar, S.; Patil, M. T.; Sun, C.-M.; Salunke, D. B. Post-Pictet-Spengler Cyclization (PPSC): A Strategy to Synthesize Polycyclic β -Carboline-Derived Natural Products and Biologically Active *N*-Heterocycles. *Adv. Synth. Catal.* **2020**, *362*, 4027-4077. (b) Gupta, V.; Sirohi, P.; Singh, N.; Singh, R. P. Design and development of fluorescence-capable novel pyrazine-based polycyclic heteroaromatics for cellular bioimaging. *New J. Chem.* **2020**, *44*, 17714. (c) Wu, H.; Zhang, J.; Ren, Y.; Zhang, Y.; Yuan, Y.; Shen, Z.; Li, S.; Wang, P. Tuning the Color Palette of Semi-Transparent Solar Cells via Lateral π -Extension of Polycyclic Heteroaromatics of Donor-Acceptor Dyes. *ACS Appl. Energy Mater.* **2020**, *3*, 4549-4558. (d) Rossi, R.; Lessia, M.; Manzinia, C.; Marianetti, G.; Bellina, F. Direct (Hetero)arylation Reactions of (Hetero)arenes as Tools for the Step- and Atom-Economical Synthesis of Biologically Active Unnatural Compounds Including Pharmaceutical Targets. *Synthesis* **2016**, *48*, 3821-3862.

(2) See reviews and references therein: (a) Nishii, Y.; Miura, M. Construction of Benzo-Fused Polycyclic Heteroaromatic Compounds through Palladium-Catalyzed Intramolecular C-H/C-H Biaryl Coupling. *Catalysts* **2023**, *13*, 12. (b) Stepień, M.; Gońka, E.; Żyła, M.; Sprutta, N. Heterocyclic Nanographenes and Other Polycyclic Heteroaromatic Compounds: Synthetic Routes, Properties, and Applications. *Chem. Rev.* **2022**, *122*, 565-788. (c) Zhao, Q.; Choy, P. Y.; Li, L.; Kwong, F. Y. Recent explorations of palladium-catalyzed regioselective aromatic extension processes. *Tetrahedron Lett.* **2021**, *62*, 152670. (d) Hagui, W.; Doucet, H.; Soule, J.-F. Application of Palladium-Catalyzed C(sp²)-H Bond Arylation to the Synthesis of Polycyclic (Hetero)Aromatics. *Chem.* **2019**, *5*, 2006-2078.

(3) For examples of synthesis of Indolo[1,2-*a*]Quinolines, see and references therein: (a) Heckershoff, R.; May, G.; Däumer, J.; Eberle, K.; Krämer, P.; Rominger, F.; Rudolph, M.; Mulks, F. F.; Hashmi, A. S. K.

Entropy-Induced Selectivity Switch in Gold Catalysis: Fast Access to Indolo[1,2-*a*]quinolines. *Chem. Eur. J.* **2022**, e202201816. (b) Yao, Y.; Alami, M.; Hamze, A.; Provot, O. Recent Advances in the Synthesis of Pyrindo[1,2-*a*]indoles. *Org. Biomol. Chem.* **2021**, *19*, 3509-3526. (c) Thanetchaiyakup, A.; Borwornpinyo, S.; Rattanarat, H.; Kanjanasirirat, P.; Jearawuttanakul, K.; Seemakhan, S.; Chuanopparat, N.; Ngermmeesri, P. Copper-catalyzed synthesis and anticancer activity evaluation of indolo[1,2-*a*]quinoline derivatives. *Tetrahedron Lett.* **2021**, *82*, 153365.

(4) (a) Sun, K.; Zhang, Y.-L.; Chen, X.-L.; Su, H.-F.; Peng, Q.-C.; Yu, B.; Qu, L.-B.; Li, K. A Type of Atypical AIEgen Used for One-Photon/Two-Photon Targeted Imaging in Live Cells. *ACS Appl. Bio Mater.* **2020**, *3*, 505-511.

(5) (a) Choi, H. H.; Najafov, H.; Kharlamov, N.; Kuznetsov, D. V.; Didenko, S. I.; Cho, K.; Briseno, A. L.; Podzorov, V. Polarization-Dependent Photoinduced Bias-Stress Effect in Single-Crystal Organic Field-Effect Transistors. *ACS Appl. Mater. Interfaces* **2017**, *9*, 34153-34161. (b) Zhu, L.; Kim, E.-G.; Yi, Y.; Ahmed, E.; Jenekhe, S.A.; Coropceanu, V.; Brédas, J.-L. Charge-Transport Properties of the Tetraphenylbis(indolo[1,2-*a*]quinoline and 5,7-Diphenylindolo[1,2-*a*]quinoline Crystals. *J. Phys. Chem. C* **2010**, *114*, 20401-20409. (c) Ahmed, E.; Briseno, A.L.; Xia, Y.; Jenekhe, S.A. High Mobility Single-Crystal Field-Effect Transistors from Bisindoloquinoline Semiconductors. *J. Am. Chem. Soc.* **2008**, *130*, 1118-1119.

(6) Baik, C.; Kim, D.; Kang, M.-S.; Song, K.; Kang, S.O.; Ko, J. Synthesis and photovoltaic properties of novel organic sensitizers containing indolo[1,2-*f*]phenanthridine for solar cell. *Tetrahedron* **2009**, *65*, 5302-5307.

(7) See review and references therein: Shang, X.-F.; Yang, C.-J.; Morris-Natschke, S. L.; Li, J.-C.; Yin, X.-D.; Liu, Y.-Q.; Guo, X.; Peng, J.-W.; Goto, M.; Zhang, J.-Y.; Lee, K.-H. Biologically active isoquinoline alkaloids covering 2014-2018. *Med Res Rev.* **2020**, *40*, 2212-2289.

(8) (a) Bian, M.; Ma, L.; Wu, M.; Wu, L.; Gao, H.; Yi, W.; Zhang, C.; Zhou, Z. Rh(III)-Catalyzed Redox-Neutral [4+2] Annulation for Direct Assembly of 3-Acyl Isoquinolin-1(2*H*)-ones as Potent Antitumor Agents. *ChemPlusChem* **2020**, *85*, 405-410. (b) Kaila, N.; Follows, B.; Leung, L.; Thomason, J.; Huang, A.; Moretto, A.; Janz, K.; Lowe, M.; Mansour, T. S.; Hubeau, C.; Page, K.; Morgan, P.; Fish, S.; Xu, X.; Williams, C.; Saiah, E. Discovery of Isoquinolinone Indole Acetic Acids as Antagonists of Chemoattractant Receptor Homologous Molecule Expressed on Th2 Cells (CRTH2) for the Treatment of Allergic Inflammatory Diseases. *J. Med. Chem.* **2014**, *57*, 1299-1322. (c) Wu, F.; Büttner, F. H.; Chen, R.; Hickey, E.; Jakes, S.; Kaplita, P.; Kashem, M. A.; Kerr, S.; Kugler, S.; Paw, Z.; Prokopowicz, A.; Shih, C.-K.; Snow, R.; Young, E.; Cywin, C. L. Substituted 2*H*-isoquinolin-1-one as potent Rho-Kinase inhibitors. Part 1: Hit-to-lead account. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3235-3239. (d) Bosanac, T.; Hickey, E.R.; Ginn, J.; Kashem, M.; Kerr, S.; Kugler, S.; Li, X.; Olague, A.; Schlyer, S.; Young, E.R.R. Substituted 2*H*-isoquinolin-1-ones as potent Rho-kinase inhibitors: Part 3, aryl substituted pyrrolidines. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3746-3749. (e) Asano, Y.; Kitamura, S.; Ohra, T.; Itoh, F.; Kajino, M.; Tamura, T.; Kaneko, M.; Ikeda, S.; Igata, H.; Kawamoto, T.; Sogabe, S.; Matsumoto, S.-I.; Tanaka, T.; Yamaguchi, M.; Kimura, H.; Fukumoto, S. Discovery, Synthesis and Biological Evaluation of Isoquinolones as Novel and Highly Selective JNK Inhibitors (2). *Bioorg. Med. Chem.* **2008**, *16*, 4699-4714.

(9) Mood, A. D.; Premachandra, I. D. U. A.; Hiew, S.; Wang, F.; Scott, K. A.; Oldenhuis, N. J.; Liu, H.; Van Vranken, D. L. Potent Antifungal Synergy of Phthalazinone and Isoquinolones with Azoles Against *Candida albicans*. *ACS Med. Chem. Lett.* **2017**, *8*, 168-173.

(10) Zhang, Z.; You, Z.; Dobrowsky, R. T.; Blagg, B. S.J. Synthesis and evaluation of a ring-constrained Hsp90 C-terminal inhibitor that exhibits neuroprotective activity. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2701-2704.

(11) Tang, Z.; Niu, S.; Liu, F.; Lao, K.; Miao, J.; Ji, J.; Wang, X.; Yan, M.; Zhang, L.; You, Q.; Xiao, H.; Xiang, H. Synthesis and biological evaluation of 2,3-diaryl isoquinolinone derivatives as anti-breast cancer agents targeting ER α and VEGFR-2. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2129-2133.

(12) See review and references therein: (a) Hua, R. Isoquinolone Syntheses by Annulation Protocols, *Catalysts* **2021**, *11*, 620.

(13) (a) Song, L.; Tian, G.; Van der Eycken, J.; Van der Eycken, E. V. Intramolecular cascade annulation triggered by rhodium(III)-catalyzed sequential C(sp²)-H activation and C(sp³)-H amination. *Beilstein J. Org. Chem.* **2019**, *15*, 571-576. (b) Song, L.; Zhang, X.; Tian,

- G.; Robeyns, K.; Meervelt, L. V.; Harvey, J. N.; Van der Eycken, E. V. Intramolecular cascade annulation triggered by C-H activation via rhodium hydride intermediate. *Mol. Catal.* **2019**, *463*, 30-36. (c) Chen, F.; Lai, S.-Q.; Zhu, F.-F.; Meng, Q.; Jiang, Y.; Yu, W.; Han, B. Cu-Catalyzed Radical Cascade Annulations of Alkyne-Tethered *N*-Alkoxyamides with Air: Facile Access to Isoxazolidine/1,2-Oxazinane-Fused Isoquinolin-1(2*H*)-ones. *ACS Catal.* **2018**, *8*, 8925-8931. (d) Swamy, T.; Maheshwar Rao, B.; Yadav, J. S.; Ravinder, V.; Sridhar, B.; Subba Reddy, B. V. Microwave-assisted, ruthenium-catalyzed intramolecular amide-alkyne annulation for the rapid synthesis of fused tricyclic isoquinolinones. *RSC Adv.* **2015**, *5*, 68510-68514. (e) Quinones, N.; Seoane, A.; Garcia-Fandino, R.; Masacrenas, J. L.; Gullás, M. Rhodium(III)-catalyzed intramolecular annulations involving amide-directed C-H activations: synthetic scope and mechanistic studies. *Chem. Sci.* **2013**, *4*, 2874-2879. (f) Xu, X.; Liu, Y.; Park, C.-M. Rhodium(III)-Catalyzed Intramolecular Annulation through C-H Activation: Total Synthesis of (±)-Antofine, (±)-Septicine, (±)-Tylophorine, and Rosettacin. *Angew. Chem. Int. Ed.* **2012**, *51*, 9372-9376.
- (14) Song, L.; Tian, G.; He, Y.; Van der Eycken, E. V. Rhodium(III)-catalyzed intramolecular annulation through C-H activation: concise synthesis of rosettacin and oxypalmatine. *Chem. Commun.* **2017**, *53*, 12394-12397.
- (15) Kumar, G. R.; Kumar, R.; Rajesh, M.; Sridhar, B.; Reddy, M. S. Rh(III)-Catalyzed Intramolecular Oxidative Annulation of Propargyl Amino Phenyl Benzamides to Access Pyrido/Isoquinolino Quinoxalinones. *Adv. Synth. Catal.* **2019**, *361*, 4825-4830.
- (16) Hua, Y.; Chen, Z.-Y.; Diao, H.; Zhang, L.; Qiu, G.; Gao, X.; Zhou, H. Copper-Catalyzed Preparation of Benzo[3,4]indolo[1,2-*b*]isoquinoline-8-ones and Photoluminescence Exploration. *J. Org. Chem.* **2020**, *85*, 9614-9621.
- (17) (a) Mali, M.; Sharma, G. V. M.; Ghosh, S.; Roisnel, T.; Carboni, B.; Berrée, F. Simmons-Smith Cyclopropanation of Alkenyl 1,2-bis(boronates): Stereoselective Access to Functionalized Cyclopropyl Derivatives. *J. Org. Chem.* **2022**, *87*, 7649-7657. (b) Mali, M.; Jayaram, V.; Sharma, G. V. M.; Ghosh, S.; Berrée, F.; Dorcet, V.; Carboni, B. Copper-Mediated Synthesis of (*E*)-1-Azido and (*Z*)-1,2-Diazido Alkenes from 1-Alkene-1,2-diboronic esters. A Direct Approach to mono- and 1,2-di-(1,2,3-Triazolyl)-Alkenes and Fused bis-(1,2,3-Triazol)-Pyrazines. *J. Org. Chem.* **2020**, *85*, 15104-15115. (c) Jayaram, V.; Sridhar, T.; Sharma, G.V.M.; Berrée, F.; Carboni, B. Synthesis of Polysubstituted Isoquinolines and Related Fused Pyridines from Alkenyl Boronic Esters via a Copper-Catalyzed Azidation/Aza-Wittig Condensation Sequence. *J. Org. Chem.* **2018**, *83*, 843-853. (d) Jayaram, V.; Sridhar, T.; Sharma, G.V.M.; Berrée, F.; Carboni, B. Synthesis of 1-Amino-1*H*-Indenes via a Sequential Suzuki-Miyaura Coupling/Petasis Condensation Sequence. *J. Org. Chem.* **2017**, *82*, 1803-1811. (e) Sridhar, T.; Berrée, F.; Sharma, G. V. M.; Carboni, B. Regio- and Stereocontrolled Access to γ -Boronated Unsaturated Amino Esters and Derivatives from (*Z*)-Alkenyl 1,2-bis(boronates). *J. Org. Chem.* **2014**, *79*, 783-789.
- (18) (a) Ganic, A.; Pfaltz, A. Iridium-Catalyzed Enantioselective Hydrogenation of Alkenylboronic Esters. *Chem. - Eur. J.* **2012**, *18*, 6724-6728. (b) Iwadate, N.; Suginome, M. Differentially Protected Diboron for Regioselective Diboration of Alkynes: Internal-Selective Cross-Coupling of 1-Alkene-1,2-diboronic Acid Derivatives. *J. Am. Chem. Soc.* **2010**, *132*, 2548-2549.
- (19) Wu, H., Ma, N.; Song, M.; Zhang, G. Dimethyl sulfoxide-aided copper(0)-catalyzed intramolecular decarbonylative rearrangement of *N*-aryl isatins leading to acridones. *Chin. Chem. Lett.* **2020**, *31*, 1580-1583.
- (20) Benedí, C.; Bravo, F.; Uriz, P.; Fernández, E.; Claver, C.; Castellón, S. Synthesis of 2-substituted-benzothiazoles by palladium-catalyzed intramolecular cyclization of *o*-bromophenylthioureas and *o*-bromophenylthioamides. *Tetrahedron Lett.* **2003**, *44*, 6073-6077.
- (21) (a) Ishiyama, T.; Matsuda, N.; Murata, M.; Ozawa, F.; Suzuki, A.; Miyaura, N. Platinum(0)-Catalyzed Diboration of Alkynes with Tetrakis(alkoxo)diborons: An Efficient and Convenient Approach to *cis*-Bis(boryl)alkenes. *Organometallics* **1996**, *15*, 713-720. (b) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. Platinum(0)-catalyzed diboration of alkynes. *J. Am. Chem. Soc.* **1993**, *115*, 11018-11019.
- (22) The structure of **51** was established by X-ray analysis (see Supporting Information). CCDC 2205942 contains the supplementary crystallographic data. These data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- (23) For examples of oxidative annulation using [Ru(*p*-cymene)Cl₂]₂ as catalyst, see and references therein: Gramage-Doria, R.; Bruneau, C. Ruthenium-catalyzed C-H bond functionalization in cascade and one-pot transformations. *Coord. Chem. Rev.* **2021**, *428*, pp.213602.
- (24) The structure of **6m** was established by X-ray analysis (see Supporting Information). CCDC 2205943 contains the supplementary crystallographic data. These data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.