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Povarov Reaction of Cycloiminium Formed in Situ via Hydroamination Cycloisomerization of Homopropargylic Amines with Electron-Rich Olefins

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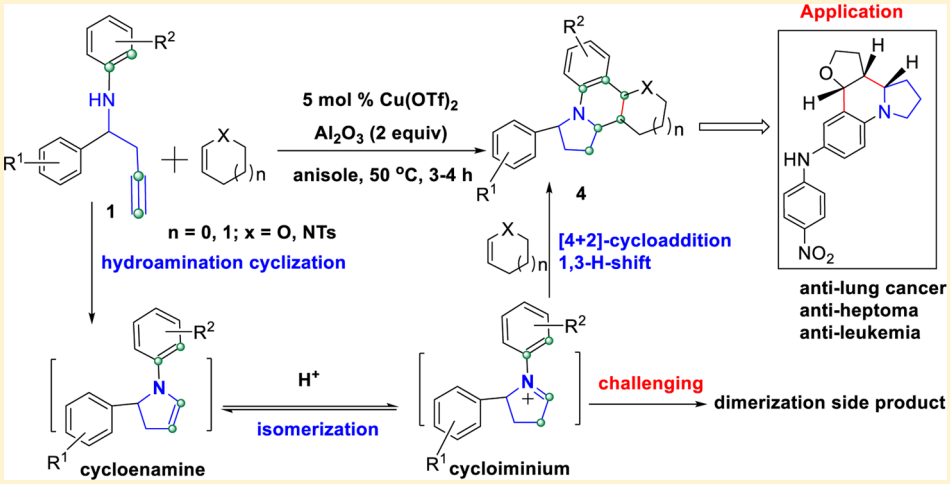
Supporting Information



ABSTRACT: A new, one-pot cascade reaction of homopropargylic amines with electron-rich olefins is developed in the presence of $Cu(OTf)_2$ and affords a series of octahydrofuro[3,2-*c*]pyrrolo[1,2-*a*]quinoline derivatives in yields of 38−80%. This reaction proceeds through an intramolecular hydroamination cyclization of homopropargylic amine to generate a highly reactive cycloenamine intermediate in situ that subsequently isomerizes to the cycloiminium cation followed by the Povarov-type reaction with dihydrofuran, dihydropyran, or dihydropyrrole. Notably, the Al_2O_3 additive plays a key role for the effective inhibition of competitive self-dimerization of homoproargylic amines.

INTRODUCTION

The Povarov reaction of *N*-arylimines with electron-rich olefins, an inverse-electron-demand aza-Diels−Alder (IEDDA), has been extensively explored.[1] For the *N*-arylimines, various strategies have been developed to access them, including cyclic amines, for example, a typical condensation in situ or preparation in advance from aldehydes (or ketones) and aromatic amines,[2] oxidation in situ of *N*-arylamines with active α-H,[3] or reduction of nitrobenzene derivatives.[4] The former is the most classical and has been widely used to develop two-component methods or three-component approaches. As a comparison, the latter two tactics were sparse. In particular, cycloiminium or oxidation of cyclic amine enables the formation of polycyclic compounds.[5] Therefore, it is highly desirable to develop novel *N*-arylimine equivalents or precursors as dienes in the Povarov reaction for the construction of diverse tetrahydroquinoline derivatives, which are ubiquitous scaffolds with a wide range of biological activities such as antifungal, antimicrobial, anti-HIV, antibacterial, anti-inflammatory, and anticancer.[6] Our research group has developed several cascade reactions of simple homopropargylic amines. It was found that the homopropargylic amines could potentially act as both **2C** and **4C** synthons. Moreover, the dual roles of **4C** and **2C** synthons or a single role of **2C** synthon has been realized with the addition of other appropriate substrate molecules, respectively (Scheme 1).[7] Based on these results, we envisioned that the single **4C** synthon identity may be also accessible. In fact, achieving a single **4C** synthon role for the homopropargylic amine is quite challenging and more difficult than for the single **2C** synthon. It is because once the cycloiminium cation is generated through isomerization of cycloenamine formed in situ via an intramolecular hydroamination cyclization of homopropargylic amine, it will inevitably react with its isomer cycloenamine to give a *formal* dimerized compound.

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Scheme 1. Diverse Reactions of Homopropargylic Amines

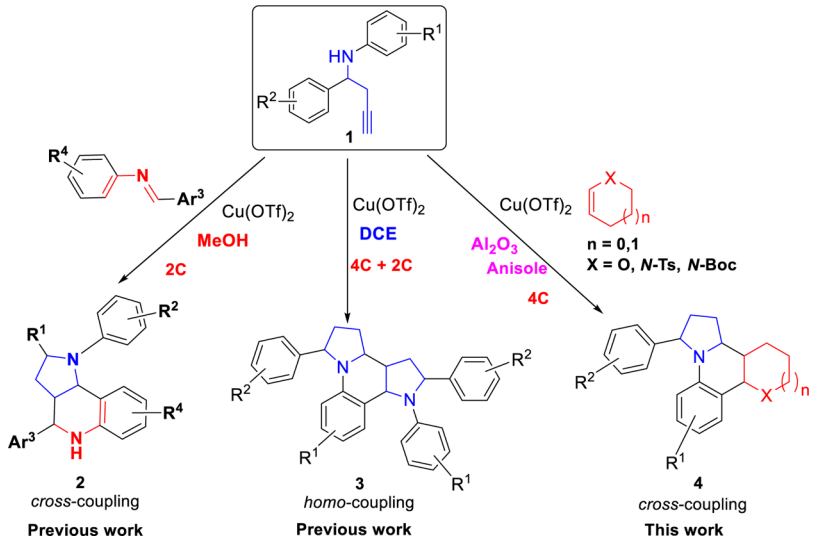
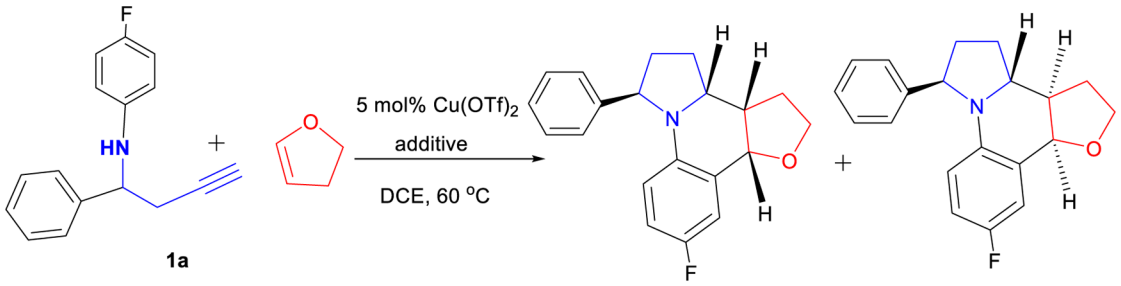
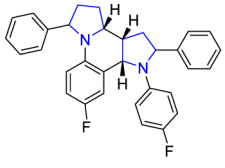


Table 1. Screening of Additives in the Cascade Reaction of Homopropargylic Amine 1a and Dihydrofuran[a]



entry	additive (equiv)	total yield[c] (**4a** + **4a'**) (%)	self-dimerized product yield[f] (**3a**) (%)
1	—	24	42
2	CF_3COOH (0.2)	31	33
3	CH_3COOH (0.2)	55	21
4	PhCOOH (0.2)	48	25
5	$Sc(OTf)_3$ (0.1)	48	15
6	NaCl (2.0)	51	28
7	Silica gel (2.0)	62	20
8	Al_2O_3 (2.0)	65	9
9[d]	Al_2O_3 (2.0)	68	11
10	acidic Al_2O_3 (2.0)	72	8
11	neutral Al_2O_3 (2.0)	52	14
12	basic Al_2O_3 (2.0)	57	11
13[e]	acidic Al_2O_3 (2.0)	68	10
14	CuO (2.0)	54	18

[a]Reaction conditions: **1a** (24 mg, 0.1 mmol, 1.2 equiv), dihydrofuran (21 mg, 0.3 mmol, 3.0 equiv), 5 mol % of $Cu(OTf)_2$ (0.005 mmol, 1.8 mg, 5 mol %), a certain amount of additive, and DCE (1 mL) were sequentially added into a tube. The reaction was carried out under the given reaction conditions, and the products were subsequently detected by TLC. [b]The diastereomeric ratios were determined based upon NMR analysis of the crude products. [c]Isolated yield. [d]1 mmol of Al_2O_3 was activated by 25 μL of H_2O. [e]The Al_2O_3 was activated and named as II-activated level (1 mmol of Al_2O_3 + 50 μL of H_2O), the above Al_2O_3 was activated and named as I-activated level (1 mmol of Al_2O_3 + 25 ul H_2O) (acidic, neutral, basic). [f]The side product is



(3a).

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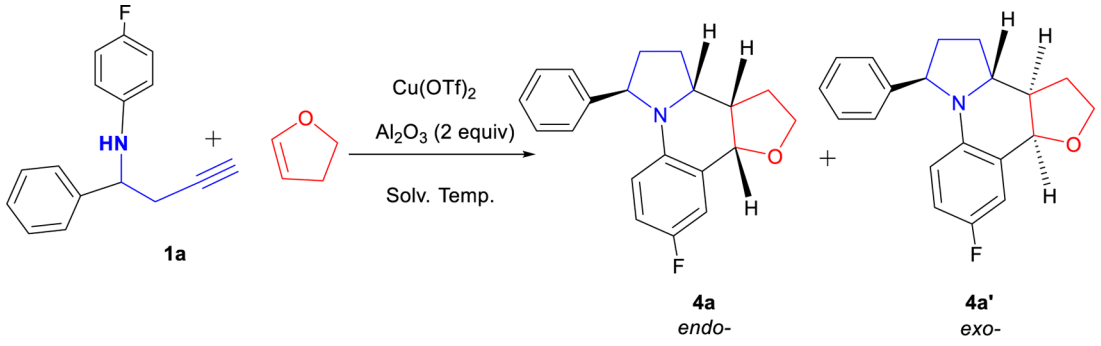
Table 2. Other Experimental Parameters Screening in the Reaction of Homopropargylic Amine 1a and Dihydrofuran[a]



entry	solvent	temp (°C)	$Cu(OTf)_2$ (mol %)	^{1}H NMR yield[b] (%)	dr (endo/exo)[c]	isolated yield (%)
1	DCE	60	5		62:38	72
2	MeOH	60	5	34/42[d]	62:38	
3	CH_3CN	60	5	trace/51[d]		
4	PhMe	60	5	72/10[d]	58:42	
5	PhOMe	60	5		67:33	72
6	THF	60	5	53/34[d]	62:38	
7	DMF	60	5	trace/67[d]		
8	1,4-dioxane	60	5	22/48[d]	58:42	
9	PhOMe	85	5		67:33	52
10[e]	PhOMe	rt	5		67:33	50
11	PhOMe	60	10		67:33	60
12	PhOMe	60	15		67:33	55
13	PhOMe	60	20		67:33	38
14	PhOMe	60	30		67:33	15
15	PhOMe	60	2		67:33	52
16[f]	PhOMe	60	5		67:33	69
17[g]	PhOMe	60	5		67:33	71

[a]Reaction conditions: **1a** (24 mg, 0.1 mmol), dihydrofuran (21 mg, 0.3 mmol, 3.0 equiv), a certain amount of $Cu(OTf)_2$, Al_2O_3 (0.2 mmol, 20.4 mg, 2.0 equiv), and solvent (1 mL) were sequentially added into a tube. The reaction was carried out under the given reaction conditions, and the products were subsequently detected by TLC (generally 3−4 h). [b]The NMR yield was calculated by adding a certain amount of DMF as an internal standard. [c]The diastereomeric ratios were determined on the basis of ^{1}H NMR analysis of the crude products. [d]The yield of self-dimerized side product. [e]The reaction time was 6 h. [f]The amount of dihydrofuran was 0.4 mmol (4.0 equiv). [g]The amount of dihydrofuran was 0.5 mmol (5.0 equiv).

In spite of this, we believe that this competitive side reaction can be reduced as low as possible by controlling the reaction conditions or introducing additional higher reactivity substrates. Thus, the electron-rich cyclic alkenes were herein employed to react with homopropargylic amines. To our delight, we could obtain the expected cycloaddition product **4** in good yields through the great amount of experimental parameters screenings (Scheme 1, this work).

RESULTS AND DISCUSSION

In our initial study, the dihydrofuran was selected as a model substrate to react with the simple homopropargylic amine **1a** under previously developed standard reaction conditions. Consequently, the cross-cycloaddition products **4a** and **4a′** were obtained in a low yield (24%) but with the major self-dimerization compound **3a** (Table 1, entry 1). In order to inhibit the self-dimerization of homopropargylic amine **1a**, we attempted to introduce some additives (Table 1). Acid additives were first selected to accelerate the isomerization of cycloenamine to cycloiminium cation. For example, the strong acid, CF_3COOH, and weak acid, CH_3COOH and PhCOOH, could indeed increase the desired product's yield (entries 2−4). The Lewis acid $Sc(OTf)_3$ was also examined (entry 5). However, no further improved results were obtained. Other microenvironment adjustments were considered through addition of NaCl,[8] silica gel,[9] and acidic Al_2O_3[10] into the reaction system (entries 6−8). Surprisingly, this reaction gave an obviously increased yield of cross-cycloaddition products **4a** and **4a′** with the addition of silica gel or Al_2O_3. More interestingly, using the Al_2O_3 activated by water, a slightly higher yield of target compound was generated (entry 9). It is noteworthy that the target compounds were obtained with an *endo*/*exo*-configuration in a 63:37 diastereomeric ratio, and the self-dimerization product **3a** was accompanied in nearly all cases (Table 1).

Why was the Al_2O_3 competent auxiliary in this reaction? With this question in mind, some exploratory experiments were further performed (Table 1, entries 10−14). The types and levels activated by water of Al_2O_3 were subtly examined. As shown in Table 1, it was found that the I-activated level of acidic Al_2O_3 gave a higher yield of cross-cycloaddition product than neutral and basic Al_2O_3 (entries 10−13). These results demonstrated that the acidic microenvironment was favored for the isomerization of cycloenamine to cycloiminium cation. Additionally, a metal oxide, CuO, acting as a Lewis acid, was tested. As a result, this reaction could also smoothly proceed and afford the corresponding product in moderate yield (Table 1, entry 14). Obviously, Al_2O_3 was superior to the CuO in this reaction. In view of these results, we surmised that the unique reticular structure property and Lewis acidity as well as weak protonic acidity of Al_2O_3 endow

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it with special catalytic activity in this reaction, accelerating the isomerization of cycloenamine formed in situ to cycloiminium cation and, thus, impeding the occurrence of self-dimerization.

Then the other experimental parameters, such as solvent, reaction temperature, and the amount of catalyst and electron-rich olefins, were investigated (Table 2). It was found that anisole displays an advantage over other commonly used organic solvents (entries 1−8) and 60 °C was the optimal temperature (entries 9 and 10). In addition, when the loading of $Cu(OTf)_2$ was increased or decreased, the reaction gave a decreased yield of target compound (Table 2, entries 11−15). In the case of 30 mol % of $Cu(OTf)_2$, most of the homopropargylic amine **1a** decomposed (entry 14). Moreover, no obvious improved results were obtained in the case of the increased amount of dihydrofuran (entries 16 and 17). On the basis of the above results, the optimal reaction conditions were determined to be 5 mol % of $Cu(OTf)_2$, 2 equiv of Al_2O_3, and 3 equiv of dihydrofuran at 60 °C in anisole.

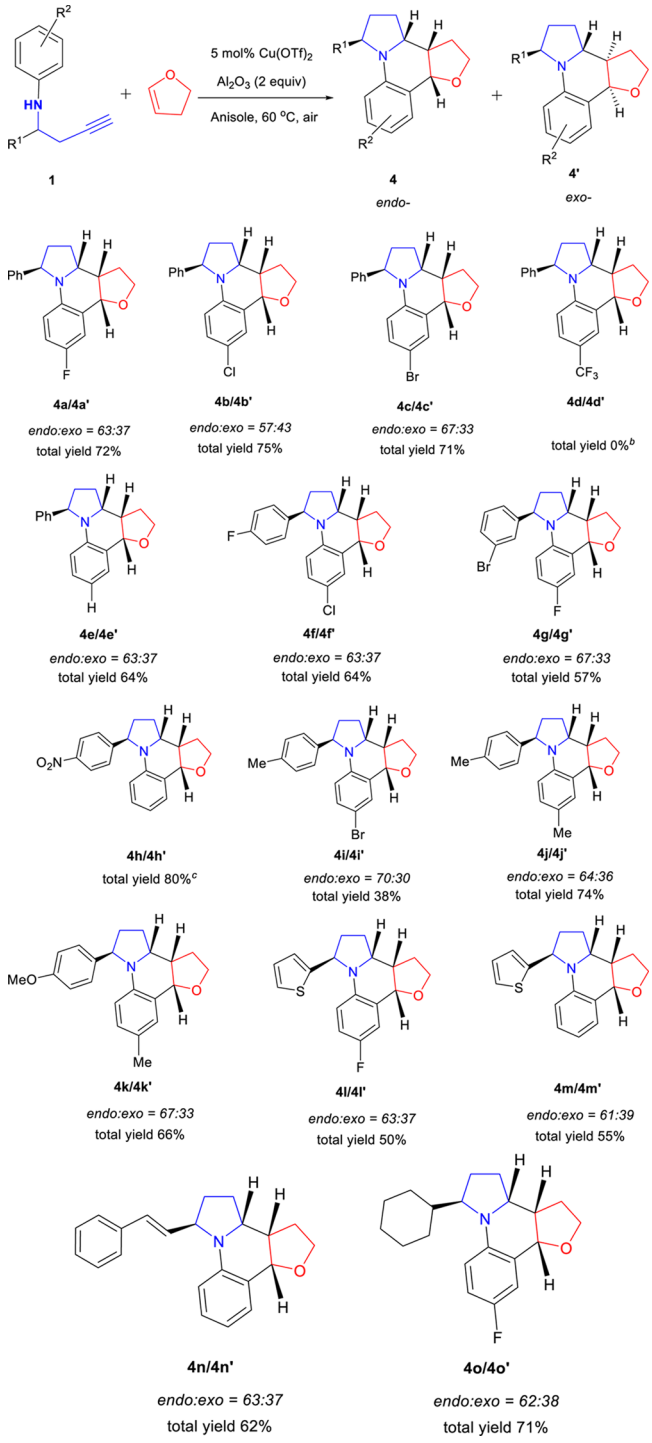
Having established the optimized reaction conditions, the scope of homopropargylic amines was scrutinized by performing the reaction with dihydrofuran (Table 3). Generally, all tested homopropargylic amines were able to tolerate this catalytic system to afford the desired product **4a−o** and **4a′−o′** in moderate to good yields (38−80%). It should be noted that all of these reactions were traced by thin-layer chromatography (TLC) with a small amount of self-dimerization side products. In the case of 4-CF_3-substituted *N*-aryl homopropargylic amine, only the self-dimerization competitive side product was obtained in 78% yield. For the homopropargylic amine with R^1 = 4-$NO_2C_6H_4$, the corresponding products contained four diastereoisomers. In addition, all products were racemic. The *endo*- or *exo*-configuration of the target compound was confirmed according to the X-ray single-crystal diffraction of *exo*-**4q′** and theirs ^{1}H NMR, and the *endo* or *exo*-configurational product contains an extremely small amount of diastereoisomers, respectively.

Several other electron-rich olefins were further employed to test this methodology application (Scheme 2). Under the above optimized reaction conditions, the reaction resulted in the expected octahydro-2*H*-pyrano[3,2-*c*]pyrrolo[1,2-*a*]quinoline product in low yield (27%) in the case of dihydropyran. Therefore, further additive screening experiments were carried out as shown in Table 4. Interestingly, $Sc(OTf)_3$ exhibited the best catalytic activity for the reaction of dihydropyran and homopropargylic amine **1a** (Table 4), and this reaction gave only one *endo*-configurational product **4p** with excellent diastereoselectivity (dr > 25:1) (Scheme 2, eq 1). Similarly, the *N*-Ts-protected dihydropyrrole rendered the corresponding products **4q** and **4q′** in 80% yield with $Cu(OTf)_2$ and $Sc(OTf)_3$ as co-catalysts. The exact configuration of *exo*-**4q′** was unambiguously determined by single-crystal X-ray diffraction (Figure 1).[11] However, this catalytic system was incompatible with vinyl *n*-butyl ether or vinyl *tert*-butyl ether (**4r,s**). Fortunately, using our developed methodology, a lung cancer inhibitor **4t** could be facilely synthesized in good yield (Scheme 2, eq 2).[12]

CONCLUSION

In summary, a novel Povarov reaction of cycloiminium with electron-rich olefins was developed for the preparation of octahydrofuro[3,2-*c*]pyrrolo[1,2-*a*]quinoline derivatives. The cycloiminium was formed in situ via a simple and efficient Cu-catalyzed intramolecular hydroamination cycloisomerization reactions of homopropargylic amines. Various homopropargylic amines were well tolerated in this methodology to give the corresponding desired products in moderate to good yields.

Table 3. Scope of Homopropargylic Amines and Dihydrofuran[a]



[a]Reaction conditions: homopropargylic amines **1** (0.1 mmol), dihydrofuran (21 mg, 0.3 mmol, 3.0 equiv), $Cu(OTf)_2$ (0.005 mmol, 1.8 mg, 5 mol %), Al_2O_3 (0.2 mmol, 20.4 mg, 2.0 equiv), and anisole (1 mL) were sequentially added into a tube. The reaction was carried out at 60 °C in the air, and the products were subsequently detected by TLC (generally 3−4 h). [b]The product was the self-dimerization compound (yield 78%). [c]The products contained four diastereoisomers (the diastereomeric ratios were determined based upon NMR analysis of the crude products).

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Scheme 2. Reactions of Homopropargylic Amine 1a and Other Electron-Rich Olefins

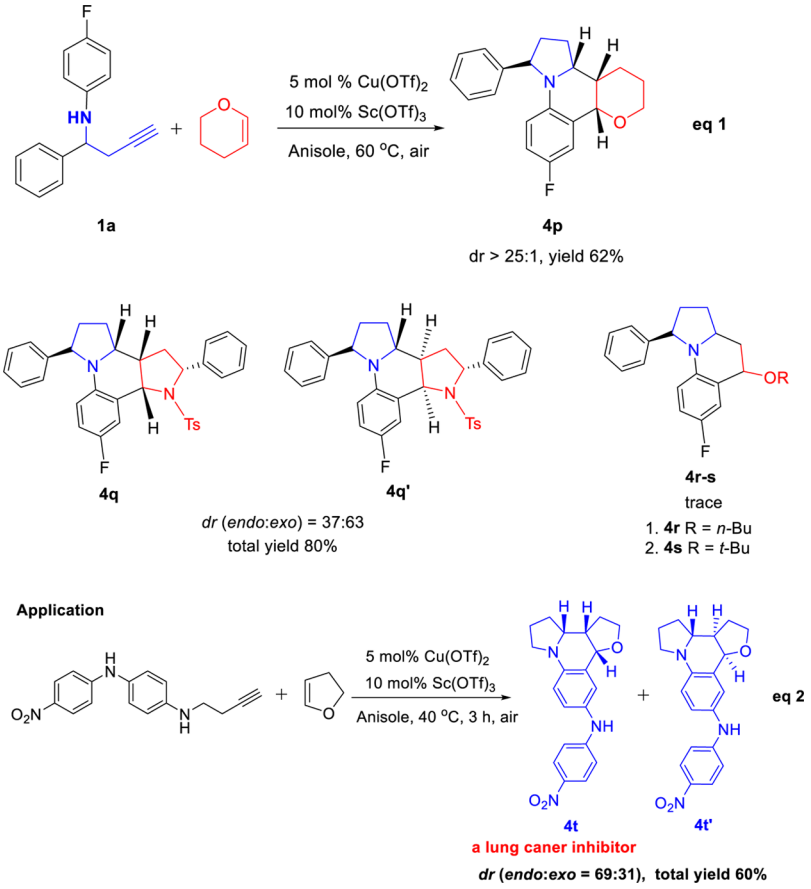
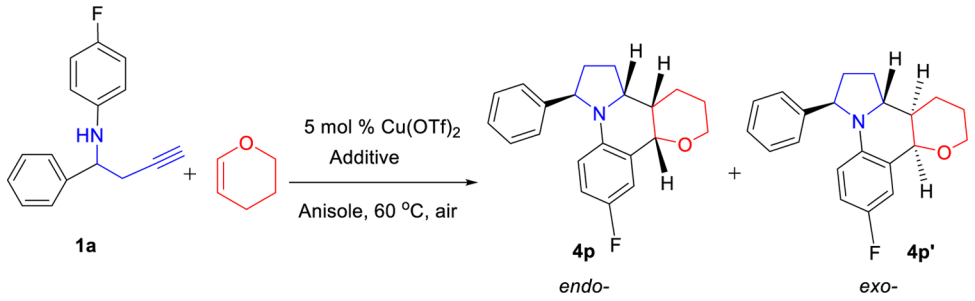


Table 4. Additive Effect on the Reaction of Homopropargylic Amine 1a and Dihydropyran[a]



entry	additive (equiv)	isolated yield (%)[b]	dr (endo/exo)[c]
1	Al_2O_3 (2.0)	27	>25:1
2	$Sc(OTf)_3$ (0.1)	62	>25:1
3	$Y(OTf)_3$ (0.05)	51	>25:1
4	$Y(OTf)_3$ (0.1)	55	>25:1
5	$Yb(OTf)_3$ (0.1)	60	>25:1
6	$In(OTf)_3$ (0.1)	30	>25:1
7	$Zn(OTf)_2$ (0.1)	44	>25:1
8	$SnCl_2$ (1.0)	41	>25:1
9	$SnCl_2$ (2.0)	36	>25:1
10	BF_3·OEt (0.1)	48	>25:1

[a]Reaction conditions: **1a** (24 mg, 0.1 mmol), dihydropyran (25.2 mg, 0.3 mmol, 3.0 equiv), 5 mol % of $Cu(OTf)_2$ (1.8 mg), additive, and anisole (1 mL) were sequentially added into a tube. The reaction was carried out under the given reaction conditions, and the products were subsequently detected by TLC. [b]Isolated yield. [c]The diastereomeric ratios were determined on the basis of NMR analysis of the crude products.

More importantly, the inevitable competitive self-dimerization of homopropargylic amines could be effectively reduced through introducing the Al_2O_3 additive or $Sc(OTf)_2$ as a cocatalyst.

EXPERIMENTAL SECTION

1. General Information. The ^1H NMR and ^{13}C NMR spectra were recorded at 400 or 600 MHz. ^1H and ^{13}C NMR chemical shifts were calibrated to tetramethylsilane as an internal reference. Chemical shifts

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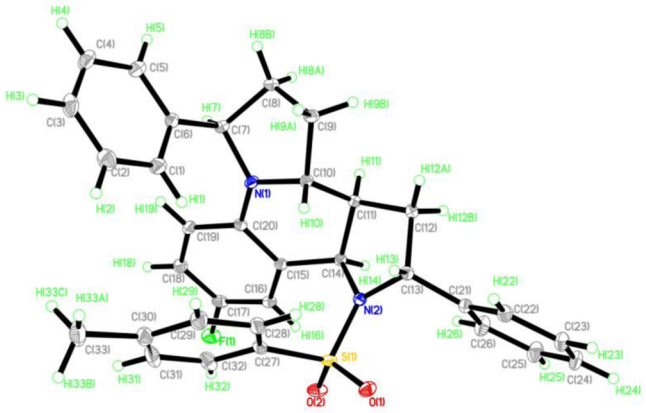

Figure 1. ORTEP drawing (30% thermal ellipsoids) of *exo*-**4q′**.

are given in ppm and coupling constants (J) in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet: t, triplet; q, quartet; m, multiplet. High resolution mass spectra (HRMS) were measured on a mass spectrometer equipped with a TOF system and an electrospray ionization (ESI) ion source.

2. Synthesis and Characterization of *N*-(4-Nitrophenyl)-benzene-1,4-diamine.[13] The 1-fluoro-4-nitrobenzene (5 mmol, 705 mg), Na_2CO_3 (5.0 mmol, 530 mg), 1,4-phenylenediamine (10 mmol, 1.08 g), and 7 mL of water were sequentially added into a flask and refluxed for 10 h. Then the reaction mixture was cooled, 10 mL of toluene was added, and the mixture was stirred vigorously for another 1 h. The precipitated product was collected by filtration and washed thoroughly with water and toluene. The *N*-(4-nitrophenyl)benzene-1,4-diamine was obtained as an orange solid (1.1 g): yield 78%; mp 210−211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.03−7.98 (m, 2H), 6.95−6.89 (m, 2H), 6.79−6.73 (m, 2H), 6.64−6.58 (m, 2H), 5.10 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.2, 146.4, 136.4, 127.7, 126.4, 124.8, 114.6, 111.7; HRMS (ESI$^+$) calcd for $C_{12}H_{12}N_3O_2$ (M + H$^+$) 230.0930, found 230.0926.

3. Synthesis and Characterization of Homopropargylic Amines. The homopropargylic amines were prepared according to the known procedures.[7] Because our research group has synthesized a series of homopropargylic amines, we herein directly used or synthesized these substrates using well-developed methods. As these substrates are all known, the characterizations are consistent with those of our synthesized compounds.

*General Procedure for Homopropargylic Amines (**1a−o**).* An aluminum amalgam was prepared from aluminum powder (0.5 g, 18.0 mmol) and a catalytic amount of mercuric chloride (10 mg) in 7.5 mL of anhydrous THF with vigorous stirring at room temperature for 1 h under a N_2 atmosphere. A solution of propargylic bromide (18.0 mmol) in 12.5 mL of anhydrous THF was then slowly added to the suspension at such a rate as to maintain the temperature between 30 and 40 °C. After the addition, the reaction mixture was continued to stir until a dark gray solution was formed. The generated propargylic aluminum sesquibromide solution was added to a solution of imine (6.0 mmol) in 20.0 mL of anhydrous THF at 0 °C under N_2 atmosphere. The reaction mixture was stirred at 0 °C for about 1 h, warmed to room temperature, and continued to stir for additional 3−4 h (monitored by TLC). The mixture was quenched by adding saturated NH_4Cl aqueous solution and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and then filtered, and the filtration was concentrated in vacuo to give the residue. The residue was purified by flash chromatography over silica gel (gradient elution of EtOAc/petroleum ether, PE/EA = 50:1).

*N-(1-Phenylbut-3-yn-1-yl)-4-(trifluoromethyl)aniline (**1d**):* white solid; 1.44 g, yield 83%; mp 34.7−35.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.17 (m, 7H), 6.47 (d, J = 8.5 Hz, 2H), 4.66 (s, 1H), 4.49 (dd, J = 7.0, 5.2 Hz, 1H), 2.72 (ddd, J = 16.9, 5.3, 2.7 Hz, 1H), 2.58 (ddd, J = 16.9, 7.0, 2.7 Hz, 1H), 2.01 (t, J = 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 141.3, 129.0, 128.0, 126.6 (d, J = 3.8 Hz), 126.4, 113.0, 79.9, 72.0, 56.1, 28.2; HRMS (ESI$^-$) calcd for $C_{17}H_{13}F_3N$ (M − H$^+$) 288.1000, found 288.1033.

*N-(1-(4-Nitrophenyl)but-3-yn-1-yl)aniline (**1h**):* orange oil liquid; 1.06 g, yield 78%; ^{1}H NMR (400 MHz, chloroform-d) δ 8.11 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.03 (t, J = 7.7 Hz, 2H), 6.63 (t, J = 7.3 Hz, 1H), 6.41 (d, J = 8.0 Hz, 2H), 4.55 (t, J = 6.0 Hz, 1H), 4.41 (s, 1H), 2.73 (ddd, J = 16.9, 5.5, 2.7 Hz, 1H), 2.60 (ddd, J = 16.9, 6.5, 2.6 Hz, 1H), 2.03 (t, J = 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 147.5, 146.3, 129.4, 127.5, 124.1, 118.6, 113.8, 79.1, 77.5, 77.2, 76.8, 72.5, 55.9, 27.9; HRMS (ESI$^-$) calcd for $C_{16}H_{13}N_2O_2$ (M − H$^+$) 265.0977, found 265.0981.

*4-Bromo-N-(1-(p-tolyl)but-3-yn-1-yl)aniline (**1i**):* light yellow oil liquid; 1.41 g, yield 75%; mp 85.5−87.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, J = 7.2, 2.0 Hz, 2H), 7.19 (ddd, J = 10.2, 8.4, 2.0 Hz, 4H), 6.45 (dd, J = 8.7, 2.1 Hz, 2H), 4.59−4.39 (m, 1H), 2.87−2.57 (m, 2H), 2.36 (d, J = 1.9 Hz, 3H), 2.11 (q, J = 2.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 138.6, 137.5, 132.0, 129.6, 126.3, 115.4, 109.6, 80.3, 71.7, 56.3, 28.2, 21.3; HRMS (ESI+) calcd for $C_{17}H_{17}BrN$ (M + H$^+$) 314.0544, found 314.0543.

*N-(1-(Thiophene-2-yl)but-3-yn-1-yl)aniline (**1m**):* orange oil liquid; 845.6 mg, yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.18 (m, 3H), 7.12 (d, J = 3.5 Hz, 1H), 7.02 (dd, J = 5.0, 3.6 Hz, 1H), 6.80 (t, J = 7.3 Hz, 1H), 6.72 (d, J = 8.0 Hz, 2H), 4.93 (t, J = 5.9 Hz, 1H), 4.41 (s, 1H), 2.96−2.79 (m, 2H), 2.15 (t, J = 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 146.7, 127.0, 124.5, 124.2, 118.6, 114.1, 80.0, 71.9, 52.7, 28.1; HRMS (ESI+) calcd for $C_{14}H_{14}NS$ (M + H$^+$) 228.0847, found 228.0845.

2-Phenyl-1-tosyl-2,3-dihydro-1H-pyrrole. The synthesis of 2-phenyl-1-tosyl-2,3-dihydro-1*H*-pyrrole was performed according to the previously reported procedure:[14] white solid; 61.5 mg, yield 70%; mp 103−105 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.65 (d, J = 7.9 Hz, 2H), 7.45−7.24 (m, 7H), 6.55 (d, J = 4.0 Hz, 1H), 5.14 (d, J = 4.0 Hz, 1H), 4.74 (dd, J = 11.0, 6.3 Hz, 1H), 2.94 (dd, J = 16.6, 11.2 Hz, 1H), 2.51 (d, J = 6.2 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 142.8, 134.0, 130.9, 129.7, 128.9, 128.6, 127.7, 127.6, 126.4, 110.3, 63.1, 40.8, 21.7; HRMS (ESI+) calcd for $C_{17}H_{18}NO_2S$ (M + H$^+$) 300.1058, found 300.1056.

*Synthesis and Characterization of Homopropargylic Amines (**1q**).* *N*-(4-Nitrophenyl)benzene-1,4-diamine (4 mmol, 916.9 mg) was added to the Ar-purged flask in DMF (24 mL). K_2CO_3 (4.2 mmol, 580.3 mg) and 4-bromo-1-butyne (4.1 mmol, 545.3 mg) were added to the reaction system, and the reaction mixture was stirred at 85 °C for 12 h. The mixture was then quenched with saturated NH_4Cl aqueous solution and extracted with ethyl acetate three times, and the combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The extracts were filtered, and the filtration was concentrated to give a yellow liquid residue. The residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether, PE/EA = 1:10) to afford the orange solid **1q**: 382.6 mg, yield 34%; mp 55−57 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 8.09−8.02 (m, 2H), 7.09−7.01 (m, 2H), 6.76−6.63 (m, 4H), 6.15 (s, 1H), 4.05 (s, 1H), 3.33 (t, J = 6.6 Hz, 2H), 2.53 (td, J = 6.5, 2.7 Hz, 2H), 2.07 (t, J = 2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 146.0, 138.8, 129.3, 126.5, 126.3, 114.0, 112.4, 81.7, 70.4, 42.7, 19.2; HRMS (ESI+) calcd for $C_{16}H_{16}N_3O_2$ (M + H$^+$) 282.1243, found 282.1242.

4. General Procedure for the Cascade Reaction of Homopropargylic Amines with Olefins. $Cu(OTf)_2$ (1.81 mg, 5 mol %) was added to a solution of homopropargylic amines (0.1 mmol), Al_2O_3 (0.2 mmol, 20.4 mg, 2.0 equiv), and 2,3-dihydrofuran (21 mg, 0.3 mmol) in 1 mL of anisole, and the mixture was stirred at 60 °C until the complete disappearance of the starting material (monitored by TLC). The mixture was passed through a short Kieselguhr column using CH_2Cl_2, and the filtrate was concentrated in vacuo and purified by column chromatography with gradient elution (silica gel, petroleum ether/EtOAc, gradient from 50:1 to 10:1) to give the final products **4**. All of the products are racemic, and the *endo*- or *exo*-configurational product contains the extremely small amount of diastereoisomers, respectively.

*10-Fluoro-6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinoline (**4a**) (endo):* orange oil liquid; 14.03 mg,

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yield 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dt, J = 7.3, 4.6 Hz, 2H), 7.17−7.10 (m, 1H), 7.07 (d, J = 7.3 Hz, 2H), 6.99 (dt, J = 9.0, 2.9 Hz, 1H), 6.61 (m, 1H), 6.06 (m, 1H), 4.70 (m, 1H), 4.37 (t, J = 3.3 Hz, 1H), 4.06−3.87 (m, 1H), 3.80 (m, 1H), 3.32 (m, 1H), 2.45−2.29 (m, 1H), 2.19 (m, 2H), 1.79 (m, 3H), 1.71−1.60 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (d, J = 235.3), 144.3, 139.9, 128.7, 126.8, 125.8, 117.4 (d, J = 21.6), 116.0 (d, J = 22.1), 113.7 (d, J = 7.1), 120.0 (d, J = 8.1 Hz), 76.8, 65.0, 64.7, 57.7, 39.8, 34.3, 29.7, 29.0; HRMS (ESI+) calcd for $C_{20}H_{20}FNO$ (M + H$^+$) 310.1607, found 310.1600.

*10-Fluoro-6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinoline (**4a′**) (exo):* orange oil liquid; 8.24 mg, yield 27%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, J = 7.2 Hz, 2H), 7.15 (q, J = 7.6 Hz, 1H), 7.08 (d, J = 7.5 Hz, 2H), 6.98 (dd, J = 9.4, 3.0 Hz, 1H), 6.50 (td, J = 8.4, 2.8 Hz, 1H), 5.88 (dd, J = 4.4, 4.4 Hz, 1H), 5.10 (d, J = 7.2 Hz, 1H), 4.66 (dd, J = 7.8, 5.2 Hz, 1H), 4.19 (m, 1H), 3.85−3.69 (m, 3H), 2.67−2.57 (m, 1H), 2.53−2.41 (m, 1H), 2.08 (m, 1H), 1.92−1.58 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (d, J = 253.3), 144.7, 138.8, 128.9, 126.8, 125.7, 115.2 (d, J = 23.0), 114.8 (d, J = 22.0), 112.3 (d, J = 7.0), 122.5 (d, J = 6.1 Hz), 75.7, 66.6, 63.7, 56.7, 41.6, 35.9, 29.7, 24.8; HRMS (ESI+) calcd for $C_{20}H_{21}FNO$ (M + H$^+$) 310.1607, found 310.1600.

*10-Chloro-6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinoline (**4b**) (endo):* colorless liquid; 13.9 mg, yield 43%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.11 (m, 4H), 7.10−7.02 (m, 2H), 6.84 (dd, J = 8.8, 2.6 Hz, 1H), 6.07 (d, J = 8.8 Hz, 1H), 4.74 (dd, J = 7.9, 3.8 Hz, 1H), 4.38 (d, J = 4.3 Hz, 1H), 3.98 (m, 1H), 3.84 (m, 1H), 3.34 (m, 1H), 2.42 (m, 1H), 2.22 (m, 2H), 1.81 (m, 3H), 1.67 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 141.9, 131.1, 129.1, 128.8, 126.9, 125.8, 120.5, 114.1, 76.7, 65.0, 64.4, 57.7, 39.9, 34.5, 29.7, 29.3.;HRMS (ESI+) calcd for $C_{20}H_{21}ClNO$ (M + H$^+$) 326.1312, found 326.1303.

*10-Chloro-6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinoline (**4b′**) (exo):* colorless liquid; 10.5 mg, yield 32%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5H), 7.28−7.21 (m, 1H), 7.17 (dd, J = 7.0, 1.7 Hz, 2H), 6.82 (dd, J = 8.8, 2.5 Hz, 1H), 5.99 (d, J = 8.7 Hz, 1H), 5.20 (d, J = 7.1 Hz, 1H), 4.77 (dd, J = 7.8, 5.6 Hz, 1H), 4.29 (td, J = 8.8, 3.5 Hz, 1H), 3.97−3.81 (m, 2H), 2.74 (m, 1H), 2.59 (m, 1H), 2.25−2.13 (m, 1H), 2.01−1.68 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 140.9, 129.0, 128.7, 128.1, 126.9, 125.7, 122.9, 121.0, 112.9, 75.4, 66.6, 63.4, 56.7, 41.3, 36.0, 29.8, 24.8; HRMS (ESI+) calcd for $C_{20}H_{21}ClNO$ (M + H$^+$) 326.1312, found 326.1303.

*10-Bromo-6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinoline (**4c**) (endo):* colorless liquid; 17.6 mg, yield 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 5.0 Hz, 1H), 7.19 (m, 3H), 7.11−7.03 (d, J = 7.2 Hz, 2H), 6.96 (dd, J = 8.8, 2.4 Hz, 1H), 6.02 (d, J = 8.8 Hz, 1H), 4.73 (dd, J = 7.9, 3.9 Hz, 1H), 4.38 (d, J = 4.0 Hz, 1H), 3.98 (m, 1H), 3.84 (m, 1H), 3.38−3.29 (m, 1H), 2.42 (m, 1H), 2.22 (m, 2H), 1.88−1.76 (m, 3H), 1.73−1.62 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 142.3, 134.0, 131.9, 128.8, 126.9, 125.8, 121.1, 114.6, 107.5, 76.7, 65.0, 64.4, 57.7, 39.9, 34.5, 29.8, 29.3; HRMS (ESI+) calcd for $C_{20}H_{21}BrNO$ (M + H$^+$) 370.0807, found 370.0794.

*10-Bromo-6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinoline (**4c′**) (exo):* colorless liquid, 8.7 mg, yield 23%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.33 (d, J = 2.0 Hz, 1H), 7.28−7.12 (m, 4H), 7.10−7.03 (m, 2H), 6.85 (dd, J = 8.8, 2.5 Hz, 1H), 5.84 (d, J = 8.8 Hz, 1H), 5.10 (d, J = 7.1 Hz, 1H), 4.66 (dd, J = 7.8, 5.6 Hz, 1H), 4.18 (td, J = 7.6, 3.2 Hz, 1H), 3.87−3.71 (m, 2H), 2.64 (m, 1H), 2.49 (m, 1H), 2.14−2.04 (m, 1H), 1.93−1.57 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 141.2, 131.5, 130.9, 129.0, 126.9, 125.7, 123.4, 113.4, 108.1, 75.4, 66.6, 63.4, 56.7, 41.3, 36.0, 29.8, 24.8; HRMS (ESI+) calcd for $C_{20}H_{21}BrNO$ (M + H$^+$) 370.0807, found 370.0793.

*6-Phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]-quinoline (**4e** and **4e′**):* colorless liquid; 18.6 mg, yield 64%, dr (*endo*/*exo*) = 63:37; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.18 (m, 6H), 7.18−7.07 (m, 5H), 6.95−6.88 (m, 1H), 6.83−6.77 (m, 0.51H), 6.54 (m, 1.48H), 6.17 (d, J = 8.2 Hz, 1H), 5.99 (d, J = 8.2 Hz, 0.53H), 5.17 (d, J = 7.3 Hz, 0.55H), 4.78 (dd, J = 8.0, 3.5 Hz, 1H), 4.72 (dd, J = 7.9, 5.1 Hz, 0.59H), 4.45 (d, J = 4.3 Hz, 1H), 4.22 (td, J = 7.1, 3.5 Hz, 0.56H), 3.99 (m, 1H), 3.89−3.71 (m, 2H), 3.38 (m, 1H), 2.69−2.59 (m, 0.42H), 2.53−2.34 (m, 1.56H), 2.30−2.13 (m, 1.81H), 2.08 (m, 0.46H), 1.90−1.74 (m, 4H), 1.74−1.62 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 144.4, 143.4, 142.4, 131.6, 129.3, 129.0, 128.8, 128.7, 128.2, 126.7, 125.9, 125.8, 121.3, 119.1, 116.2, 115.8, 113.0, 111.8, 75.8, 66.5, 65.0, 64.4, 63.4, 57.6, 56.6, 41.8, 39.8, 35.8, 34.4, 29.9, 29.6, 29.2, 24.9; HRMS (ESI+) calcd for $C_{20}H_{22}NO$ (M + H$^+$) 292.1701, found 292.1698.

*6-(4-Chlorophenyl)-10-fluoro-2,3,3a,3b,4,5,6,11b-octahydrofuro-[3,2-c]pyrrolo[1,2-a]quinoline (**4f**) (endo):* light green oil liquid; 13.9 mg, yield 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.23 (m, 2H), 7.15−7.08 (m, 3H), 6.76 (td, J = 8.6, 3.0 Hz, 1H), 6.13 (dd, J = 9.0, 4.6 Hz, 1H), 4.79 (dd, J = 7.9, 3.1 Hz, 1H), 4.49 (d, J = 4.4 Hz, 1H), 4.08 (m, 1H), 3.94 (m, 1H), 3.42 (m, 1H), 2.51 (m, 1H), 2.41−2.20 (m, 2H), 1.99−1.74 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8 (d, J = 253.3), 142.9, 139.7, 132.5, 128.9, 127.3, 117.6 (d, J = 21.2), 116.1 (d, J = 22.2), 113.7 (d, J = 7.1), 120.2 (d, J = 6.1 Hz), 76.8, 65.1, 64.2, 57.7, 39.8, 34.3, 29.8, 29.0; HRMS (ESI+) calcd for $C_{20}H_{20}ClFNO$ (M + H$^+$) 344.1217, found 344.1217.

*6-(4-Chlorophenyl)-10-fluoro-2,3,3a,3b,4,5,6,11b-octahydrofuro-[3,2-c]pyrrolo[1,2-a]quinoline (**4f′**) (exo):* light green oil liquid; 8.1 mg, yield 24%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 2H), 7.06−6.95 (m, 3H), 6.52 (td, J = 8.6, 3.1 Hz, 1H), 5.83 (dd, J = 8.9, 4.5 Hz, 1H), 5.09 (d, J = 7.2 Hz, 1H), 4.63 (dd, J = 8.1, 4.9 Hz, 1H), 4.17 (td, J = 7.0, 3.5 Hz, 1H), 3.81 (q, J = 8.1 Hz, 1H), 3.73 (td, J = 9.0, 3.5 Hz, 1H), 2.63 (m, 1H), 2.48 (m, 1H), 2.13−2.03 (m, 1H), 1.86 (m 1H), 1.78−1.59 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3 (d, J = 253.3), 143.2, 138.6, 132.5, 129.1, 127.2, 115.4 (d, J = 22.2), 114.8 (d, J = 22.2), 112.2 (d, J = 7.1), 122.7 (d, J = 6.1 Hz), 75.6, 66.6, 63.2, 56.7, 41.5, 35.9, 29.7, 24.8; HRMS (ESI+) calcd for $C_{20}H_{20}ClFNO$ (M + H$^+$) 344.1217, found 344.1220.

*6-(3-Bromophenyl)-10-fluoro-2,3,3a,3b,4,5,6,11b-octahydrofuro-[3,2-c]pyrrolo[1,2-a]quinoline (**4g**) (endo):* yellowish-green liquid, 14.8 mg, yield 38%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.25 (m, 2H), 7.09 (t, J = 7.6 Hz, 1H), 7.01 (m, 2H), 6.67 (td, J = 8.6, 3.1 Hz, 1H), 6.05 (dd, J = 8.9, 4.6 Hz, 1H), 4.67 (dd, J = 7.9, 3.1 Hz, 1H), 4.39 (d, J = 4.4 Hz, 1H), 3.98 (td, J = 8.6, 6.3 Hz, 1H), 3.83 (td, J = 9.5, 5.7 Hz, 1H), 3.33 (m, 1H), 2.46−2.33 (m, 1H), 2.30−2.12 (m, 2H), 1.86−1.64 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5 (d, J = 236.3 Hz), 147.0, 140.0, 130.4, 130.1, 128.9, 124.4, 123.0, 120.2 (d, J = 6.1 Hz), 117.6 (d, J = 22.2 Hz), 116.2 (d, J = 22.2 Hz), 113.8 (d, J = 7.1 Hz), 76.7, 65.1, 64.6, 57.7, 39.6, 34.2, 29.7, 28.8; HRMS (ESI+) calcd for $C_{20}H_{20}BrFNO$ (M + H$^+$) 388.0712, found 388.0712.

*6-(3-Bromophenyl)-10-fluoro-2,3,3a,3b,4,5,6,11b-octahydrofuro-[3,2-c]pyrrolo[1,2-a]quinoline (**4g′**) (exo):* yellowish-green liquid; 7.4 mg, yield 19%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.22 (m, 2H), 7.10 (t, J = 7.8 Hz, 1H), 7.00 (m, 2H), 6.53 (td, J = 8.6, 3.1 Hz, 1H), 5.85 (dd, J = 8.9, 4.5 Hz, 1H), 5.11 (d, J = 7.1 Hz, 1H), 4.61 (dd, J = 7.8, 5.0 Hz, 1H), 4.19 (td, J = 6.9, 3.5 Hz, 1H), 3.82 (q, J = 8.1 Hz, 1H), 3.74 (td, J = 9.0, 3.4 Hz, 1H), 2.63 (m, 1H), 2.54−2.43 (m, 1H), 2.09 (m, 1H), 1.86 (m, 1H), 1.80−1.51 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (d, J = 235.3 Hz), 147.4, 138.5, 130.6, 130.1, 130.0, 128.8, 124.3, 123.1, 122.7 (d, J = 6.1 Hz), 115.3 (d, J = 22.2 Hz), 114.9 (d, J = 22.2 Hz), 112.1 (d, J = 7.1 Hz), 75.6, 66.6, 63.5, 56.7, 41.5, 35.8, 29.7, 24.8; HRMS (ESI+) calcd for $C_{20}H_{20}BrFNO$ (M + H$^+$) 388.0712, found 388.0696.

*6-(4-Nitrophenyl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinoline (**4h** and **4h′**):* orange liquid; 26.9 mg, dr (*endo*/*exo*) = 69:31, yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (t, J = 1.8 Hz, 0.52H), 8.10 (m, 6H), 7.39−7.24 (m, 8H), 7.10−6.99 (m, 2H), 6.96−6.88 (m, 1.41H), 6.83−6.77 (m, 0.56H), 6.64−6.50 (m, 3H), 6.36 (t, J = 7.2, 0.49H), 6.14 (d, J = 8.1 Hz, 0.39H), 6.03 (d, J = 8.2 Hz, 1H), 5.91−5.86 (m, 0.51H), 5.64 (d, J = 6.1 Hz, 0.55H), 5.19 (d, J = 5.4 Hz, 0.43H), 5.09 (dd, J = 8.5, 3.4 Hz, 0.50H), 5.01 (dd, J = 4.4, 1.5 Hz, 0.55H), 4.92−4.83 (m, 1.67H), 4.76 (q, J = 7.4 Hz, 1H), 4.46 (d, J = 4.2 Hz, 1H), 4.39−4.30 (m, 0.58H), 4.00 (td, J = 8.6, 6.3 Hz, 1H), 3.87 (m, 1H), 3.79 (dd, J = 7.5, 5.9 Hz, 1.29H), 3.65−3.53 (m, 0.93H), 3.44−3.29 (m, 1.73H), 2.79 (m, 0.47H), 2.65 (m, 0.80H), 2.57−2.46 (m, 1H), 2.43 (td, J = 7.1, 1.8 Hz, 1H), 2.36−2.14 (m, 2.48H), 2.12−1.92 (m, 0.77H), 1.92−1.64 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 152.4, 152.2, 147.4, 147.1, 147.0, 146.1, 142.7, 141.5, 131.9, 129.8, 129.5, 129.4, 129.1, 128.7, 128.35, 128.3, 127.4, 127.2, 126.7, 126.5, 126.4, 124.5, 124.4, 124.2, 124.1, 121.8, 121.5, 119.4, 117.7, 117.5,

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116.7, 116.6, 115.8, 115.7, 114.7, 114.1, 112.8, 111.6, 111.5, 103.9, 77.4, 77.0, 67.1, 66.2, 66.1, 65.1, 64.0, 63.7, 61.0, 60.3, 58.7, 57.7, 57.2, 57.1, 41.2, 39.9, 39.7, 36.9, 35.8, 35.1, 34.6, 34.3, 33.2, 32.4, 29.8, 29.8, 29.4, 23.6, 22.8; HRMS (ESI+) calcd for $C_{20}H_{21}N_2O_3$ (M + H^+) 337.1552, found 337.1553.

*10-Bromo-6-(p-tolyl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinoline (**4i**) (endo):* yellowish-green liquid; 10.2 mg, yield 27%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 7.9 Hz, 2H), 6.98−6.93 (m, 3H), 6.04 (d, J = 8.7 Hz, 1H), 4.70 (dd, J = 7.9, 3.8 Hz, 1H), 4.37 (d, J = 4.3 Hz, 1H), 3.97 (m, 1H), 3.88−3.77 (m, 1H), 3.31 (ddd, J = 11.2, 7.4, 5.7 Hz, 1H), 2.46−2.31 (m, 1H), 2.25 (s, 3H), 2.19 (ddd, J = 12.5, 8.4, 4.3 Hz, 1H), 1.84−1.73 (m, 3H), 1.66 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 140.8, 136.5, 133.9, 131.9, 129.5, 125.7, 121.1, 114.5, 107.4, 76.7, 65.0, 64.1, 57.6, 39.9, 34.6, 29.8, 29.3, 21.2; HRMS (ESI+) calcd for $C_{21}H_{23}BrNO$ (M + H^+) 384.0963, found 384.0960.

*10-Bromo-6-(p-tolyl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinoline (**4i′**) (exo):* yellowish-green liquid; 4.4 mg, yield 11%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 2.4, 1H), 7.04 (d, J = 7.8 Hz, 2H), 6.95 (d, J = 7.8 Hz, 2H), 6.85 (dd, J = 8.7, 2.5 Hz, 1H), 5.86 (d, J = 8.7 Hz, 1H), 5.09 (d, J = 7.1 Hz, 1H), 4.63 (dd, J = 7.7, 5.6 Hz, 1H), 4.16 (td, J = 6.8, 2.4 Hz, 1H), 3.86−3.71 (m, 3H), 2.68−2.57 (m, 1H), 2.53−2.42 (m, 1H), 2.25 (s, 3H), 2.14−2.02 (m, 1H), 1.91−1.59 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 141.1, 136.5, 131.5, 130.9, 129.6, 125.6, 123.4, 113.4, 108.0, 75.4, 66.6, 63.1, 56.6, 41.3, 36.0, 29.8, 24.7, 21.2; HRMS (ESI+) calcd for $C_{21}H_{23}BrNO$ (M + H^+) 384.0963, found 384.0950.

*10-Methyl-6-(p-tolyl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinoline (**4j** and **4j′**):* light green liquid; 23.6 mg, yield 74%, dr (*endo*/*exo*) = 64:36; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11−7.06 (m, 1.59H), 7.05−6.95 (m, 5.62H), 6.73 (dd, J = 8.4, 1H), 6.62 (dd, J = 8.0, 0.46H), 6.10 (d, J = 8.4 Hz, 1H), 5.92 (d, J = 8.0 Hz, 0.44H), 5.14 (d, J = 7.2 Hz, 0.45H), 4.70 (m, 1.47H), 4.41 (d, J = 4.4 Hz, 1H), 4.18 (td, J = 7.0, 3.3 Hz, 0.48H), 3.97 (m, 1H), 3.80 (m, 2H), 3.33 (m, 1H), 2.61 (m, 0.21H), 2.49−2.30 (m, 1H), 2.24 (m, 5H), 2.11 (s, 3H), 1.78 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 141.6, 141.2, 140.3, 136.2, 136.2, 131.9, 129.9, 129.5, 129.4, 129.3, 128.8, 125.8, 125.8, 125.0, 124.8, 121.3, 119.0, 113.0, 111.9, 77.2, 76.0, 66.6, 65.0, 64.2, 63.1, 57.6, 56.6, 42.1, 39.9, 35.8, 34.4, 29.9, 29.5, 29.0, 25.0, 21.2, 20.5, 20.3; HRMS (ESI+) calcd for $C_{22}H_{26}NO$ (M + H^+) 320.2014, found 320.2008.

*6-(4-Methoxyphenyl)-10-methyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo [1,2-a]quinoline (**4k** and **4k′**):* white solid; 22.1 mg, yield 66%; mp 169.8−172.4 °C; dr (*endo*/*exo*) = 67:33; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (m, 1.78H), 7.01 (m, 3H), 6.77−6.70 (m, 4H), 6.62 (d, J = 8.0, 0.55H), 6.11 (d, J = 8.3 Hz, 1H), 5.93 (d, J = 8.2 Hz, 0.54H), 5.13 (d, J = 7.3 Hz, 0.54H), 4.68 (m, 1.66H), 4.41 (d, J = 4.4 Hz, 1H), 3.97 (td, J = 8.4, 6.3 Hz, 1H), 3.81 (m, 1H), 3.70 (s, 5H), 3.32 (m, 1H), 2.61 (m, 0.58H), 2.49−2.39 (m, 0.51H), 2.34 (m, 0.91H), 2.21 (m, 1.45H), 2.11 (s, 5H), 2.05 (m, 0.52H), 1.89−1.60 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 141.2, 140.3, 136.9, 136.6, 131.9, 129.9, 129.4, 128.8, 127.0, 126.9, 125.0, 124.8, 121.3, 119.0, 114.1, 114.0, 113.0, 111.9, 76.0, 66.6, 65.0, 63.9, 62.8, 57.5, 56.5, 55.4, 42.1, 39.9, 35.9, 34.4, 29.9, 29.4, 29.0, 25.0, 20.5, 20.3; HRMS (ESI+) calcd for $C_{22}H_{26}NO_2$ (M + H^+) 336.1964, found 336.1965.

*10-Fluoro-6-(thiophene-2-yl)-2,3,3a,3b,4,5,6,11b-octahydrofuro-[3,2-c]pyrrolo[1,2-a]quinoline (**4l** and **4l′**):* colorless liquid; 15.8 mg, yield 50%; dr (*endo*/*exo*) = 63:37; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (m, 2H), 6.99 (m, 2H), 6.86 (m, 2H), 6.77 (t, J = 4.5 Hz, 2H), 6.71 (td, J = 8.4, 2.8 Hz, 1H), 6.59 (td, J = 8.4, 2.8 Hz, 1H), 6.38 (dd, J = 9.0, 4.6 Hz, 1H), 6.20 (dd, J = 8.9, 4.6 Hz, 1H), 5.08 (d, J = 7.5 Hz, 1H), 4.98 (m, 2H), 4.37 (d, J = 4.6 Hz, 1H), 4.09 (td, J = 7.2, 3.3 Hz, 1H), 3.96 (m, 1H), 3.85−3.69 (m, 4H), 3.26 (m, 1H), 2.63 (m, 1H), 2.50−2.12 (m, 5H), 1.98−1.62 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (d, J = 236.3 Hz), 148.8, 139.9, 130.7, 127.11, 127.07, 127.0, 126.9, 124.0, 123.7, 123.46, 122.7, 120.8 (d, J = 7.1 Hz), 120.6, 117.4 (d, J = 21.2 Hz), 116.0 (d, J = 23.2 Hz), 115.5 (d, J = 22.2 Hz), 114.9 (d, J = 22.2 Hz), 114.1 (d, J = 7.1 Hz), 113.8, 117.7 (d, J = 7.1 Hz), 100.2, 76.6, 75.9, 67.2, 66.8, 65.1, 61.0, 59.3, 58.3, 56.6, 55.8, 41.9, 39.9, 35.4, 35.1, 34.2, 32.4, 29.8, 29.7, 29.1, 28.9, 28.4, 24.7, 23.5; HRMS (ESI+) calcd for $C_{18}H_{19}FNOS$ (M + H^+) 316.1171, found 316.1169.

*6-(Thiophene-2-yl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinoline (**4m** and **4m′**):* colorless liquid; 16.4 mg, yield 55%, dr (*endo*/*exo*) = 61:39; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, J = 7.6, 1.6 Hz, 1H), 7.24 (d, J = 7.6, 1H), 7.07 (m, 1H), 7.04−6.95 (m, 1H), 6.94−6.86 (m, 1H), 6.84 (m, 2H), 6.78 (m, 2H), 6.59 (m, 2H), 6.46 (dd, J = 8.2, 1.0 Hz, 1H), 6.30 (dd, J = 8.2, 1.1 Hz, 1H), 5.14 (d, J = 7.5 Hz, 1H), 5.06−4.99 (m, 2H), 4.42 (d, J = 4.4 Hz, 1H), 4.11 (m, 1H), 3.96 (m, 1H), 3.85−3.69 (m, 3H), 3.29 (m, 1H), 2.64 (m, 1H), 2.30 (m, 2H), 2.26−2.11 (m, 2H), 1.98−1.67 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7, 143.3, 142.4, 131.6, 129.3, 129.2, 128.3, 126.9, 126.8, 123.88, 123.86, 123.6, 123.5, 122.7, 122.1, 119.7, 116.9, 116.6, 113.2, 112.0, 76.9, 76.0, 66.6, 65.0, 60.7, 59.0, 56.4, 55.7, 42.0, 39.8, 35.4, 34.2, 29.8, 28.9, 28.5, 24.8; HRMS (ESI+) calcd for $C_{18}H_{20}NOS$ (M + H^+) 298.1266, found 298.1266.

*(E)-6-Styryl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline (**4n** and **4n′**):* colorless liquid; 19.7 mg, yield 62%, dr (*endo*/*exo*) = 63:37; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.17 (m, 16H), 7.13 (t, J = 7.1 Hz, 3H), 7.04 (t, J = 7.9 Hz, 2H), 6.95 (t, J = 7.9 Hz, 1H), 6.59 (t, J = 7.3 Hz, 4H), 6.48 (d, J = 8.1 Hz, 1H), 6.41 (m, 3H), 6.15 (d, J = 5.9 Hz, 1H), 6.11 (d, J = 6.2 Hz, 1H), 6.07 (d, J = 6.6 Hz, 0.41H), 5.13 (d, J = 7.6 Hz, 1H), 4.41 (t, J = 6.5 Hz, 5H), 4.24 (t, J = 6.6 Hz, 1H), 3.95 (m, 3H), 3.78 (m, 4H), 3.18 (m, 1.55H), 2.69−2.55 (m, 1H), 2.31−1.98 (m, 7H), 1.74 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 143.1, 137.0, 136.9, 131.6, 131.2, 130.1, 129.9, 129.4, 129.2, 128.7, 128.4, 127.5, 127.5, 126.5, 126.4, 122.0, 119.3, 116.4, 116.0, 113.1, 112.0, 77.1, 76.0, 66.6, 64.9, 62.1, 60.8, 56.3, 55.6, 41.8, 39.9, 32.0, 30.9, 29.8, 29.0, 28.9, 24.8; HRMS (ESI+) calcd for $C_{18}H_{19}FNOS$ (M + H^+) 316.1171, found 316.1169.

*6-Cyclohexyl-10-fluoro-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinoline (**4o** and **4o′**):* yellowish-green liquid; 22.4 mg, yield 71%, dr (*endo*/*exo*) = 62:38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (m, 2H), 6.82 (td, J = 8.7, 3.0 Hz, 1H), 6.71 (td, J = 8.7, 3.0 Hz, 1H), 6.44 (dd, J = 9.0, 4.5 Hz, 1H), 6.26 (dd, J = 9.0, 4.5 Hz, 1H), 4.98 (d, J = 7.0 Hz, 1H), 4.29 (d, J = 4.2 Hz, 1H), 3.91 (q, J = 7.9 Hz, 1H), 3.79 (m, 4H), 3.64 (m, 4H), 3.08−2.94 (m, 1H), 2.54−2.44 (m, 1H), 2.26−2.12 (m, 3H), 2.00 (m, 1H), 1.82 (m, 8H), 1.73−1.39 (m, 11H), 1.18 (m, 3H), 1.10−0.88 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (d, J = 234.3.3 Hz), 139.3, 121.9 (d, J = 5.1 Hz), 117.8 (d, J = 22.2 Hz), 116.0 (d, J = 22.2 Hz), 115.3 (d, J = 22.2 Hz), 114.8 (d, J = 22.2 Hz), 111.0 (d, J = 6.1 Hz), 75.5, 66.3, 64.9, 63.5, 56.6, 55.3, 41.4, 40.3, 40.0, 39.8, 30.4, 30.2, 30.2, 29.9, 29.8, 27.8, 27.2, 26.8, 26.7, 26.69, 26.66, 26.4, 26.3, 25.5, 24.8, 24.3; HRMS (ESI+) calcd for $C_{20}H_{27}FNO$ (M + H^+) 316.2077, found 316.2073.

*11-Fluoro-7-phenyl-3,4,4a,4b,5,6,7,12b-octahydro-2H-pyrano-[3,2-c]pyrrolo[1,2-a]quinoline (**4p**):* white solid; 47 mg, yield 51%; mp 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.17 (m, 2H), 7.16−7.10 (m, 3H), 6.84 (dd, J = 8.8, 3.0 Hz, 1H), 6.56 (td, J = 8.7, 3.1 Hz, 1H), 5.90 (dd, J = 9.0, 4.6 Hz, 1H), 4.61 (t, J = 7.6 Hz, 1H), 4.25−4.15 (m, 2H), 4.12−4.04 (m, 1H), 3.67 (m, 1H), 2.49 (m, 1H), 2.18 (m, 1H), 1.88 (m, 3H), 1.75 (m, 1H), 1.62−1.48 (m, 2H), 1.41−1.34 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2 (d, J = 235.3 Hz), 144.9, 139.7, 128.9, 126.8, 125.7, 121.3 (d, J = 6.1 Hz), 117.1 (d, J = 21.2 Hz), 116.0 (d, J = 22.2 Hz), 122.2 (d, J = 8.1 Hz), 76.1, 69.2, 64.0, 55.9, 37.2, 36.1, 31.4, 24.8, 21.6; HRMS (ESI+) calcd for $C_{21}H_{23}FNO$ (M + H^+) 324.1764, found 324.1757.

*10-Fluoro-2,6-diphenyl-1-tosyl-2,3,3a,3b,4,5,6,11b-octahydro-1H-dipyrrolo[1,2-a:3′,2′-c]quinoline (**4q** and **4q′**):* white solid; 43.1 mg, yield 80%; mp 188.3−191.2 °C; dr (*endo*/*exo*) = 37:63; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 10.3, 2.9 Hz, 1H), 7.42 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.3 Hz, 4H), 7.19−7.14 (m, 1H), 7.09 (m, 3H), 7.05−6.86 (m, 9H), 6.84 (d, J = 8.1 Hz, 1H), 6.56 (m, 2H), 5.93 (dd, J = 9.0, 4.7 Hz, 1H), 5.81 (dd, J = 9.0, 4.6 Hz, 1H), 5.48 (d, J = 6.3 Hz, 1H), 5.21 (t, J = 8.4 Hz, 1H), 4.81 (d, J = 3.9 Hz, 1H), 4.66−4.60 (m, 1H), 4.47 (dd, J = 7.6, 5.4 Hz, 1H), 4.24 (m, 1H), 3.46 (dt, J = 11.4, 6.4 Hz, 1H), 2.92−2.82 (m, 1H), 2.48−2.27 (m, 3H), 2.24 (s, 5H), 2.12 (m, 2H), 1.88−1.65 (m, 2H), 1.62−1.47 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8 (d, J = 233.3 Hz), 154.1, 144.5, 144.5, 142.3, 141.9, 141.2, 140.6, 139.4, 139.2, 139.1, 128.93, 128.87, 128.7, 128.0, 127.5, 127.2, 126.9, 126.8, 126.4, 126.0, 125.6, 125.5, 120.6, 120.4, 117.2 (d, J = 24.3 Hz), 116.4 (d, J = 22.2 Hz),

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115.1 (d, J = 22.2 Hz), 114.4 (d, J = 7.1 Hz), 112.5 (d, J = 7.1 Hz), 112.3 (d, J = 7.1 Hz), 66.3, 64.2, 62.9, 62.4, 61.8, 61.4, 57.0, 56.7, 41.2, 39.5, 38.2, 35.8, 35.0, 34.9, 29.8, 29.4, 21.7, 21.5; HRMS (ESI+) calcd for $C_{33}H_{31}FN_2NaO_2S$ (M + Na^+) 561.1988, found 561.1988.

*N-(4-Nitrophenyl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]-pyrrolo[1,2-a]quinolin-10-amine (**4t** and **4t′**):* orange solid; 46.5 mg, yield 44%; mp 160−162 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (d, J = 3.2 Hz, 1H), 8.01 (dt, J = 9.4, 2.4 Hz, 2H), 7.09 (t, J = 2.8 Hz, 1H), 7.04 (dq, J = 8.0, 2.6 Hz, 1H), 6.79 (dt, J = 9.3, 2.4 Hz, 2H), 6.54 (dt, J = 8.7, 2.5 Hz, 1H), 4.40 (q, J = 3.2, 1.9 Hz, 1H), 3.89−3.75 (m, 1H), 3.70 (tt, J = 9.0, 3.6 Hz, 1H), 3.14 (dq, J = 10.3, 5.0, 4.6 Hz, 1H), 2.67 (tt, J = 9.2, 3.6 Hz, 1H), 2.26−2.13 (m, 2H), 2.07−1.72 (m, 5H), 1.51 (p, J = 11.3, 10.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9, 142.4, 136.6, 127.6, 126.4, 126.3, 124.6, 121.2, 112.0, 111.9, 76.2, 64.3, 57.5, 46.7, 40.8, 30.7, 29.1, 22.5; HRMS (ESI+) calcd for $C_{24}H_{31}N_2O_2$ (M + H^+) 379.2386, found 379.2371.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02496.

Characterization data, NMR and HR-MS spectra of all pyrroloquinoline derivatives, and X-ray data for *exo*-**4q′** (PDF)

X-ray crystallographic data for *exo*-**4q′** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) Crystal data for the compound *exo*-**4q′**: $C_{33}H_{31}FN_2O_2S$, MW) 538.66, tetragonal, *P*-42(1)*c*. Final *R* indices [$I > 2\theta(I)$], R1) 0.0262, wR2) 0.0707, R indices (all data) R1) 0.0284, wR2) 0.0720, *a* 23.493(17) Å, *b* 23.493(17) Å, *c* 9.703(9) Å, *V* = 5355.2(7) Å3, *T* 113(2) K, *Z* 8. Reflections collected/unique: 67777/6129 [*R*(int) 0.0444], number of observations [$>2\theta(I)$] 6129, parameters 353, goodness-of-fit on *F*2 1.037. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre. CCDC 1503242.

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