EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402869

Transition-Metal-Catalyzed Selective Cyclization Strategy to 2-Substituted Benzofurans and Indoles en Route to the Oxa Analogues of Isocryptolepine

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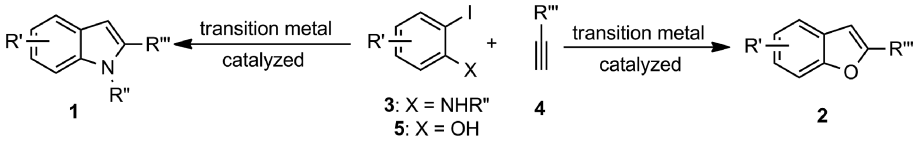
Keywords: Synthetic methods / Cross-coupling / Cyclization / Domino reactions

A selective catalytic route to benzofurans and indoles from similar starting materials has been developed. A two-step protocol that involves a transition-metal-catalyzed domino Sonogashira coupling between 2-ethynylanilines and 2-iodophenols followed by selective *O*- and *N*-cyclizations afforded 2-(benzofuran-2-yl)anilines and 2-(indol-2-yl)phenols, respectively. The 2-(benzofuran-2-yl)anilines were further utilized in a Lewis acid catalyzed Pictet–Spengler-type cyclization to prepare the oxa analogues of isocryptolepine.

Introduction

Selective catalysis that leads to different products by starting from similar materials is widely regarded as an important tool for divergent synthesis.[1] 2-Substituted indoles **1** and benzofurans **2** are versatile building blocks for the syntheses of several natural products and biologically active molecules.[2,3] Since the pioneering work of Larock,[4] in which he prepared substituted indoles by using the Pd-catalyzed heteroannulation of 2-iodoanilines with internal alkynes, a whole new approach towards the preparation of 2-substituted indoles has been developed. Henceforth, similar strategies have extended towards the synthesis of both 2-substituted benzofurans[5–7] and indoles.[7,8] Of these, several reports include the use of a domino Sonogashira coupling reaction followed by an in situ cyclization (see Scheme 1) to provide 2-substituted benzofurans and indoles.[5a–5e,7a]

In most cases, substrates with free amine groups are incompatible in metal-catalyzed reactions because of the inherent tendency of the nitrogen atom to coordinate with the metal catalyst, thereby rendering the catalyst inactive. Notably, most of the abovementioned reports do not contain any examples of Sonogashira couplings that involve a free $-NH_2$ group in either of the starting materials. Only few groups have reported successful Sonogashira coupling reactions with substrates that have free $-NH_2$ groups, albeit they occurred in poor yields and by employing other additives,[8g] and some efforts have failed.[7c] A divergent catalytic route for selective cyclization reactions that give 2-substituted indoles **1** and benzofurans **2** by starting from substrates similar to **3** and varying the catalytic conditions have not been reported (see Scheme 2). Herein, we achieved selective *N*- and *O*-cyclizations by starting from similar substrates and using different catalytic conditions. We also demonstrated that a palladium-free, copper-catalyzed



Scheme 1. Cyclization strategy for formation of 2-substituted benzofurans and indoles.

Sonogashira coupling followed by an *O*-cyclization to give 2-(benzofuran-2-yl)anilines **7** could be achieved in decent yields even with substrates that have a free $-NH_2$ group. Furthermore, we describe a very similar route to 2-(1*H*-indol-2-yl)phenols **8** by using a selective *N*-cyclization strat-

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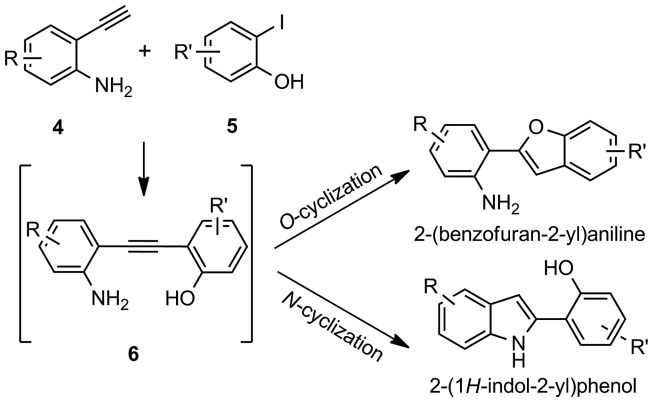
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402869.

egy under different catalytic conditions, but with similar starting materials.



Scheme 2. Selective *N*- and *O*-cyclization strategy to benzofurans and indoles.

To further increase the scope of our work, we prepared the oxa analogues of isocryptolepine (**9**), which is an indole alkaloid that was isolated from *Cryptolepis sanguinolenta* and has a linear 5*H*-indolo[3,2-*c*]quinoline framework **10**. Isocryptolepine was first isolated by Pousset and co-workers in 1994[9] and is used as an antimalarial agent[10] and as a DNA intercalating agent to strongly inhibit human topoisomerase II.[11] A number of total syntheses of isocryptolepine have been reported.[12,13] Assuming that the oxa analogues of isocryptolepine (see Figure 1), with a benzofuran in place of the indole moiety [i.e., benzofuro[3,2-*c*]-quinoline **11**] or a chromene in place of quinoline unit [i.e., chromeno[4,3-*b*]indole **12**] might have similar biological activities, we devised a route for their synthesis. Of the various reports for the total synthesis of isocryptolepine, there were only few that involve a Pictet–Spengler-type cyclization of 2-(1*H*-indol-2-yl)aniline to provide the tetracyclic core.[13e–13g] In relation to our current interest in the preparation of indoles and benzofurans along with our long-standing interest in the transition-metal-catalyzed synthesis of natural products and biologically active molecules,[14] we planned to synthesize the oxa analogues of isocryptolepine.

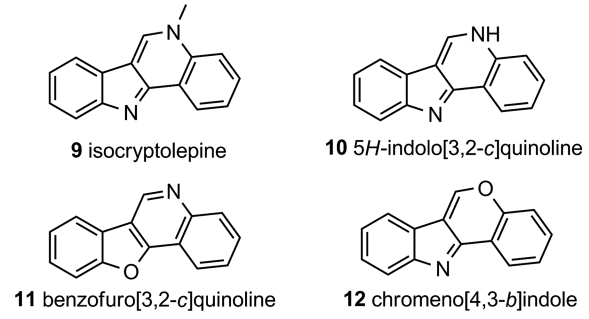
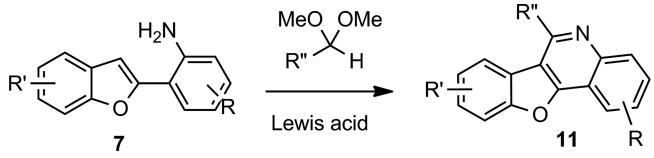


Figure 1. Isocryptolepine and its oxa analogues.

Herein, we have further utilized the free $-NH_2$ groups of 2-(benzofuran-2-yl)anilines **7** to extend our synthetic approach to a Pictet–Spengler-type cyclization and provide the benzofuro[3,2-*c*]quinoline framework, as one of the oxa analogues of isocryptolepine (see Scheme 3).[15]



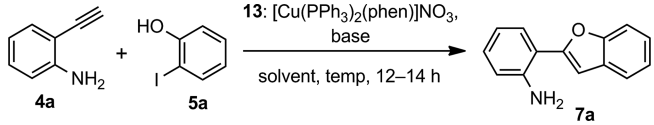
Scheme 3. Preparation of the oxa analogues of isocryptolepine.

Results and Discussion

For the preparation of benzofuro[3,2-*c*]quinoline derivatives **11**, we used 2-ethynylanilines **4** and substituted 2-iodophenols **5** as starting materials in a Cu-catalyzed cyclization to obtain the benzofuran core **7**. This was followed by a Pictet–Spengler-type cyclization of **7** that employed various acetals in the presence of a Lewis Acid to arrive at **11**. As for the chromeno[4,3-*b*]indole derivatives, we envisaged a similar route that started from the same starting materials and used the same two-step strategy.

For the preparation of 2-[benzofuran-2-yl]anilines **7**, *ortho*-ethynylaniline derivatives **4** were prepared by using a known two-step protocol that started from the corresponding 2-iodoanilines.[16] To optimize the formation of the benzofurans, we screened the reaction between 2-ethynylaniline (**4a**) and 2-iodophenol (**5a**) by employing different bases, solvents, and catalyst loadings. Finally, the optimized conditions were determined to use 0.1 equiv. of Venkataraman's catalyst[5a] $[Cu(PPh_3)_2(phen)]NO_3$ (**13**, phen = 1,10-phenanthroline) and 2.0 equiv. of Cs_2CO_3 in toluene at 110 °C to give **7a** in a yield of 68% (see Table 1, Entry 2). K_2CO_3, which is less soluble in toluene, gave a poorer yield even at higher temperatures when it was used as a base, whereas K_3PO_4 gave benzofuran **7a** in only 17% yield (see Table 1, Entries 4–6).

Table 1. Optimization of *O*-cyclization for preparation of the 2-(benzofuran-2-yl)anilines.

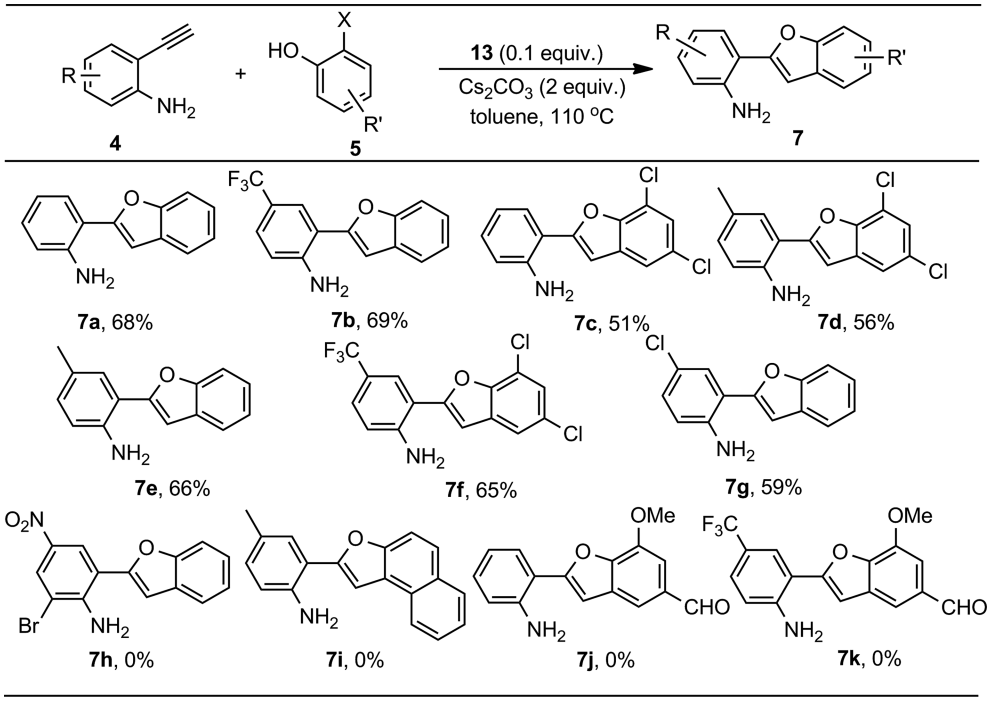


Entry	Catalyst [equiv.]	Base[a]	Solvent	Temp. [°C]	Yield[b] [%]
1	0.1	Cs_2CO_3	DMF[c]	110	44
2	0.1	Cs_2CO_3	toluene	110	68
3	0.1	Cs_2CO_3	THF[c]	110	60
4	0.1	K_2CO_3	toluene	110	46
5	0.1	K_2CO_3	toluene	140	48
6	0.1	K_3PO_4	toluene	110	17

[a] 2 equiv. of base were employed. [b] Isolated yields. [c] DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

Next we studied the scope of the substrates by investigating the coupling reaction of various substituted 2-ethynylanilines **4** and 2-halophenols **5** under the optimized

Table 2. Substrate scope for formation of 2-(benzofuran-2-yl)anilines.[a]



[a] All yields are isolated yields.

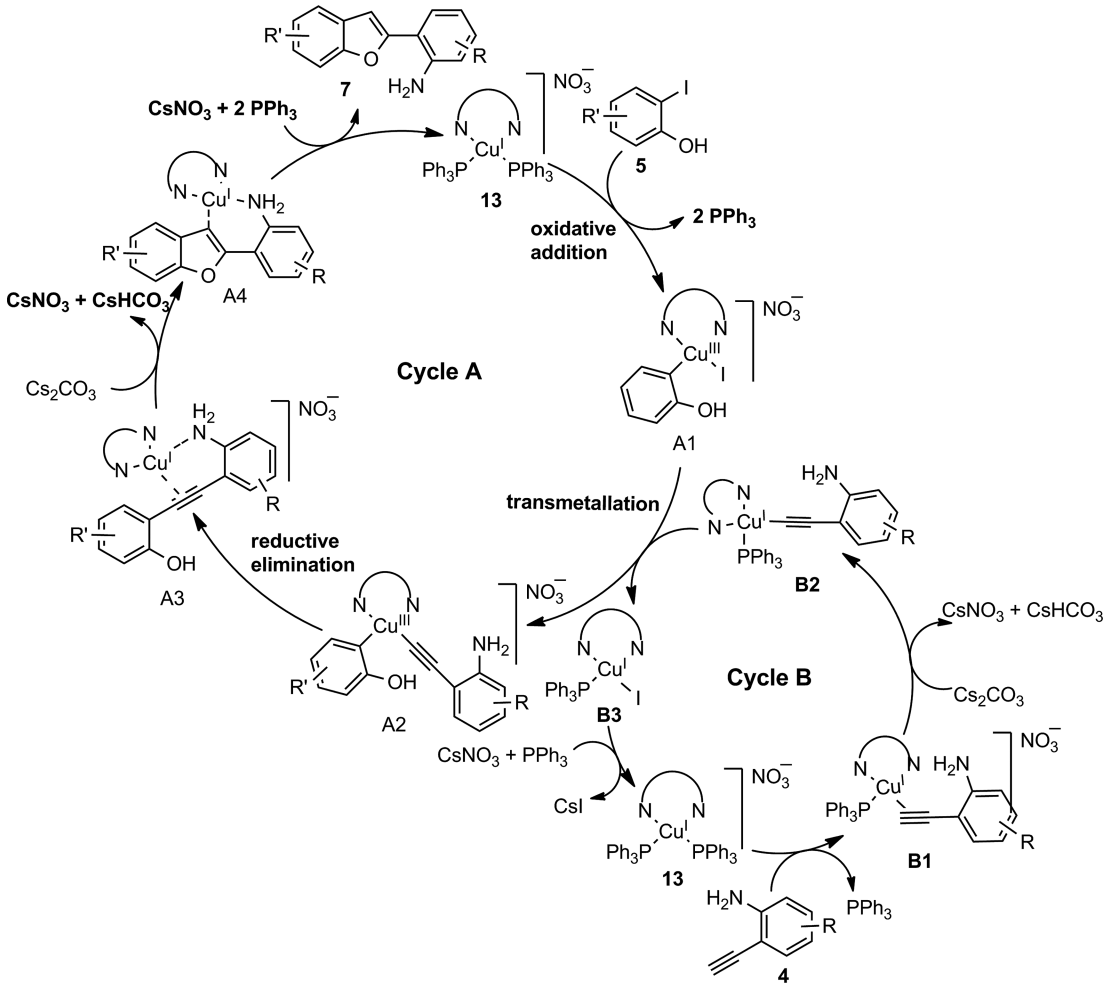
conditions (see Table 2). The reaction tolerated both electron-donating and electron- withdrawing groups such as CH_3 and CF_3 with regard to the aniline. The tolerance of the reaction towards the variation of the phenol substrate proved to be more selective with only the 2,4-dichloro-substituted iodophenol undergoing the reaction satisfactorily to give the corresponding benzofurans (i.e., **7c**, **7d**, and **7f**). The 2-bromophenols did not cyclize to give the corresponding benzofurans, thereby demonstrating the greater reactivity of the aryl iodide substrates towards this transition-metal-catalyzed coupling reaction. Electron-deficient 2-bromo-5-ethynyl-4-nitroaniline gave a decomposed mixture when treated with 2-iodophenol, and no trace of the cyclized product **7h** was obtained. 1-Bromo-2-naphthol did not undergo a reaction, probably as a result of the highly hindered position of the bromo group, and thus **7i** was not produced. In addition, the reaction with 5-iodovanillin did not proceed to give the desired benzofurans **7j** and **7k**.

A probable mechanism for the formation of the benzofurans is proposed in Scheme 4. First, Cu^I complex **13** undergoes π-coordination with 2-ethynylaniline **4** to form the π-complex **B1**. The Cs_2CO_3 acts as a base to abstract the terminal proton from **B1**, and, thus, copper acetylide **B2** is formed, whereupon the copper undergoes a ligand exchange to give iodo complex **B3**. Finally, the bulky triphenylphosphine returns as a ligand, which results in the formation of CsI and the completion of Cycle B.

In Cycle A, the copper(I) in Venkataraman's catalyst (**13**) undergoes an oxidative addition with iodophenol **5** to give copper(III) species **A1**.[8e] The 2-aminoacetylide group of **B2** then undergoes a transmetalation with **A1** to give **A2**, which then undergoes a reductive elimination to form the Sonogashira coupled product **A3**. At this stage, the Cu^I coordinates to the triple bond, thereby activating it towards a 5-*endo-dig* cyclization by the phenoxide group to form **A4**. Finally, product **7** is eliminated from the cycle, and catalyst **13** is regenerated.

Having obtained the benzofurans with various functional groups, we proceeded to submit them to the Pictet–Spengler-type cyclizations to form isocryptolepine analogues **15**. The corresponding acetal **14** was employed in each reaction to arrive at the tetracyclic product. The reactions with benzofurans **7** proceeded smoothly at room temperature in the presence of the Lewis acid $BF_3{\cdot}OEt_2$ and provided the oxa analogues in good to excellent yields (see Table 3). Several acetals **14** were examined, but only the dimethyl acetals of benzaldehyde and 5-bromothiophene-2-carbaldehyde gave decent results. In many cases, we obtained secondary amine **16**, which was formed from an apparent reductive amination of the free amine group of the 2-(benzofuran-2-yl)anilines.

A possible explanation for the formation of the reduced products could be that trialkylboranes are known to act as radical initiators under oxygen through a homolytic cleavage of the boron-alkyl bond to give rise to alkyl radicals.[17] Under our reaction conditions, trace amounts of dissolved oxygen in the solvent or $BF_3{\cdot}OEt_2$ might have facilitated the radical formation. The methanol, which is released into the system from the dimethyl acetal, would act as a source of a hydrogen radical, and this might in turn reduce the



Scheme 4. Probable mechanism for the formation of 2-(benzofuran-2-yl)anilines.

imine that is generated in situ from the condensation of the acetal and the (benzofuran-2-yl)aniline to give the reduced side product. To check the accuracy of our hypothesis, we carried out a few experiments to gain insight into the mechanism behind the formation the uncyclized reduced products **16** (see Scheme 5).

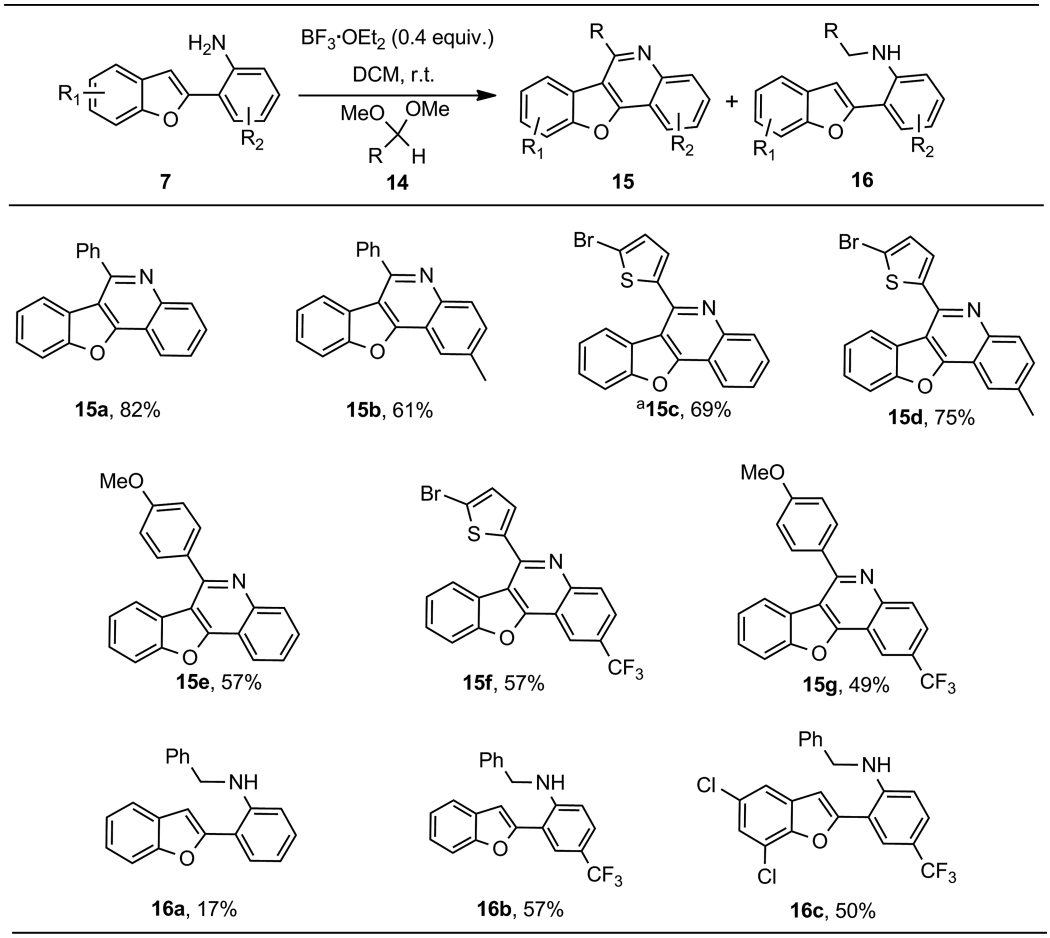
In presence of oxygen, we found that the formation of cyclized compound **15a** decreased to 36%, and the formation of reduced side product **16a** increased to 48%. To further support this radical pathway, when we carried out the reaction in presence of the well-known radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the reduced product was not even formed in a trace amount. The combination of these two results confirmed that formation of the reduced product was facilitated by the presence of radicals, which were formed under an oxygen atmosphere.

After achieving the selective *O*-cyclization to form (benzofuran-2-yl)anilines **7** and then exploiting them to prepare benzofuro[3,2-*c*]quinoline derivatives **15**, we set out to explore the selective *N*-cyclization, which would lead to the preparation of indole derivatives **8**. To suppress the more facile *O*-cyclization reaction, we chose a more suitable protocol by employing standard Sonogashira conditions with $Pd(PPh_3)_2Cl_2$ and CuI along with weak organic bases such as triethylamine and diisopropylamine (DIPA). We found, however, that cyclization did not take place under the abovementioned conditions, and we obtained only the uncyclized Sonogashira coupled product (i.e., **6**) that contained a free $–NH_2$ and a free –OH group.

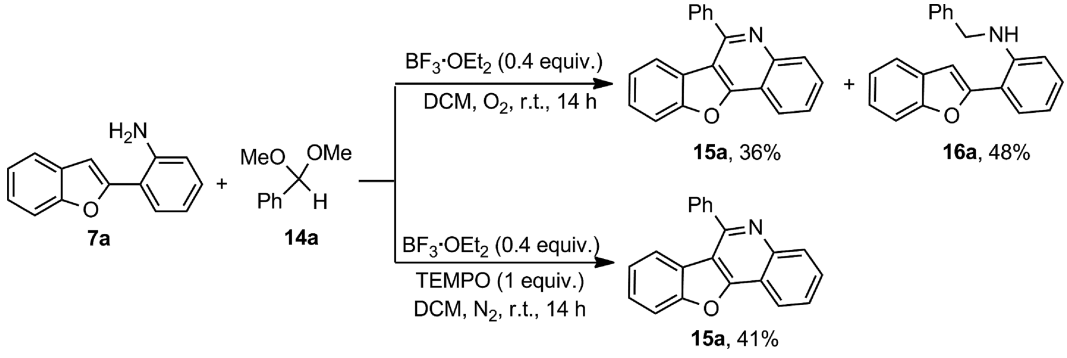
A possible reason for this may be the facile coordination of the free amine with the metal, which makes the metal unavailable to activate the alkyne, thereby preventing the cyclization that would provide the indole product. To trigger the *N*-cyclization following the Sonogashira coupling, we activated the amine by installing an electron-withdrawing group (tosyl or pivaloyl), which would make it softer in nature and prevent its coordination to the metal.[14e,18] Starting with *N*-tosyl-2-ethynylaniline and 2-iodophenol, we screened for different reaction conditions by varying the solvent and catalyst loading (see Table 4).

Upon identifying the optimized conditions, we proceeded to prepare indoles **18a**–**18d** by changing the substituents of

Table 3. Preparation of the oxa analogues of isocryptolepine.[a]



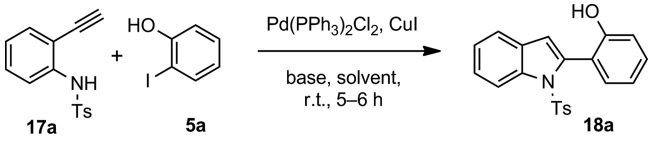
[a] Yield based on recovered starting material (brsm).



Scheme 5. Mechanistic studies of the formation of the uncyclized product.

the aniline and the phenol (see Table 5). Unfortunately, indole derivatives **18a**–**18d** failed undergo a reaction under the same BF_3·OEt_2 conditions. This may be because of the electron-withdrawing protecting groups on the nitrogen atom, which can reduce the nucleophilicity at the C-3 center. Several conditions, which included Cs_2CO_3/EtOH, Mg/MeOH, tetra-*n*-butylammonium fluoride (TBAF)/THF and NaOH/DMF/H_2O, failed to removed the indole protecting group (see Scheme 6). This is probably a result of the formation of an isomer of *N*-tosyl-2-(indol-2-yl)phenol (i.e., **18a′**), which prevents any nucleophilic reagent from reaching the sulfur center. A similar tautomeric form can be envisaged for *N*-pivaloyl-2-(indol-2-yl)phenol (**18b**), in which the phenol oxygen atom undergoes an addition to the carbonyl carbon.

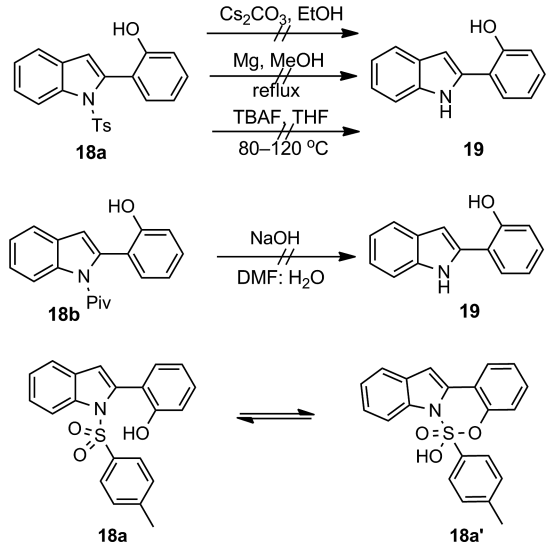
Table 4. Optimization of *N*-cyclization to yield the 2-(indol-2-yl) phenol derivatives.



17a 5a 18a

Entry	Pd catalyst [equiv.]	CuI [equiv.]	Solvent	Base	Yield[a] [%]
1	0.01	0.03	toluene	Et_3N	47
2	0.03	0.09	toluene	Et_3N	67
3	0.03	0.09	THF	Et_3N	54
4	0.03	0.09	benzene	DIPA	53

[a] Isolated yields.



Scheme 6. Failed deprotection of indole derivatives (Piv = pivaloyl).

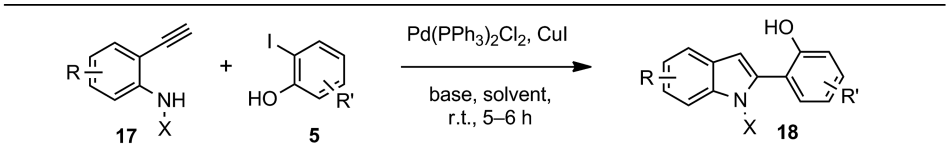
(benzofuran-2-yl)-anilines were converted into benzofuro[3,2-*c*]quinolines **15** by employing a Lewis acid mediated Pictet–Spengler-type cyclization to obtain the oxa analogues of isocryptolepine.

Experimental Section

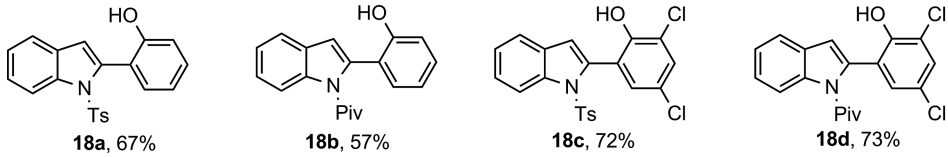
General Methods: Unless otherwise noted, all starting materials and reagents were obtained from commercial suppliers and used after further purification as detailed below. Dichloromethane was freshly distilled from calcium hydride, and toluene was distilled over sodium wire. All solvents that were used for the routine isolation of products and for chromatography were reagent grade and glass distilled. Reaction flasks were dried in an oven at 130 °C for 12 h. Air and moisture-sensitive reactions were performed under an argon/ultra high purity (UHP) nitrogen atmosphere. Column chromatography was performed by using silica gel (100–200 mesh, Acme) with the indicated solvents. Thin layer chromatography was conducted with Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized by UV light and potassium permanganate, ceric ammonium molybdate, or iodine staining as appropriate. IR spectra were recorded with a Perkin–Elmer Spectrum One and JASCO V-570 spectrophotometers. Mass spectra were obtained with a Bruker ESI-QTOF spectrometer (maXis impact 282001.00081). The ^1H NMR spectroscopic data were recorded with Bruker 400 MHz and 500 MHz spectrometers, and the data are reported in ppm by using the residual solvent as the internal standard ($CHCl_3$ at δ = 7.26 ppm). The proton decoupled ^{13}C NMR spectroscopic data were recorded with Bruker 400 MHz and 500 MHz spectrometers, and the data are reported in ppm by using the solvent as the internal standard ($CDCl_3$ at δ = 77.2 ppm).

General Procedure A for the Preparation of 2-(Benzofuro-2-yl)anilines 7a–7g: In a round-bottomed flask or a tightly capped reaction tube was added iodophenol **5** in the respective dried solvent, and the mixture was stirred with a magnetic stirrer under nitrogen. Venkataraman's catalyst (**13**, 10 mol-%) and the 2-ethynylaniline **4** (1 equiv.) were added to the mixture. Cs_2CO_3 (2 equiv.) was then added, and the reaction mixture was degassed with nitrogen as it was stirred for 10–15 min. The mixture was then stirred at 110 °C for 12–14 h under nitrogen, whereupon it was quenched by the addition of water. The compound was extracted with dichloromethane, and the organic layer was washed several times with water, dried with anhydrous Na_2SO_4, and concentrated under vacuum.

Table 5. Substrate scope for formation of 2-(indol-2-yl)phenol derivatives; X = Ts, Piv.



17 5 18



18a, 67% **18b**, 57% **18c**, 72% **18d**, 73%

Conclusions

In summary, we have devised a divergent pathway to give 2-(benzofuro-2-yl)anilines **7** and *N*-protected 2-(indol-2-yl)-phenols **18** from similar starting materials by using a domino Sonogashira coupling followed by selective in situ *O*- and *N*-cyclizations, respectively. Furthermore, the 2-

The crude product was purified by chromatography on a silica gel column (100–200 mesh, hexanes/ethyl acetate).

General Procedure B for the Formation of Oxa Analogues of Isocryptolepine 15a–15f: In a tightly capped reaction tube that was charged with a magnetic bead was added 2-(benzofuro-2-yl)aniline **7** in dry dichloromethane. Acetal **14** (1.2 equiv.) and $BF_3{\cdot}OEt_2$ (0.04 equiv.) were added, and the reaction mixture was stirred at room temperature for 6–8 h under nitrogen. The reaction was quenched with water, and the compound was extracted with dichloromethane. The organic layer was washed with water, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by chromatography on a silica gel column (100–200 mesh, hexanes/ethyl acetate).

General Procedure C for the Preparation of 2-(1*H*-Indol-2-yl)phenols 18a–18d: In a two-necked round-bottomed flask that was charged with a magnetic stirrer under nitrogen was added iodophenol **5** in the respective dried solvent. $Pd(PPh_3)_2Cl_2$ (0.03 equiv.), CuI (0.09 equiv.), and the *N*-protected 2-ethynylaniline **17** (1 equiv.) were added sequentially. Et_3N (1 equiv.) was then added. The reaction mixture was degassed with nitrogen at room temperature for 10–20 min, whereupon it was stirred for 5–6 h. The reaction was then quenched with water, and the mixture was extracted with dichloromethane. The organic layer was washed with water several times, dried with anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography on a silica gel column (100–200 mesh, hexanes/ethyl acetate).

2-(Benzofuran-2-yl)aniline (7a): General Procedure A was employed by starting with 2-ethynylaniline (180 mg, 1.536 mmol) to give compound **7a** (218 mg, 68%) as a pale yellow solid; m.p. 64–66 °C; R_f = 0.6 (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (dd, J = 7.8, 1.5 Hz, 1 H), 7.62–7.58 (m, 1 H), 7.53 (d, J = 7.9 Hz, 1 H), 7.31–7.23 (m, 2 H), 7.19 (td, J = 7.9, 1.7 Hz, 1 H), 6.95 (d, J = 0.8 Hz, 1 H), 6.85 (t, J = 7.8 Hz, 1 H), 6.80 (d, J = 8.1 Hz, 1 H), 4.10 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 154.4, 144.4, 130.1, 129.1, 128.8, 124.2, 123.2, 120.9, 118.7, 117.0, 115.7, 111.2, 103.2 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –61.4 ppm. IR (KBr): $\tilde{\nu}$ = 3342, 3172, 2922, 1653, 1087, 1012 cm^{-1}. HRMS [ESI-QTOF (quadrupole time-of-flight)]: calcd. for $C_{14}H_{11}NNaO$ $[M + Na]^+$ 232.0738; found 232.0737.

2-(Benzofuran-2-yl)-4-(trifluoromethyl)aniline (7b): General Procedure A was employed by starting with 2-ethynyl-4-(trifluoromethyl)aniline (50 mg, 0.270 mmol) to give compound **7b** (49 mg, 69%) as a yellow amorphous substance; R_f = 0.25 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (dd, J = 8.3, 1.5 Hz, 1 H), 7.64–7.59 (m, 1 H), 7.54 (dd, J = 4.6, 3.7 Hz, 1 H), 7.40 (dd, J = 8.5, 1.7 Hz, 1 H), 7.36–7.30 (m, 1 H), 7.30–7.25 (m, 1 H), 7.00 (d, J = 0.9 Hz, 1 H), 6.81 (d, J = 8.5 Hz, 1 H), 4.83 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 154.4, 147.0, 128.7, 126.7, 126.2, 126.1, 124.8, 123.5, 121.2, 120.6, 116.6, 114.9, 111.3, 104.0 ppm. IR (KBr): $\tilde{\nu}$ = 3411, 2926, 2851, 1629, 1327, 1276, 1151, 1115, 1080, 823, 692, 629 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{15}H_{11}F_3NO$ $[M + H]^+$ 278.0793; found 278.0787.

2-(5,7-Dichlorobenzofuran-2-yl)aniline (7c): General Procedure A was employed by starting with 2-ethynylaniline (80 mg, 0.683 mmol) to give compound **7c** (96 mg, 51%) as a white solid; m.p. 122–123 °C; R_f = 0.4 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dd, J = 7.9, 1.4 Hz, 1 H), 7.43 (d, J = 1.9 Hz, 1 H), 7.29–7.25 (m, 1 H), 7.24–7.18 (m, 1 H), 6.89 (s, 1 H), 6.87–6.81 (m, 1 H), 6.79 (dd, J = 8.1, 0.7 Hz, 1 H), 4.56 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 148.8, 144.6, 131.3, 130.8, 128.9, 128.7, 124.0, 118.9, 118.7, 117.3, 117.0, 114.2, 102.6 ppm. IR (KBr): $\tilde{\nu}$ = 3408, 3019, 1523, 1422, 1216, 928, 669 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{14}H_{10}Cl_2NO$ $[M + H]^+$ 278.0139; found 278.0137.

2-(5,7-Dichlorobenzofuran-2-yl)-4-methylaniline (7d): General Procedure A was employed by starting with 2-ethynyl-4-methylaniline (50 mg, 0.381 mmol) to give compound **7d** (62 mg, 56%) as a white amorphous substance; R_f = 0.5 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, J = 1.9 Hz, 1 H), 7.43 (dd, J = 1.4, 0.5 Hz, 1 H), 7.27 (d, J = 1.9 Hz, 1 H), 7.03 (ddd, J = 8.2, 2.1, 0.6 Hz, 1 H), 6.91 (s, 1 H), 6.72 (d, J = 8.2 Hz, 1 H), 4.41 (br. s, 1 H), 2.30 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 142.2, 131.7, 131.4, 128.9, 128.8, 128.1, 124.0, 118.9, 117.6, 117.1, 114.3, 102.7, 20.6 ppm. IR (KBr): $\tilde{\nu}$ = 3449, 3324, 2923, 2853, 1585, 1500, 1443, 1412, 1326, 1251, 1168, 1159, 1097, 1013, 980, 837, 808 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{15}H_{11}Cl_2NNaO$ $[M + Na]^+$ 314.0110; found 314.0109. Note: The integration of the peak for $–NH_2$ corresponded to one proton. All other data supported the structure of the product.

2-(Benzofuran-2-yl)-4-methylaniline (7e): General Procedure A was employed by starting with 2-ethynyl-4-methylaniline (200 mg, 1.524 mmol) to give compound **7e** (208 mg, 66%) as a pale yellow amorphous substance; R_f = 0.4 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.57 (m, 1 H), 7.52 (dd, J = 6.8, 5.9 Hz, 1 H), 7.48–7.45 (m, 1 H), 7.36–7.20 (m, 2 H), 7.01 (dd, J = 8.1, 1.6 Hz, 1 H), 6.95 (d, J = 0.8 Hz, 1 H), 6.72 (d, J = 8.2 Hz, 1 H), 4.19 (br. s, 2 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 154.4, 141.9, 130.8, 129.1, 128.8, 127.9, 124.1, 123.1, 120.9, 117.3, 115.7, 111.2, 103.1, 20.6 ppm. IR (KBr): $\tilde{\nu}$ = 3302, 3098, 2951, 1666, 1011, 997 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{15}H_{13}NNaO$ $[M + Na]^+$ 246.0889; found 246.0992.

2-(5,7-Dichlorobenzofuran-2-yl)-4-(trifluoromethyl)aniline (7f): General Procedure A was employed by starting with 2-ethynyl-4-(trifluoromethyl)aniline (50 mg, 0.270 mmol) to give compound **7f** (60 mg, 65%) as a white amorphous substance; R_f = 0.2 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 1.2 Hz, 1 H), 7.47 (d, J = 1.9 Hz, 1 H), 7.42 (dd, J = 8.5, 1.8 Hz, 1 H), 7.30 (d, J = 1.9 Hz, 1 H), 6.97 (s, 1 H), 6.82 (d, J = 8.5 Hz, 1 H), 4.94 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 148.9, 147.2, 130.9, 129.4, 127.5, 127.5, 126.2, 126.2, 124.6, 120.6, 119.2, 117.2, 117.0, 113.4, 103.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –61.5 ppm. IR (KBr): $\tilde{\nu}$ = 3446, 2922, 2853, 1629, 1440, 1329, 1309, 1232, 1178, 1155, 1112, 1081, 837 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{15}H_8Cl_2F_3NNaO$ $[M + Na]^+$ 367.9827; found 367.9833.

2-(Benzofuran-2-yl)-4-chloroaniline (7g): General Procedure A was employed by starting with 4-chloro-2-ethynylaniline (100 mg, 0.659 mmol) to give compound **7g** (95 mg, 59%) as a yellow liquid; R_f = 0.25 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (d, J = 2.5 Hz, 1 H), 7.62–7.59 (m, 1 H), 7.53 (dd, J = 8.1, 0.7 Hz, 1 H), 7.34–7.25 (m, 2 H), 7.12 (dd, J = 8.6, 2.5 Hz, 1 H), 6.96 (d, J = 0.9 Hz, 1 H), 6.71 (d, J = 8.6 Hz, 1 H), 4.49 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.4, 154.2, 142.8, 129.7, 128.8, 127.9, 124.6, 123.4, 123.3, 121.1, 118.2, 116.8, 111.2, 103.9 ppm. HRMS (ESI-QTOF): calcd. for $C_{14}H_{11}ClNO$ $[M + H]^+$ 244.0524; found 244.0518. Note: The compound was extremely unstable and began to decompose immediately upon isolation.

6-Phenylbenzofuro[3,2-*c*]quinoline (15a): General Procedure B was employed by starting with 2-(benzofuran-2-yl)aniline (60 mg, 0.287 mmol) to give compound **15a** (69 mg, 82%) as a white solid and the side product 2-(benzofuran-2-yl)-*N*-benzylaniline (**16a**; 15 mg, 17%) as a white amorphous substance. Data for **15a**: M.p. 169–171 °C; R_f = 0.65 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49–8.44 (m, 1 H), 8.31 (dd, J = 5.1, 4.1 Hz, 1 H),

7.98–7.92 (m, 2 H), 7.81 (ddd, J = 8.5, 7.0, 1.5 Hz, 1 H), 7.77 (d, J = 8.3 Hz, 1 H), 7.73–7.67 (m, 2 H), 7.66–7.56 (m, 3 H), 7.50 (ddd, J = 8.4, 7.3, 1.3 Hz, 1 H), 7.32–7.27 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5, 156.2, 156.0, 147.2, 139.9, 129.9, 129.8, 129.6, 129.2, 128.9, 127.2, 126.9, 123.8, 123.1, 122.5, 120.9, 116.4, 114.7, 112.1 ppm. IR (KBr): $\tilde{\nu}$ = 3271, 2923, 2852, 1604, 1447, 1362, 1217, 1030, 703 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{21}H_{14}NO$ $[M + H]^+$ 296.1075; found 296.1068. Data for **16a**: R_f = 0.75 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (dt, J = 5.2, 2.6 Hz, 1 H), 7.62–7.58 (m, 1 H), 7.53–7.48 (m, 1 H), 7.43 (d, J = 7.1 Hz, 2 H), 7.38 (dd, J = 10.1, 4.8 Hz, 2 H), 7.34–7.21 (m, 3 H), 6.95 (d, J = 0.8 Hz, 1 H), 6.81 (tt, J = 7.4, 2.2 Hz, 1 H), 6.74 (d, J = 8.3 Hz, 1 H), 5.66 (br. s, 1 H), 4.48 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 154.5, 145.7, 139.3, 130.5, 129.1, 129.0, 128.9, 127.4, 127.3, 124.2, 123.2, 120.9, 117.3, 115.5, 111.9, 111.2, 103.4, 48.2 ppm. IR (KBr): $\tilde{\nu}$ = 3453, 2926, 2853, 1619, 1585, 1454, 1255, 1046, 909, 649 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{21}H_{18}NO$ $[M + H]^+$ 300.1383; found 300.1378.

2-Methyl-6-phenylbenzofuro[3,2-*c*]quinoline (15b): General Procedure B was employed by starting with 2-(benzofuran-2-yl)-4-methylaniline (85 mg, 0.381 mmol) to give compound **15b** (71 mg, 61%) as a pale yellow solid; m.p. 167–170 °C; R_f = 0.5 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (t, J = 5.4 Hz, 2 H), 7.96–7.91 (m, 2 H), 7.74 (t, J = 7.3 Hz, 1 H), 7.69 (d, J = 7.9 Hz, 1 H), 7.65–7.54 (m, 4 H), 7.48 (ddd, J = 8.4, 7.4, 1.3 Hz, 1 H), 7.26 (tt, J = 4.5, 2.2 Hz, 1 H), 2.64 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 156.2, 155.1, 145.8, 140.1, 137.0, 132.0, 129.7, 129.4, 129.1, 128.9, 127.1, 123.7, 123.2, 122.4, 119.8, 116.3, 114.6, 112.0, 22.0 ppm. IR (KBr): $\tilde{\nu}$ = 3052, 2917, 1556, 1446, 1359, 1181, 1116, 1015, 921, 819 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{22}H_{16}NO$ $[M + H]^+$ 310.1226; found 310.1228.

6-(5-Bromothiophen-2-yl)benzofuro[3,2-*c*]quinoline (15c): General Procedure B was employed by starting with 2-(benzofuran-2-yl)aniline (50 mg, 0.239 mmol) to give compound **15c** (44 mg, 69% brsm) as a white solid; m.p. 175–176 °C; R_f = 0.6 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (ddd, J = 8.2, 1.5, 0.6 Hz, 1 H), 8.24–8.17 (m, 2 H), 7.82–7.75 (m, 2 H), 7.67 (ddd, J = 8.1, 7.0, 1.1 Hz, 1 H), 7.64 (d, J = 3.8 Hz, 1 H), 7.55 (ddd, J = 11.6, 6.4, 2.8 Hz, 1 H), 7.44–7.38 (m, 1 H), 7.24 (d, J = 3.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 156.2, 148.4, 146.9, 145.1, 130.5, 130.1, 129.7, 128.5, 127.5, 127.1, 124.0, 122.6, 122.3, 121.0, 116.4, 116.3, 113.9, 112.4 ppm. IR (KBr): $\tilde{\nu}$ = 2815, 2721, 1595, 1382, 1355, 971 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{19}H_{11}BrNOS$ $[M + H]^+$ 379.9739; found 379.9739.

6-(5-Bromothiophen-2-yl)-2-methylbenzofuro[3,2-*c*]quinoline (15d): General Procedure B was employed by starting with 2-(benzofuran-2-yl)-4-methylaniline (50 mg, 0.224 mmol) to give compound **15d** (66 mg, 75%) as a white solid; m.p. 186–189 °C; R_f = 0.6 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, J = 6.6 Hz, 2 H), 8.10 (d, J = 8.6 Hz, 1 H), 7.76 (d, J = 8.3 Hz, 1 H), 7.64–7.58 (m, 2 H), 7.54 (t, J = 7.7 Hz, 1 H), 7.39 (t, J = 7.3 Hz, 1 H), 7.23 (d, J = 3.8 Hz, 1 H), 2.64 (d, J = 8.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 156.1, 147.4, 145.5, 145.1, 137.3, 132.3, 130.4, 129.4, 128.2, 127.4, 123.9, 122.7, 122.2, 119.8, 116.3, 115.9, 113.8, 112.3, 22.0 ppm. IR (KBr): $\tilde{\nu}$ = 2921, 2852, 1613, 1581, 1556, 1499, 1441, 1355, 1185, 1018, 971, 908, 823, 797, 662 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{20}H_{12}BrNNaOS$ $[M + Na]^+$ 415.9715; found 415.9715.

6-(4-Methoxyphenyl)benzofuro[3,2-*c*]quinoline (15e): General Procedure B was employed by starting with 2-(benzofuran-2-yl)aniline (50 mg, 0.239 mmol) to give compound **15e** (44 mg, 57%) as a white solid; m.p. 207–209 °C; R_f = 0.2 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (ddd, J = 8.2, 1.5, 0.6 Hz, 1 H), 8.31–8.26 (m, 1 H), 7.95–7.89 (m, 2 H), 7.83–7.74 (m, 3 H), 7.67 (ddd, J = 8.1, 6.9, 1.1 Hz, 1 H), 7.50 (ddd, J = 8.4, 7.3, 1.3 Hz, 1 H), 7.31 (ddd, J = 8.2, 7.4, 1.0 Hz, 1 H), 7.18–7.12 (m, 2 H), 3.95 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 156.0, 155.6, 147.1, 132.4, 130.5, 129.7, 129.6, 126.9, 126.4, 123.6, 123.1, 122.3, 120.8, 116.1, 114.1, 111.9, 55.5 ppm. IR (KBr): $\tilde{\nu}$ = 2961, 2923, 2852, 1607, 1587, 1499, 1440, 1360, 1250, 1180, 1057, 1024, 952, 839, 661 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{22}H_{16}NO_2$ $[M + H]^+$ 326.1176; found 326.1177.

6-(5-Bromothiophen-2-yl)-2-(trifluoromethyl)benzofuro[3,2-*c*]quinoline (15f): General Procedure B was employed by starting with 2-(benzofuran-2-yl)-4-(trifluoromethyl)aniline (50 mg, 0.180 mmol) to give compound **15f** (46 mg, 57%) as a white solid; m.p. 165–167 °C; R_f = 0.75 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.71 (s, 1 H), 8.30 (d, J = 8.8 Hz, 1 H), 8.23 (d, J = 7.9 Hz, 1 H), 7.93 (dd, J = 8.9, 1.9 Hz, 1 H), 7.80 (d, J = 8.3 Hz, 1 H), 7.70 (d, J = 3.8 Hz, 1 H), 7.62–7.56 (m, 1 H), 7.44 (t, J = 7.6 Hz, 1 H), 7.26 (d, J = 3.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 156.4, 150.4, 130.7, 130.6, 129.2, 128.2, 125.8, 124.4, 122.5, 122.1, 119.3, 117.4, 115.5, 114.7, 112.6 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.3 ppm. IR (KBr): $\tilde{\nu}$ = 2921, 2851, 1620, 1589, 1460, 1443, 1364, 1315, 1162, 1123, 1106, 1061 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{20}H_9BrF_3NNaO_3$ $[M + Na]^+$ 471.9592; found 471.9596.

6-(4-Methoxyphenyl)-2-(trifluoromethyl)benzofuro[3,2-*c*]quinoline (15g): General Procedure B was employed by starting with 2-(benzofuran-2-yl)-4-(trifluoromethyl)aniline (220 mg, 0.794 mmol) to give compound **15g** (153 mg, 49%) as a white solid; m.p. 238–241 °C; R_f = 0.3 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.78–8.72 (m, 1 H), 8.37 (d, J = 8.8 Hz, 1 H), 7.94 (d, J = 8.6 Hz, 3 H), 7.84 (d, J = 7.9 Hz, 1 H), 7.77 (d, J = 8.2 Hz, 1 H), 7.54 (ddd, J = 8.4, 7.3, 1.3 Hz, 1 H), 7.37–7.30 (m, 1 H), 7.19–7.13 (m, 2 H), 3.96 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.2, 158.6, 157.9, 156.4, 148.1, 132.0, 130.9, 130.7, 128.4, 128.2, 127.8, 125.4, 125.4, 124.1, 123.2, 122.8, 122.7, 119.2, 119.2, 115.6, 115.5, 114.4, 112.3, 55.7 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.1 ppm. IR (KBr): $\tilde{\nu}$ = 2920, 1608, 1444, 1322, 1297, 1251, 1163, 1116, 929, 840, 784, 522 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{22}H_{15}F_3NO_2$ $[M + H]^+$ 394.1055; found 394.1065.

2-(Benzofuran-2-yl)-*N*-benzyl-4-(trifluoromethyl)aniline (16b): General Procedure B was employed by starting with 2-(benzofuran-2-yl)-4-(trifluoromethyl)aniline (30 mg, 0.108 mmol) to give compound **16b** (22 mg, 57%) as a white solid; m.p. 164–166 °C; R_f = 0.65 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 1.7 Hz, 1 H), 7.64–7.59 (m, 1 H), 7.53–7.49 (m, 1 H), 7.45–7.35 (m, 5 H), 7.35–7.25 (m, 3 H), 7.00 (d, J = 0.9 Hz, 1 H), 6.73 (d, J = 8.7 Hz, 1 H), 6.04 (t, J = 5.1 Hz, 1 H), 4.51 (t, J = 5.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 147.8, 138.3, 129.1, 128.6, 127.7, 127.2, 126.3, 124.7, 123.5, 121.1, 119.2, 115.1, 111.4, 111.3, 104.3, 47.9 ppm. IR (KBr): $\tilde{\nu}$ = 3438, 2925, 2853, 1621, 1444, 1324, 1168, 1122 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{22}H_{17}F_3NO$ $[M + H]^+$ 368.1257; found 368.1254.

***N*-Benzyl-2-(5,7-dichlorobenzofuran-2-yl)-4-(trifluoromethyl)aniline (16c):** General Procedure B was employed by starting with 2-(benzofuran-2-yl)-4-(trifluoromethyl)aniline (39 mg, 0.113 mmol) to give compound **16c** (23 mg, 50%) as a white amorphous substance; R_f = 0.6 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (dd, J = 2.1, 0.4 Hz, 1 H), 7.51–7.36 (m, 6 H), 7.35–7.30 (m, 1 H), 7.27 (t, J = 2.1 Hz, 1 H), 6.96 (s, 1 H), 6.78 (d, J = 8.7 Hz, 1 H), 6.16 (dd, J = 7.2, 2.6 Hz, 1 H), 4.48 (d, J =

5.1 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.4, 148.9, 148.3, 147.9, 137.9, 130.8, 129.4, 129.1, 128.1, 127.9, 127.6, 126.4, 124.6, 119.2, 117.3, 113.5, 111.8, 103.7, 48.1 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –61.3 ppm. IR (KBr): $\tilde{\nu}$ = 3559, 2983, 2856, 1588, 1461, 1389, 1324, 1203, 1159, 1103, 1018, 808 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{22}H_{15}Cl_2F_3NO$ $[M + H]^+$ 436.0477; found 436.0476.

2-(1-Tosyl-1*H*-indol-2-yl)phenol (18a): General Procedure C was employed by starting with *N*-(2-ethynylphenyl)-4-methylbenzenesulfonamide (246 mg, 0.908 mmol) to give compound **18a** (221 mg, 67%) as a white solid; m.p. 136–138 °C; R_f = 0.3 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (br. s, 1 H), 7.69 (dt, *J* = 6.5, 3.3 Hz, 1 H), 7.57–7.46 (m, 3 H), 7.41–7.32 (m, 4 H), 7.31–7.25 (m, 1 H), 7.22 (td, *J* = 7.7, 1.2 Hz, 1 H), 6.85 (t, *J* = 9.4 Hz, 2 H), 6.60 (s, 1 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 153.9, 143.7, 135.7, 133.9, 130.1, 129.4, 128.7, 128.3, 126.9, 126.2, 125.4, 125.1, 123.7, 123.2, 121.0, 111.4, 104.9, 21.5 ppm. IR (KBr): $\tilde{\nu}$ = 3350, 2926, 1596, 1448, 1401, 1340, 1165, 812, 668, 570 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{21}H_{17}NNaO_3S$ $[M + Na]^+$ 386.0821; found 386.0822.

1-[2-(2-Hydroxyphenyl)-1*H*-indol-1-yl]-2,2-dimethylpropan-1-one (18b): General Procedure C was employed by starting with *N*-(2-ethynylphenyl)pivalamide (100 mg, 0.497 mmol) to give compound **18b** (83 mg, 57%) as an orange solid; R_f = 0.40 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.26 (br. s, 1 H), 8.51 (dd, *J* = 8.4, 1.1 Hz, 1 H), 7.68–7.63 (m, 2 H), 7.53–7.49 (m, 1 H), 7.43–7.38 (m, 1 H), 7.37–7.28 (m, 2 H), 7.20–7.14 (m, 1 H), 7.01–6.98 (m, 1 H), 1.36 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 155.3, 154.7, 135.8, 130.1, 128.6, 128.5, 124.9, 124.2, 123.8, 122.3, 121.4, 119.8, 110.9, 104.8, 40.3, 27.7 ppm. IR (KBr): $\tilde{\nu}$ = 3440, 2963, 2930, 2870, 1683, 1588, 1529, 1477, 1439, 1306, 1256, 1163, 1017, 928, 668 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{19}H_{19}NNaO_2$ $[M + Na]^+$ 316.1308; found 316.1309.

2,4-Dichloro-6-(1-tosyl-1*H*-indol-2-yl)phenol (18c): General Procedure C was employed by starting with *N*-(2-ethynylphenyl)-4-methylbenzenesulfonamide (50 mg, 0.184 mmol) to give compound **18c** (57 mg, 72%) as a white solid; m.p. 190–193 °C; R_f = 0.5 (50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (br. s, 1 H), 7.71 (dd, *J* = 8.2, 1.0 Hz, 1 H), 7.55–7.50 (m, 1 H), 7.48–7.39 (m, 4 H), 7.36 (d, *J* = 1.9 Hz, 1 H), 7.28–7.23 (m, 1 H), 6.92 (dd, *J* = 8.6, 0.6 Hz, 2 H), 6.64 (s, 1 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 148.9, 143.7, 135.7, 133.9, 130.8, 130.3, 129.3, 128.6, 126.9, 126.2, 125.8, 124.8, 122.1, 119.0, 117.3, 104.5, 99.9, 21.5 ppm. IR (KBr): $\tilde{\nu}$ = 3445, 2922, 2852, 1596, 1586, 1456, 1438, 1411, 1392, 1325, 1307, 1163, 1150, 1094, 1015, 914, 813, 680, 569 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{21}H_{15}Cl_2NNaO_3S$ $[M + Na]^+$ 454.0042; found 454.0040.

1-[2-(3,5-Dichloro-2-hydroxyphenyl)-1*H*-indol-1-yl]-2,2-dimethylpropan-1-one (18d): General Procedure C was employed by starting with *N*-(2-ethynylphenyl)pivalamide (50 mg, 0.249 mmol) to give compound **18d** (68 mg, 73%) as a pale yellow solid; m.p. 128–131 °C; R_f = 0.3 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (br. s, 1 H), 8.40 (d, *J* = 8.4 Hz, 1 H), 7.60 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.50 (d, *J* = 1.9 Hz, 1 H), 7.48–7.40 (m, 1 H), 7.33 (d, *J* = 1.9 Hz, 1 H), 7.22–7.15 (m, 1 H), 6.95–6.90 (m, 1 H), 1.33 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 157.7, 149.2, 135.8, 130.8, 130.8, 129.5, 129.2, 124.9, 124.3, 123.0, 119.4, 119.3, 116.9, 104.9, 40.0, 27.6 ppm. IR (KBr): $\tilde{\nu}$ = 3452, 2960, 2922, 2866, 1659, 1612, 1579, 1519, 1481, 1438, 1411, 1309, 1280, 1226, 1168, 1018, 913, 864, 839, 631 cm^{-1}. HRMS (ESI-QTOF): calcd. for $C_{19}H_{18}Cl_2NO_2$, $[M + H]^+$ 362.0709; found 362.0710.

Supporting Information (see footnote on the first page of this article): ^{1}H, ^{13}C, and ^{19}F NMR spectra of new compounds.

Acknowledgments

The authors thank the Indian Institute of Technology, IIT Bombay and the Department of Science and Technology (DST), New Delhi for the financial support. K. P. K. thanks the DST for the award of a Swarnajayanti fellowship. S. I. and P. S. thank the Council of Scientific and Industrial Research (CSIR), New Delhi and the University Grants Commission (UGC), New Delhi, respectively, for their fellowships.

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Received: July 6, 2014
Published Online: ■

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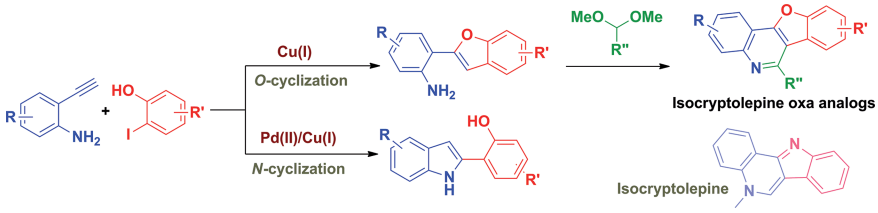

We have described a selective cyclization strategy to prepare 2-substituted benzofurans and indoles from similar starting materials. Substrates with free $-NH_2$ groups, which are traditionally reluctant to undergo Sonogashira coupling reactions, afforded good yields of product. The resulting benzofurans were further employed in the preparation of oxa analogues isocryptolepine.

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Transition-Metal-Catalyzed Selective Cyclization Strategy to 2-Substituted Benzofurans and Indoles en Route to the Oxa Analogues of Isocryptolepine

Keywords: Synthetic methods / Cross-coupling / Cyclization / Domino reactions

