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[1,2]-Aryl migration in the synthesis of substituted indoles: scope, mechanism, and high throughput experimentation

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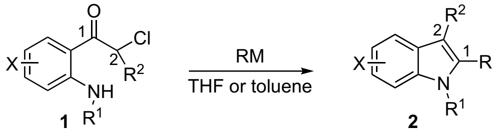
ABSTRACT

A mild regioselective synthesis of substituted indoles from readily accessible 1-(2-aminophenyl)-2-chloroethanones is described. Addition of a range of carbon nucleophiles to α-chloro acetophenones **1** generates 2-substituted indoles **2** in moderate to excellent yields. A reaction mechanism involving a [1,2]-aryl migration is proposed. This useful transformation is further examined using high throughput experimentation.

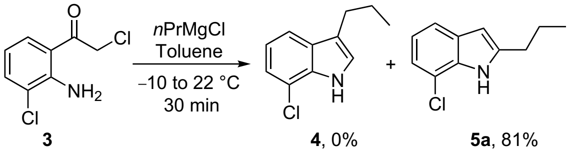
1. Introduction

Indole is a common substructure of many natural products and biologically active compounds.[1] The need for efficient and practical synthesis of indole bearing a variety of substitution patterns provides a continual challenge to organic chemists. The classic Fisher synthesis converts aryl hydrazones to indoles at elevated temperature (180–250 °C) in the presence of Bronsted or Lewis acid.[2–4] As a result, the method suffers from poor regioselectivity when alkyl ketones are used to make 2,3-disubstituted indole. The selectivity problem also limits the more recently developed Pd-catalyzed indole syntheses from *o*-haloanilines. In Larock's method, a mixture of isomers is obtained when a simple internal alkyne, such as 2-pentyne, is used.[5] A similar problem arises when an acyclic ketone is used in Chen's indole synthesis.[6] Lu and co-workers recently reported a one-pot, three-component, regioselective procedure to synthesize 2,3-disubstituted indoles that was limited to aryl substituents.[7] Despite these and many other creative approaches that have been used to assemble the indoles,[8] general and efficient syntheses that control the introduction of substituents at C-2 and C-3 are still lacking. The development of such general methods is of contemporary significance.

We recently reported a highly efficient synthesis of substituted indoles from readily accessible 1-(2-aminophenyl)-2-chloroethanones[9] and commercially available organometallic reagents (Scheme 1).[10] This new method is characterized by its high regioselectivity and good generality achieved under mild reaction conditions making this transformation viable for the preparation of structurally diverse indoles. For example, ketone **3** was treated with 2.5 equiv of ^{n}PrMgCl for 30 min and afforded 2-substituted indole **5a** as the sole product in 81% isolated yield (Scheme 2). We envisioned that addition of a wide variety of organometallic reagents to related α-chloro acetophenones would provide a direct access to 2-substituted indoles with diverse functionalities. In this manuscript, we continue to define the scope of the reaction.



Scheme 1.



Scheme 2.

2. Results and discussion

Based on the observed regioselectivity in this transformation, we propose the following reaction sequence (Fig. 1): nucleophilic addition of an organometallic reagent to the chloroketone **6a** to form tertiary alkoxide **8**, followed by a facile [1,2]-aryl rearrangement[11] to form ketone **10**, ring-closure and dehydration to form 2-substituted indole **7**. The aniline moiety serves as a key driver for the success of the reaction, wherein the aniline nitrogen promotes the net

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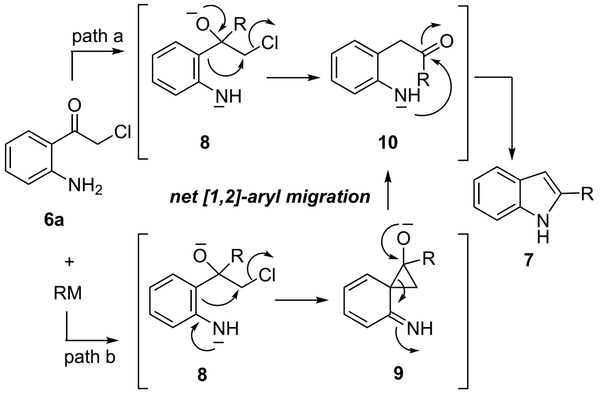
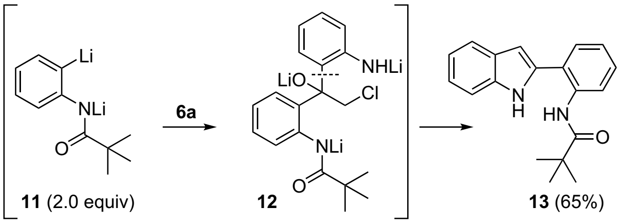


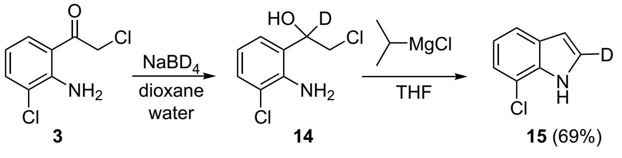
Figure 1. Proposed mechanism.

[1,2]-aryl rearrangement either through a conventional aryl migration or the formation of a bicyclic anion intermediate, such as **9**, and favors its migration.[12,13] The aniline nitrogen could also serve as an effective trap for the ketone in intermediate **10** and thus prevents reaction of the ketone with an additional equivalent of the organometallic reagent.

This net [1,2]-aryl migration mechanism is supported by two simple experiments. When the dianion **11**[14] derived from *N*-2-bromophenyl pivaloyl amide reacts with ketone **6a**, the only product observed, **13** results from migration of the unprotected aniline group. Under the assumption that the intermediate **12** forms, there are two possible aniline derivatives, which could participate in this [1,2]-aryl migration. The presence of the *N*-pivaloyl group disfavors its migration (Scheme 3).[14] Another experiment which supports the proposed rearrangement mechanism involves reaction of deuterium labeled alcohol **14** with ^{i}PrMgCl in THF, which produces 2-*D*-7-chloroindole (**15**) in 69% yield (Scheme 4). An alternative reaction pathway involving epoxide formation and subsequent rearrangement to form an aldehyde is ruled out since it would lead to a 3-substituted indole after a [1,2]-hydride shift.[15]



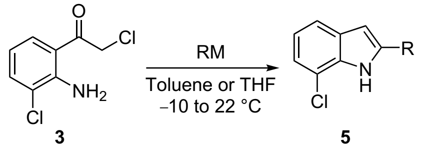
Scheme 3.

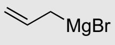
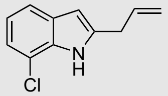
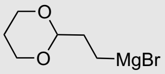
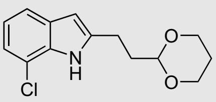
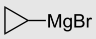
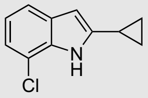
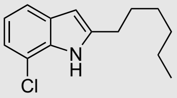
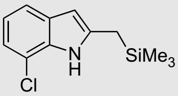
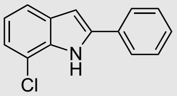
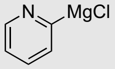
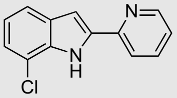
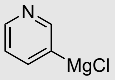
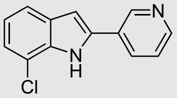
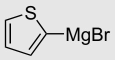
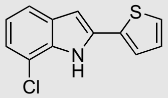
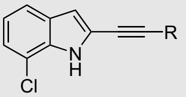


Scheme 4.

To explore the generality of this transformation, the addition of different organometallic reagents to 1-(2-amino-3-chlorophenyl)-2-chloroethanone (**3**) was studied and the results are summarized in Table 1. Similar to ^{n}PrMgCl, other primary alkyl Grignard reagents reacted with **3** to give C-2 substituted indoles in excellent yields. For example, 2-allyl-7-chloroindole (**5b**) and 7-chloro-2-[2-(1,3-

Table 1
Synthesis of 2-substituted indoles from ketone **3**[a]



Entry	RM	Product	Yield[g] (%)
1[f]		 **5b**	89
2[e]		 **5c**	86
3[f]		 **5d**	45
4[b,e]	^{n}HexLi	 **5e**	76
5[b,f]	Me_3SiCH_2Li	 **5f**	70
6[e]	PhMgCl	 **5g**	91
7[c,e]		 **5h**	78
8[c,e]		 **5i**	76
9[e]		 **5j**	72
10[d,e]	$Me_3Si-C\equiv C-MgCl$	 **5k** R = Sime$_3$ **5l** R = *n*Bu	54
11[d,e]	$Bu-C\equiv C-MgCl$		55

[a] Reaction conditions: all reactions were carried out without optimization; ketone **3** (1.0 mmol) in either THF or toluene (2 mL) and nucleophile (2.5 mmol) were stirred at −10 °C for 15 min, then at room temperature for 15 min to 2 h.

[b] Addition of nucleophile at −40 °C.

[c] Nucleophile was generated in situ from corresponding aryl iodide and ^{i}PrMgCl.

[d] Nucleophile was generated in situ from the corresponding alkynes and ^{i}PrMgCl.

[e] Solvent=THF.

[f] Solvent=toluene.

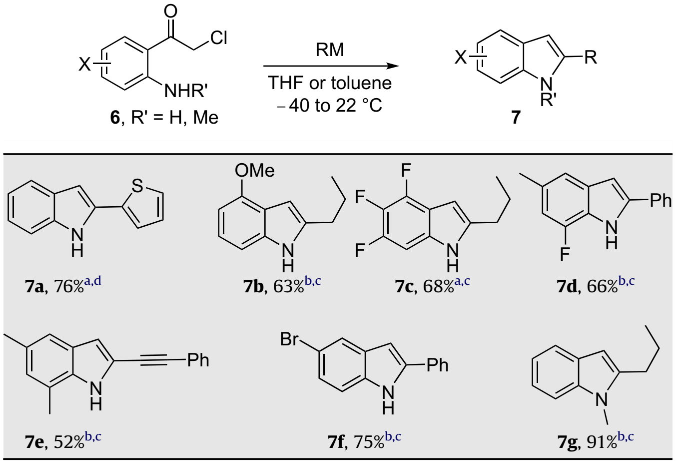
[g] Yields refer to isolated product based on ketone **3**.

dioxan-2-yl)ethan-1-yl]indole (**5c**) were readily prepared from the corresponding Grignard reagents in 89% and 86% yield, respectively (Table 1, entries 1 and 2). Moreover, addition of organolithium species such as *n*-hexyl lithium and trimethylsilylmethyl lithium afforded 7-chloro-2-hexan-1-ylindole (**5e**) and 7-chloro-2-trimethylsilylmethylindole (**5f**) in 76% and 70% yield, respectively (Table 1, entries 4 and 5).

A number of aromatic and heteroaromatic functional groups were readily introduced at the C-2 position of indoles by addition of aryl and heteroaryl magnesium reagents to ketone **3**. For example, 2-phenyl-7-chloroindole (**5g**) was prepared in excellent yield (91%) using phenyl magnesium chloride (entry 6). Heteroaryl nucleophiles, such as 2- and 3-pyridinylmagnesium chloride, and 2-thienylmagnesium bromide gave the corresponding 2-heteroaryl indoles (**5h–j**) in 78%, 76%, and 72% yield, respectively (entries 7–9). Furthermore, 2-alkyn-1-ylindoles were directly synthesized from alkynyl magnesium species (entries 10 and 11).

Having successfully employed various carbon nucleophiles for the preparation of a range of 2-substituted indoles from ketone **3**, we decided to extend our method to other substituted ketones (Table 2). Not surprisingly, 1-(2-aminophenyl)-2-chloroethanone (**6a**, X, R′=H) worked well in the reaction, affording 2-thien-2-ylindole (**7a**) in 76% yield. The presence of either electron-donating or electron-withdrawing substituents on the phenyl ring had little impact on the transformation. 1-(2-Amino-6-methoxyphenyl)-2-chloroethanone (**6b**, X=6-MeO, R′=H) containing an electron-rich methoxy group was converted to 4-methoxy-2-propylindole (**7b**) in 63% yield, while the substrate containing a trifluorosubstituted phenyl ring reacted with ^{n}PrMgCl to form 4,5,6-trifluoro-2-propylindole (**7c**) in 68% yield. 7-Fluoro-5-methyl-2-phenylindole (**7d**) and 5,7-dimethyl-2-phenylethynylindole (**7e**) were readily prepared by addition of either phenyl or phenylethynyl magnesium chloride, respectively. Under the same condition, phenyl bromide of aniline **6f** (X=5-Br, R′=H) was not reactive toward Mg–Br exchange, and 5-bromo-2-phenylindole (**7f**) was prepared in 75% yield. N-Substitution was also tolerated in this reaction as demonstrated in the reaction of 1-(*N*-methyl-2-aminophenyl)-2-chloroethanone (**6g**, X=H, R′=Me) with ^{n}PrMgCl to form *N*-methyl-2-propylindole (**7g**) in very high yield (91%).

Table 2
Synthesis of 2-substituted indoles from ketone **6**



7a, 76%[a,d] **7b**, 63%[b,c] **7c**, 68%[a,c] **7d**, 66%[b,c]

7e, 52%[b,c] **7f**, 75%[b,c] **7g**, 91%[b,c]

All reactions were carried out without optimization. Yields refer to isolated material based on ketone **6**.

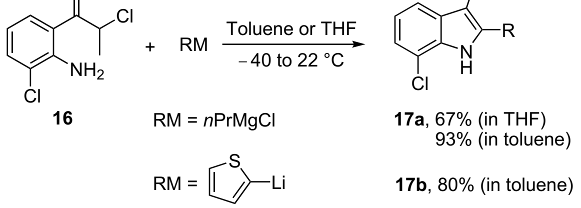
[a] Solvent=toluene.

[b] Solvent=THF.

[c] RM=Grignard reagent.

[d] RM=organolithium reagent.

The versatility of this method was further extended to the preparation of 2,3-disubstituted indoles with excellent control of regioselectivity, which would be difficult to prepare selectively by other means. Hence, treatment of ketone **16** with 2.5 equiv of ^{n}PrMgCl at −10 °C to 22 °C afforded 7-chloro-3-methyl-2-propylindole (**17a**) in 93% yield. Likewise, 7-chloro-3-methyl-2-thien-2-ylindole (**17b**) was easily obtained in 80% yield employing 2.0 equiv of 2-thienyllithium (Scheme 5). These particular examples clearly highlight the remarkable efficiency of this method, which should be broadly applicable to other substrates for the regioselective synthesis of 2,3-disubstituted indoles.



Scheme 5.

We next sought to apply this method to the synthesis of a library of indole derivatives[16] with the goal of preparing milligram quantities of interesting substrates for biological evaluation and to help us refine our capabilities for throughput experimentation. The selected ketone and Grignard reagents are illustrated in

Table 3
96-Well plate indole synthesis

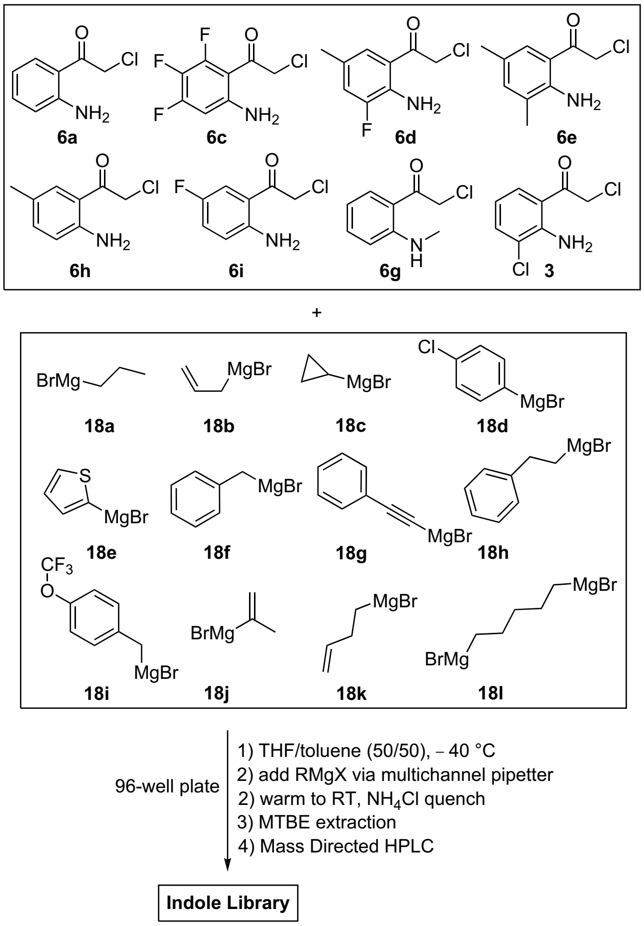
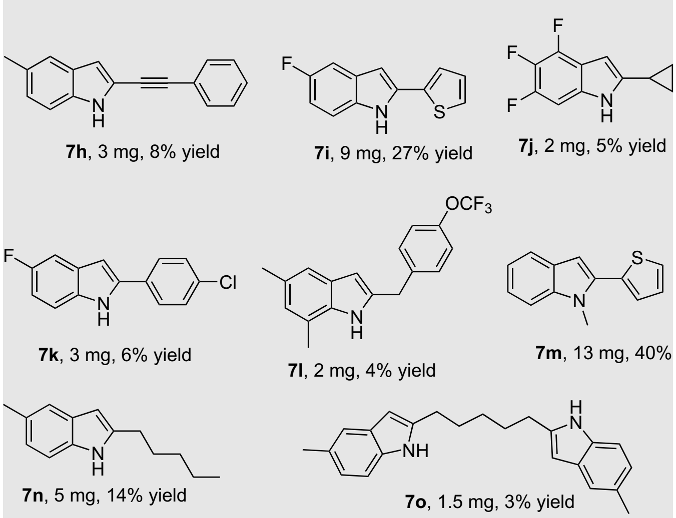


Table 3. The library synthesis was performed in a 96-well plate using 160 μmol (∼30 mg) of ketone and 300 μL of solvent per well.[17] The ketones were dispensed across rows and the Grignard reagents were dispensed across columns. For example, ketone **6a** was dispensed in positions A1–A12 and Grignard **18a** was dispensed in positions A1, B1, C1, etc. through H1. All manipulations were performed inside an inert atmosphere glovebox in order to simplify handling of the Grignard reagents. The temperature and solvent mixture (THF/toluene) chosen were viewed as the most general thereby offering the greatest opportunity to synthesize a diverse array of substrates.

Following Grignard addition, aqueous ammonium chloride quench, and extraction into MTBE, the reaction mixture was analyzed by HPLC and high resolution mass spectrometry to determine conversion and confirm product identity. Complete details regarding synthesis, yield, and purification can be found in Section 4 and Supplementary data. Moderate to good conversions were obtained in nearly all cases. Automated mass-directed chromatography was used to purify each sample directly from the work-up mixture.[18] After separation, the solvent in each sample was lyophilized and the samples were re-analyzed by HPLC to assess for purity. A total of 62 indoles were isolated in greater than >90 HPLC area percent purity. The remaining indoles from the 96-well library were either isolated in unacceptable yields (<0.5 mg) or contained an unacceptable level of impurities attributed to decomposition.[19] A selection of the indoles prepared with this technique are shown in Table 4 and serve to highlight the diversity of substrates acceptable via use of this methodology. These compounds were not prepared in the serial manner and have therefore allowed us to define the scope of accessible derivatives. It should be noted that for Grignard **18l**, a mixture of monomer **7n** and dimer **7o** (80/20) was obtained, which were characterized and separated based on their molecular weights.

While the recoveries are moderate to poor compared to those obtained via sequential compound synthesis (Tables 1 and 2), the application of this methodology to high throughput parallel synthesis allows rapid access to a large number of indole structures with yields that are suitable for biological activity screening. It should be stressed that the main focus was to expand our capabilities in high throughput experimentation and build a platform for future optimization. Reaction set-up, execution, and work-up took approximately 0.5 day while compound isolation and purification was completed in approximately two days in a completely automated manner.

Table 4
A selection of indoles prepared in library synthesis[a]



7h, 3 mg, 8% yield

7i, 9 mg, 27% yield

7j, 2 mg, 5% yield

7k, 3 mg, 6% yield

7l, 2 mg, 4% yield

7m, 13 mg, 40%

7n, 5 mg, 14% yield

7o, 1.5 mg, 3% yield

[a] Isolated quantity of product and yields are shown.

3. Summary

We have discovered a new and practical method for the efficient and regioselective synthesis of substituted indoles from 1-(2-aminophenyl)-2-chloroethanones. The reaction proceeds via a [1,2]-aryl rearrangement followed by intramolecular condensation to form the indole. The method introduces substituents at the C-2 position of the indole and tolerates different substitution patterns on the α-chloro ketone. We believe that this method can serve as a valuable tool for the modular synthesis of indole-containing medicinal agents, and with some refinement a useful platform for reaction optimization is achievable. In summary, this simple procedure, which proceeds under mild reaction conditions with inexpensive starting materials renders this method a valuable addition to those that have already been popularized.

4. Experimental

4.1. General methods

Reagents and solvents obtained from commercial suppliers were used without purification or drying unless otherwise noted. All reactions were conducted in standard RB-flasks under a nitrogen atmosphere. NMR spectra were obtained on Burker DPX-400 and DPX-500 spectrometer. Flash column chromatography was performed employing 200–400 mesh silica gel (Aldrich) eluting with mixtures of hexanes and ethyl acetate. HPLC was performed on an Agilent 1100 series machine using a Agilent ZORBAX (Eclipse Plus C18) column (4.6×50 mm, 1.8 μm, 600 bar), 1.50 mL/min flowrate, 215 nm detection, 28 °C column temperature; mobile phase MeCN/0.1 wt % aqueous H_3PO_4 10/90 ramp to 95/5 over 9 min and stay for 1 min.

4.2. General procedure for the acylation of anilines

A modified procedure of Sugasawa reaction was used to react anilines with nitriles.[9]

Aniline (100 mmol, 1.0 equiv) and chloroacetonitrile (250 mmol, 2.5 equiv) were added sequentially to a mixture of $AlCl_3$ pellets (120 mmol, 1.2 equiv) and BCl_3 solution (1.0 M in dichloromethane, 120 mmol, 1.2 equiv) with extra 60 mL dichloromethane cooled in ice bath. The cloudy solution was stirred for 0.5 h at room temperature before being heated at reflux for 12 h. The reaction mixture was then cooled in ice bath, quenched with 2 N HCl 150 mL, heated at reflux for 20 min, cooled, and extracted with dichloromethane (2×100 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed to afford corresponding 2-chloroethanone.

*4.2.1. 1-(2-Amino-3-chlorophenyl)-2-chloroethanone (**3**)*

Bright yellow solid, mp 104–106 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.61 (dd, J=8.2, 1.2 Hz, 1H), 7.46 (dd, J=7.8, 1.2 Hz, 1H), 6.85 (br s, 2H), 6.63 (m, 1H), 4.68 (s, 2H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 192.3, 147.2, 134.8, 129.5, 121.0, 116.0, 115.5, 46.5. Anal. Calcd for $C_8H_7Cl_2NO$: C, 47.09; H, 3.46; N, 6.86. Found: C, 46.95; H, 3.29; N, 6.78.

*4.2.2. 1-(2-Amino-4,5,6-trifluorophenyl)-2-chloroethanone (**6c**)*

White solid, mp 105–106 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 6.39 (br s, 2H), 6.28 (ddd, J=11.6, 6.0, 2.3 Hz, 1H), 4.68 (d, J=4.7 Hz, 2H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 190.1 (m), 156.5 (dd, J=11.1, 6.8 Hz), 154.5 (dd, J=11.1, 3.2 Hz), 153.8 (dd, J=10.8, 6.5 Hz), 151.8 (dd, J=11.8, 6.5 Hz), 148.0 (dd, J=7.4, 12.9 Hz), 132.4 (m), 130.5 (dd, J=17.2, 16.0 Hz), 103.0 (dt, J=14.2, 2.5 Hz), 99.4 (ddd, J=20.3, 3.1, 1.2 Hz), 50.6 (d, J=18.4 Hz). ^{19}F {^{1}H} NMR (470 MHz, $CDCl_3$): δ −124.7 (dd, J=22.9, 13.7 Hz), −128.9 (dd, J=22.9, 15.3 Hz), −175.6 (m). Anal. Calcd for $C_8H_5ClF_3NO$: C, 42.98; H, 2.25; N, 6.26. Found: C, 42.64; H, 2.09; N, 6.20.

4.2.3. *1-(2-Amino-3-fluoro-5-methylphenyl)-2-chloroethanone (**6d**)*

Yellow solid, mp 98–91 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (s, 1H), 7.01 (dd, J=11.9, 1.9 Hz, 1H), 5.99 (br s, 2H), 4.67 (s, 2H), 2.27 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.2 (d, J=2.4 Hz), 152.4, 150.5, 138.2 (d, J=14.2 Hz), 125.2 (d, J=3.0 Hz), 124.3 (d, J=6.7 Hz), 120.5 (d, J=17.8 Hz), 116.7 (d, J=4.3 Hz), 46.6, 20.5 (d, J=1.8 Hz). ^{19}F {^{1}H} NMR (470 MHz, $CDCl_3$): δ −136.4. Anal. Calcd for C_9H_9ClFNO: C, 53.61; H, 4.50; N, 6.95. Found: C, 53.80; H, 4.37; N, 6.83.

4.2.4. *1-(2-Amino-3-chlorophenyl)-2-chloropropanone (**16**)*

Yellow solid, mp 54–55 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (dd, J=8.2, 1.2 Hz, 1H), 7.47 (dd, J=7.7, 1.3 Hz, 1H), 6.89 (br s, 2H), 6.65 (m, 1H), 5.30 (q, J=6.6 Hz, 1H), 1.74 (d, J=6.6 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.0, 147.7, 134.6, 129.8, 121.0, 115.7, 115.3, 53.0, 20.3. Anal. Calcd for $C_9H_9Cl_2NO$: C, 49.57; H, 4.16; N, 6.42. Found: C, 49.35; H, 4.07; N, 6.35.

4.3. General procedure for the preparation of indoles

To a solution of α-chloro acetophenone (1.00 mmol) in 2.0 mL either toluene or THF at −10 °C was added dropwise a solution of RMgX or RLi (2.50 mmol). The reaction was kept <10 °C during addition and stirred in cold bath for 15 min before removal of the bath. After 15 min to 2 h at room temperature, the mixture was quenched with diluted aqueous NH_4Cl, extracted with MTBE, washed with brine, and dried over $MgSO_4$. After concentration, the crude residue was chromatographed to afford the desired indole.

4.3.1. *7-Chloro-2-propylindole (**5a**)*

Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (br s, 1H), 7.45 (d, J=7.9 Hz, 1H), 7.14 (d, J=7.6 Hz, 1H), 7.03 (m, 1H), 6.31 (s, 1H), 2.78 (t, J=7.5 Hz, 2H), 1.80 (m, 2H), 1.05 (t, J=7.4 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 140.7, 133.1, 130.3, 120.4, 120.3, 118.4, 115.8, 100.7, 30.3, 22.4, 13.9. HRMS calcd for $C_{11}H_{13}ClN$ $(M+H)^+$: 194.0737; found: 194.0726.

4.3.2. *2-Allyl-7-chloroindole (**5b**)*

Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (br s, 1H), 7.49 (d, J=7.7 Hz, 1H), 7.18 (dd, J=7.6, 0.8 Hz, 1H), 7.06 (t, J=7.8 Hz, 1H), 6.37 (m, 1H), 6.06 (ddt, J=17.0, 10.1, 6.7 Hz, 1H), 5.28 (m, 2H), 3.58 (m, 2H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 137.9, 134.4, 133.4, 130.3, 120.7, 120.5, 118.6, 117.7, 116.0, 101.4, 32.8. HRMS calcd for $C_{11}H_{11}ClN$ $(M+H)^+$: 192.0580; found: 192.0573.

4.3.3. *7-Chloro-2-(2-[1,3]-dioxan-2-ylethyl)indole (**5c**)*

Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (br s, 1H), 7.42 (d, J=7.7 Hz, 1H), 7.11 (d, J=7.5 Hz, 1H), 6.99 (t, J=7.7 Hz, 1H), 6.27 (d, J=1.8 Hz, 1H), 4.66 (t, J=4.8 Hz, 1H), 4.20 (m, 2H), 3.82 (m, 2H), 2.95 (t, J=7.1 Hz, 2H), 2.20 (m, 1H), 2.05 (m, 2H), 1.41 (m, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 140.1, 133.2, 130.2, 120.2, 120.2, 118.4, 115.9, 100.2, 100.5, 67.0, 34.1, 25.7, 22.2. HRMS calcd for $C_{14}H_{17}ClNO_2$ $(M+H)^+$: 266.0948; found: 266.0954.

4.3.4. *7-Chloro-2-cyclopropylindole (**5d**)*

Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (br s, 1H), 7.41 (d, J=7.8 Hz, 1H), 7.12 (d, J=7.4 Hz, 1H), 7.01 (t, J=7.9 Hz, 1H), 6.20 (d, J=2.3 Hz, 1H), 2.00 (tt, J=5.1, 3.3 Hz, 1H), 1.02 (m, 2H), 0.82 (m, 2H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 142.5, 132.9, 130.0, 120.4, 120.3, 118.2, 115.5, 98.6, 8.7, 7.4. Anal. Calcd for $C_{11}H_{10}ClN$: C, 68.93; H, 5.26; N, 7.31. Found: C, 68.77; H, 5.24; N, 7.14.

4.3.5. *7-Chloro-2-hexan-1-ylindole (**5e**)*

Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (br s), 7.44 (m, 1H), 7.12 (m, 1H), 7.01 (m, 1H), 6.30 (m, 1H), 2.79 (t, J=7.7 Hz, 2H), 1.74 (m, 2H), 1.38 (m, 6H), 0.93 (m, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 140.9, 133.1, 130.3, 120.4, 120.3, 118.3, 115.8, 100.5, 31.6, 29.1, 29.0, 28.3, 22.7, 14.1. HRMS calcd for $C_{14}H_{19}ClN$ $(M+H)^+$: 236.1206; found: 236.1198.

4.3.6. *2-Trimethylsilylmethylindole (**5f**)*

Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 1H), 7.37 (m, 1H), 7.06 (m, 1H), 6.98 (m, 1H), 6.11 (m, 1H), 2.21 (s, 2H), 0.11 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 138.8, 132.9, 131.0, 120.3, 119.6, 117.6, 115.4, 99.7, 19.1, −1.8. HRMS calcd for $C_{12}H_{18}ClNSi$ $(M+H)^+$: 238.0819; found: 238.0823.

4.3.7. *7-Chloro-2-pyridin-2-ylindole (**5h**)*

Pale yellow solid, mp 118–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (br s, 1H), 8.62 (m, 1H), 7.79 (m, 1H), 7.73 (td, J=7.3, 1.7 Hz, 1H), 7.55 (d, J=7.9 Hz, 1H), 7.21 (m, 2H), 7.06 (t, J=7.8 Hz, 1H), 7.04 (d, J=2.3 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 149.7, 149.2, 137.3, 136.5, 133.8, 130.4, 122.4, 122.3, 120.8, 119.8, 119.6, 116.8, 101.1. HRMS calcd for $C_{13}H_{10}ClN_2$ $(M+H)^+$: 229.0533; found: 229.0539.

4.3.8. *7-Chloro-2-pyridin-3-ylindole (**5i**)*

White solid, mp 207–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$ and CD_3COD): δ 8.93 (dd, J=2.3, 0.7 Hz, 1H), 8.40 (dd, J=5.0, 1.5 Hz, 1H), 8.13 (dt, J=8.0, 2.0 Hz, 1H), 7.43 (m, 1H), 7.40 (m, 1H), 7.10 (dd, J=7.6, 1.0 Hz, 1H), 6.95 (t, J=7.7 Hz, 1H), 6.84 (s, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$ and CD_3COD): δ 146.7, 145.3, 135.1, 135.0, 134.8, 130.5, 129.6, 124.7, 122.6, 121.1, 119.5, 117.0, 102.4. HRMS calcd for $C_{13}H_{10}ClN_2$ $(M+H)^+$: 229.0533; found: 223.0528.

4.3.9. *7-Chloro-2-thien-2-ylindole (**5j**)*

Pale yellow solid, mp 86–88 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (br s, 1H), 7.52 (d, J=7.9 Hz, 1H), 7.34 (m, 2H), 7.22 (dd, J=7.6, 0.6 Hz, 1H), 7.12 (dd, J=5.0, 3.7 Hz, 1H), 7.07 (t, J=7.8 Hz, 1H), 6.77 (d, J=2.3 Hz, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 134.9, 133.8, 133.1, 130.5, 128.0, 125.2, 123.6, 121.8, 121.2, 119.1, 116.2, 101.2. Anal. Calcd for $C_{12}H_8ClNS$: C, 61.67; H, 3.45; N, 5.99. Found: C, 61.34; H, 3.39; N, 5.81.

4.3.10. *7-Chloro-2-(2-trimethylsilylacetyn-1-yl)indole (**5k**)*

White solid, mp 62–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (br s, 1H), 7.48 (dd, J=8.0, 0.5 Hz, 1H), 7.24 (d, J=7.6 Hz, 1H), 7.06 (t, J=7.9 Hz, 1H), 6.81 (d, J=2.2 Hz, 1H), 0.31 (s, 9H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 133.1, 128.7, 122.7, 121.1, 119.4, 119.3, 116.1, 109.8, 99.2, 96.1, −0.3. Anal. Calcd for $C_{13}H_{14}ClNSi$: C, 63.01; H, 5.69; N, 5.65. Found: C, 63.20; H, 5.88; N, 5.44.

4.3.11. *7-Chloro-2-hexyn-1-ylindole (**5l**)*

Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (br s, 1H), 7.48 (dd, J=8.0, 0.4 Hz, 1H), 7.22 (dd, J=7.6, 0.7 Hz, 1H), 7.06 (td, J=7.9, 1.1 Hz, 1H), 6.71 (m, 1H), 2.50 (t, J=7.1 Hz, 2H), 1.65 (m, 2H), 1.43 (m, 2H), 1.00 (t, J=7.3 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 133.0, 129.2, 122.2, 121.0, 120.5, 119.2, 116.0, 108.2, 94.7, 72.5, 30.6, 22.1, 19.3, 13.6. HRMS calcd for $C_{14}H_{15}ClN$ $(M+H)^+$: 232.0893; found: 232.0900.

4.3.12. *4,5,6-Trifluoro-2-propylindole (**7c**)*

Light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (br s, 1H), 6.88 (m, 1H), 6.31 (m, 1H), 2.71 (t, J=7.5 Hz, 2H), 1.75 (m, 2H), 1.02 (t, J=7.4 Hz, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.9 (dd, J=12.8, 2.4 Hz), 146.5 (dd, J=12.8, 2.4 Hz), 144.2 (dd, J=11.2, 2.8 Hz), 141.7 (dd, J=11.2, 5.6 Hz), 141.2 (d, J=3.2 Hz), 136.0 (dd, J=17.6, 14.4 Hz), 133.6 (dd, J=17.6, 14.4 Hz), 130.6 (t, J=12.8 Hz), 114.2 (d, J=18.4 Hz), 95.7 (d, J=4.8 Hz), 93.6 (dd, J=21.7, 4.0 Hz), 30.0, 22.1, 13.6. ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ −144.3 (d, J=20.7 Hz), −146.3 (d, J=20.7 Hz), −174.1 (m). HRMS calcd for $C_{11}H_{11}F_3N$ (M+H)$^+$: 214.0844; found: 214.0837.

4.3.13. *5,7-Dimethyl-2-phenylethynylindole (**7e**)*

Light brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (br s, 1H), 7.62 (m, 2H), 7.43 (m, 3H), 7.30 (s, 1H), 6.94 (s, 1H), 6.84 (d, J=2.0 Hz, 1H), 2.49 (s, 3H), 2.48 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 134.3, 131.5, 130.1, 128.6, 128.5, 127.7, 125.9, 122.8, 119.7, 118.5, 118.1, 109.0, 92.4, 82.3, 21.4, 16.6. HRMS calcd for $C_{18}H_{16}N$ (M+H)$^+$: 246.1283; found: 246.1278.

4.3.14. *7-Fluoro-5-methyl-2-phenylindole (**7d**)*

White solid, mp 145–147 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (br s, 1H), 7.68 (d, J=7.2 Hz, 2H), 7.47 (t, J=7.7 Hz, 2H), 7.37 (t, J=7.4 Hz, 1H), 7.21 (s, 1H), 6.79 (m, 2H), 2.47 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.0 (d, J=243.0 Hz), 138.8, 132.9 (d, J=4.9 Hz), 132.0, 130.5 (d, J=5.6 Hz), 129.1, 128.0, 125.2, 123.3 (d, J=12.9 Hz), 115.9 (d, J=3.1 Hz), 108.7 (d, J=16.0 Hz), 100.1 (d, J=2.4 Hz), 21.5. ^{19}F {^{1}H} NMR (470 MHz, $CDCl_3$): δ −136.5. Anal. Calcd for $C_{15}H_{12}FN$: C, 79.98; H, 5.37; N, 6.22. Found: C, 79.71; H, 5.32; N, 6.06.

4.3.15. *7-Chloro-3-methyl-2-propylindole (**17a**)*

Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (br s, 1H), 7.46 (d, J=7.9 Hz, 1H), 7.20 (dd, J=7.5, 0.6 Hz, 1H), 7.10 (t, J=7.7 Hz, 1H), 2.77 (t, J=7.5 Hz, 2H), 2.31 (s, 3H), 1.77 (m, 2H), 1.06 (t, J=7.4 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 136.1, 132.4, 131.0, 120.4, 119.8, 116.8, 115.8, 108.2, 28.2, 23.0, 13.9, 8.7. HRMS calcd for $C_{12}H_{15}ClN$ (M+H)$^+$: 208.0893; found: 208.0889.

4.3.16. *7-Chloro-3-methyl-2-thien-2-ylindole (**17b**)*

Off-white solid; mp 111–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (br s, 1H), 7.48 (d, J=7.9 Hz, 1H), 7.40 (m, 1H), 7.30 (m, 1H), 7.18 (m, 2H), 7.08 (m, 1H), 2.49 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 134.6, 133.0, 131.3, 129.2, 127.7, 125.4, 124.7, 121.9, 120.5, 117.6, 116.0, 110.4, 10.0. HRMS calcd for $C_{13}H_{11}ClNS$ (M+H)$^+$: 248.0301; found: 248.0292.

4.4. 2-(*N*-Trimethylacetyl-2-aminophenyl)indole (13)[14]

Pale brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (br s, 1H), 8.39 (d, J=7.9 Hz, 1H), 8.22 (br s, 1H), 7.68 (d, J=7.9 Hz, 1H), 7.45 (m, 2H), 7.39 (m, 1H), 7.26 (m, 1H), 7.20 (m, 2H), 6.65 (s, 1H), 1.22 (s, 9H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.2, 136.6, 135.8, 134.2, 129.3, 128.7, 124.3, 123.7, 122.8, 121.7, 120.7, 120.6, 120.5, 111.1, 102.6, 39.9, 27.5. HRMS calcd for $C_{19}H_{21}N_2O$ (M+H)$^+$: 293.1654; found: 293.1660.

4.5. 1-(2-Amino-3-chlorophenyl)-2-chloro-1-*D*-ethan-1-ol (14)

To a solution of 1-(2-amino-3-chlorophenyl)-2-chloroethanone (**3**, 1.02 g, 5.0 mmol) in 1,4-dioxane (9.0 mL) and water (1.0 mL) was added $NaBD_4$ (256 mg, 6.0 mmol) at room temperature, aged for 1 h, quenched with saturated NH_4Cl, extracted with MTBE, washed with brine, and dried over $MgSO_4$. After concentration, the crude residue was chromatographed to give alcohol **14** (0.78 g, 75%) as a white solid. Mp 61–63 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (dd, J=7.9, 1.5 Hz, 1H), 6.97 (dd, J=7.7, 1.4 Hz, 1H), 6.66 (m, 1H), 4.01 (d, J=11.3 Hz, 1H), 3.74 (d, J=11.3 Hz, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 142.0, 129.6, 126.8, 123.6, 120.9, 118.1, 74.6 (t, J=22.5 Hz), 47.8. HRMS calcd for $C_8H_9DCl_2NO$ (M+H)$^+$: 207.0202; found: 207.0201.

4.6. 7-Chloro-2-*D*-indole (15)

To a solution of 1-(2-amino-3-chlorophenyl)-2-chloro-1-*D*-ethan-1-ol (**14**, 207 mg, 1.0 mmol) in THF (2.0 mL) cooled at −10 °C was added ^{i}PrMgCl (2.0 M in THF, 1.25 mL, 2.5 mmol), warmed to room temperature for 1 h, quenched with saturated NH_4Cl, extracted with MTBE, washed with brine, and dried over $MgSO_4$. After concentration, the crude residue was chromatographed to give indole **15** (105 mg, 69%) as a white solid. Mp 52–54 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35, 7.61 (d, J=7.9 Hz, 1H), 7.27 (dd, J=7.6, 0.9 Hz, 1H), 7.12 (t, J=7.8 Hz, 1H), 6.65 (d, J=2.2 Hz, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 133.2, 129.4, 124.6 (t, J=28.0 Hz), 121.4, 120.7, 119.4, 116.7, 103.6. HRMS calcd for C_8H_6DClN (M+H)$^+$: 153.0330; found: 153.0325.

4.7. High throughput indole library synthesis

4.7.1. *Procedure for preparation of indole library*

A THF stock solution of each ketone was prepared in THF (0.3 M) and 530 μL (160 μmol ketone) was transferred via multichannel pipetter to 1 mL vials containing micro-stirbars in the appropriate row of an aluminum 96-well plate. The THF was removed via evaporation in a Genevac® Centrifuge Evaporator. The 96-well plate was brought into an inert atmosphere glovebox, placed on a tumble stirrer equipped to a circulating cooler, and THF/toluene (1:1, 150 μL total) was added to each well. The plate was cooled to −40 °C and Grignard reagent (2.5 equiv) was added in four portions via a multichannel pipetter over the course of 45 min. After addition, the reactions were warmed to 20 °C over 1 h. Upon completion of an additional 1 h age, the solutions were cooled to 5 °C and diluted aqueous ammonium chloride (200 μL) and MTBE (300 μL) were added to each vial. After warming to room temperature, the 96-well plate was removed from the glovebox and the organic layer was separated and washed with brine using a 12-channel pipetter to introduce and remove liquids. To assess conversion, purity, and identity, a portion of each solution (20 μL) was sampled, diluted, and analyzed by HPLC. The remaining solution was concentrated under reduced pressure and re-dissolved in DMSO for preparative mass-directed HPLC purification. Supplementary data contains the product indole structures, reaction conversions, and yields of each compound.

4.7.2. *Chromatography and mass spectrometry*

Analytical HPLC–MS to assess purity and area percent conversion were obtained on a Waters Acquity UPLC with PDA UV Detector and on a Waters Acquity SQD (single quad) using Electrospray ionization equipped with a Waters Acquity BEH column (2.1×50 mm, 1.7 μm particles). Mass-directed HPLC purification was performed on a Waters Auto purification system in conjunction with a Waters 3100 SQ Detector with Electrospray positive ionization equipped with a Waters Xbridge Prep C18 column (30 mm (id)×75 mm, 5 μm particles). The instrument was set to trigger collection by M+H or M+Na. Fractions were collected into pre-tared high recovery 20 mL vials. Selected fractions were evaporated to dryness in a Genevac HT-24 and the vials were reweighed to calculate yields/recovery. The following gradient was employed for all the indoles:

Mobile phase: A=water+0.1% formic acid, B=acetonitrile+0.1% formic acid
Flow rate: 70 mL/min
Run time: 8.0 min

Time	Gradient (for most samples)	
	%A	%B
0.0	65	35
1.0	65	35
5	5	95
5.2	5	95
7.5	5	95
7.7	65	35

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.026.

References and notes

1. Recent reviews on indole alkaloids and references to the biological activity of compounds containing the indole substructure: (a) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2007**, *24*, 843 and references therein; (b) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: San Diego, CA, 1998; Vol. 51; (c) Saxton, J. E. *Nat. Prod. Rep.* **1997**, *14*, 559; (d) Brancale, A.; Silvestri, R. *Med. Res. Rev.* **2007**, *27*, 209; (e) Harper, S.; Avolio, S.; Pacini, B.; Di Filippo, M.; Altamura, S.; Tomei, L.; Paonessa, G.; Di Marco, S.; Carfi, A.; Giuliano, C.; Padron, J.; Bonelli, F.; Migliaccio, G.; De Francesco, R.; Laufer, R.; Rowley, M.; Narjes, F. *J. Med. Chem.* **2005**, *48*, 4547.
2. A review of Fisher indole synthesis: Robinson, B. *Chem. Rev.* **1963**, *63*, 373.
3. An improved synthesis was developed to allow the conversion happen under milder condition using *N*-trifluoroacetyl enehydrazines as substrates; see: Miyata, O.; Kimura, Y.; Muroya, K.; Hiramatsu, H.; Naito, T. *Tetrahedron Lett.* **1999**, *40*, 3601.
4. Leading references to current application of Fisher indole synthesis: (a) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 609; (b) Wagaw, S.; Yang, B. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.
5. Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.
6. Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, R. J. *J. Org. Chem.* **1997**, *62*, 2676.
7. Lu, B. Z.; Zhao, W.; Wei, H. X.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3271.
8. Recent reviews on indole synthesis: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875; (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873; (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285; (d) Joule, J. In *Science of Synthesis*; Thomas, E. J., Ed.; Thieme: Stuttgart, 2000; Vol. 10, p 361; (e) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491; (f) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045; (g) Sunderberg, R. J. *Indoles*; Academic: San Diego, CA, 1996.
9. These compounds can be easily prepared via Friedel–Crafts acylation from corresponding anilines and nitriles; see: Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* **1978**, *100*, 4842.
10. Pei, T.; Chen, C.; Dormer, P. G.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4231.
11. Huang, R. L. *J. Org. Chem.* **1954**, *19*, 1363.
12. (a) Cram, D. J. *J. Am. Chem. Soc.* **1949**, *71*, 3863; (b) Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1957**, *79*, 756.
13. The chlorohydrin was isolated in high yield in the reaction of 2-chloroacetophenone with Grignard reagent even after prolonged aging; see: Barluenga, J.; Florez, J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 3019.
14. The dilithium reagent generated from *N*-2-bromophenyl pivaloyl amide reacted with α-chloroketone to form the 3-substituted indole; see: Wender, P. A.; White, A. W. *Tetrahedron* **1983**, *39*, 3767.
15. (a) Geissman, T. A.; Akawie, R. I. *J. Am. Chem. Soc.* **1951**, *73*, 1993; (b) Crombie, L.; Hardy, R.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1373.
16. Recent publications on parallel synthesis of indole library: (a) Lindquist, C.; Ersoy, O.; Somfai, P. *Tetrahedron* **2006**, *62*, 3439; (b) Fokas, D.; Yu, L.; Baldino, C. M. *Mol. Diversity* **2005**, *9*, 81; (c) Smart, B. P.; Pan, Y. H.; Weeks, A. K.; Bollinger, J. G.; Bahnson, B. J.; Gelb, M. H. *Bioorg. Med. Chem.* **2004**, *12*, 1737.
17. For examples of applying this technique to reaction screening, see: (a) Maligres, P. E.; Krska, S. W.; Humphrey, G. R. *Org. Lett.* **2004**, *6*, 3147; (b) Shultz, C. S.; Dreher, S. D.; Ikemoto, N.; Williams, J. M.; Grabowski, E. J. J.; Krska, S. W.; Sun, Y.; Dormer, P. G.; DiMichele, L. *Org. Lett.* **2005**, *7*, 3405; (c) Tellers, D. M.; Bio, M.; Song, Z. J.; McWilliams, J. C.; Sun, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 550; (d) Tellers, D. M.; McWilliams, J. C.; Humphrey, G.; Journet, M.; DiMichele, L.; Hinksmon, J.; McKeown, A. E.; Rosner, T.; Sun, Y.; Tillyer, R. D. *J. Am. Chem. Soc.* **2006**, *128*, 17063.
18. (a) Shin, Y. G.; Van Breemen, R. B. *Biopharm. Drug Dispos.* **2001**, *22*, 353; (b) Cappiello, A.; Famiglini, G.; Palma, P.; Siviero, A. *Mass Spectrom. Rev.* **2005**, *24*, 978.
19. The decomposition is attributed to the prolonged solution exposure necessitated during the chromatography. In our hands, these 2-substituted indoles should be stored below ambient temperature in the solid state.