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# Multiple component Fischer indole reactions

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**Abstract**—New 3-component variations of the Fischer synthesis of substituted indoles have been developed based on the reaction of organometallic reagents with nitriles or carboxylic acids. The new variations expand the scope and synthetic utility of the method.


## 1. Introduction

Multiple component condensation (MCC) reactions, defined as processes 'in which three or more reactants come together in a single reaction to form a new product that contains portions of all the components,'[1] play a central role in diversity-oriented synthesis. Despite their utility, such reactions remain a small subset of known organic reactions. Recent discoveries by our group[2] and others[3] have expanded the repertoire of useful MCC reactions. However, significant advances in this area might also be achieved by modifying known MCC reactions, either by broadening input types or increasing reaction dimensionality (i.e., >3-component Mannich or >4-component Ugi condensations). Here, we use a combination of those approaches to demonstrate that the well-known 2-component Fischer indole synthesis can be re-engineered into a higher-order, more broadly based 3-component process.

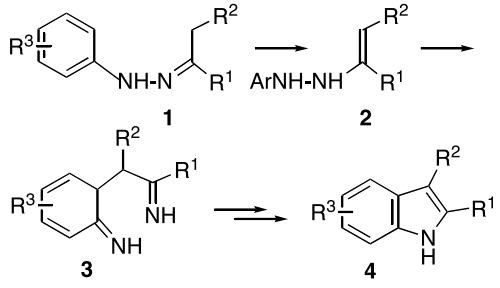
## 2. Background

Over a century ago Emil Fischer discovered that hydrazones **1**, prepared from arylhydrazines and enolizable ketones, rearranged upon heating in acid with loss of ammonia to afford indoles **4** (Scheme 1).[4] The process involved initial tautomerization to an ene-hydrazine **2** that underwent a [3,3]-sigmatropic rearrangement to **3** followed by ring closure and aromatization. We reasoned that identifying other reactant combinations leading to intermediates in Scheme 1 might increase the dimensionality of the Fisher indole synthesis, thus widening its scope.

With three contiguous bonds involving two well-differentiated heteroatoms, arylhydrazone **1** presented a particularly attractive target. Such arylhydrazones have previously been formed by Pd-catalyzed cross-coupling of benzophenone hydrazones with aryl bromides, leading to indoles in excellent yield.[5] Substituted indoles have also been prepared by alkyne hydroamination with hydrazines[6] and by the tandem hydroformylation/hydrazination of alkenes.[7] However, each of these methods uses only two variable components.

By contrast, metallated ketimines **5** (Scheme 2), generated by the reaction of nitriles with Grignard[8] or organolithium[9] compounds, should react in situ (after protonation) with arylhydrazines to form arylhydrazones **1**. Rearrangement to the corresponding indoles would thus incorporate structural diversity from three different inputs. Moreover, species like **5** could in most cases be formed from two complementary reactant combinations as shown, thus making the overall synthesis plan even more flexible.

Here, we report this 3-component condensation can be successfully implemented as a one pot process. By using anhydrous ether as solvent in the addition of organometallic reagents, byproducts arising from competing deprotonation




**Scheme 1.**

*Keywords*: Deprotonation; Fisher cyclization; Tandem hydroformylation.
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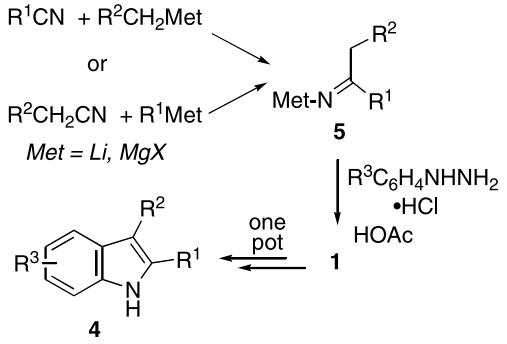



**Scheme 2.**

reactions of α-acidic nitriles[10] could be suppressed so as to obtain metallated ketimines **5** in good yield.[11]

## 3. Results and discussion

Protonation of **5** and conversion of the corresponding arylhydrazones **1** to indoles **4** was achieved by brief heating (90 °C, 3 h) in glacial acetic acid containing 2.1 equiv of the appropriate arylhydrazine hydrochloride.[12] This method, first reported by Dave, avoids the use of toxic, air- and light-sensitive $PhNHNH_2$ as well as the customary higher temperatures and more corrosive Lewis acids. Representative examples of the reaction, shown in Table 1, illustrate the scope and generality of the method.

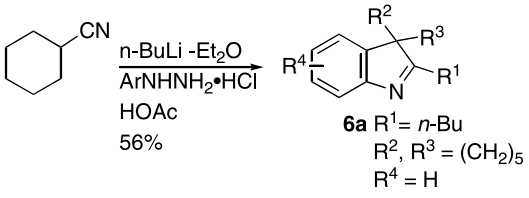
The new 3-component route afforded indoles in yields similar to the classical 2-component Fischer synthesis. In most cases, a small amount (ca. 15% yield based on phenylhydrazine) of $PhNHNHCOCH_3$ was also obtained as a byproduct.[13] Condensation of propionitrile with BuLi or BuMgCl led to the same 2:1 mixture of indoles **4h** and **4i**, in agreement with earlier observations on the rearrangement of α,α′-unbranched arylhydrazones.

The Dave conditions for Fischer cyclization, originally applied only to $PhNHNH_2 \cdot HCl$, could be extended to ring-substituted arylhydrazine hydrochloride salts leading to 4, 5, 6, and 7-substituted indoles (e.g., **4b**, **4c**, **4f**, **4j**), albeit in slightly lower yields. Cyclizations leading to 2-arylindoles required somewhat longer heating (15–19 h).

Table 1 also showed that the scope of the method could be extended beyond commercially available organometallic reagents. For example, the synthesis of indoles **4e**, **4f** and **4k** demonstrated the successful use of organolithium reagents prepared by halogen–metal exchange methods, which significantly expanded the utility of the 3CC indole synthesis.

One limitation of the method was encountered in efforts to transform halo-substituted nitriles (e.g., 3-bromopropionitrile, 4-chlorobutyronitrile) into the correspondingly functionalized indoles. All attempts to trap metallated imine **5**, the corresponding ketone or hydrazone **1** failed, suggesting that **5** might be susceptible to inter- or intramolecular decomposition.

The method was successful in preparing indolenines by way of α-branched arylhydrazones. Reaction of cyclohexylcarbonitrile with BuLi followed by $PhNHNH_2 \cdot HCl$ afforded **6a** (Eq. 1) in 56% yield, in accordance with literature precedent.[14]




(1)

An alternative 3-component route to indoles has also been devised from the well-known reaction of a carboxylic acid with 2 equiv of an organolithium reagent in ether.[15] The method affords a useful synthetic approach to ketones, by hydrolysis of the intermediate dialkoxides **7** (Scheme 3).

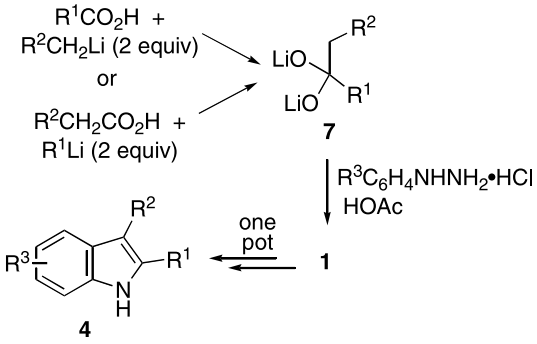
In the present variation, stepwise reaction of a carboxylic acid with RLi was followed by the addition of a sufficient quantity of arylhydrazine hydrochloride. By using 3.1 equiv of $ArNHNH_2 \cdot HCl$ in HOAc, it proved possible to protonate dianion **7** and generate the corresponding ketone. Arylhydrazone formation in situ and Fischer cyclization catalyzed by the residual hydrochloride salt in glacial HOAc at 90 °C afforded indoles **4**. Table 2 presents representative examples of indoles that could be prepared in this fashion.

The higher-order variants of the Fischer synthesis reported

**Table 1**. 3-Component condensations of nitriles, RMet and $ArNHNH_2$ leading to indoles **4**[a]

| Nitrile | RMet | $ArNHNH_2Ar=$ | Product (% yield) |
|---|---|---|---|
| PhCN | BuLi | Ph[b] | **4a** 2-Phenyl-3-propylindole (60) |
| PhCN | BuLi | *m*-Cl-Ph[b] | **4b** 4-Chloro-2-phenyl-3-propylindole (19), **4c** 6-Chloro-2-phenyl-3-propylindole (19) |
| PhCN | BuMgCl | Ph | **4a** (42) |
| *n*-$C_5H_{11}CN$ | PhLi | Ph | **4d** 3-Butyl-2-phenylindole (49) |
| *n*-$C_5H_{11}CN$ | PhMgCl | Ph | **4d** (45) |
| *n*-$C_5H_{11}CN$ | *p*-OMe-$C_6H_4Li$ | Ph[a] | **4e** 3-Butyl-2-(*p*-$CH_3OPh$)-indole (64) |
| *n*-$C_5H_{11}CN$ | *p*-OMe-$C_6H_4Li$ | *o*-Cl-Ph[b] | **4f** 3-Butyl-7-chloro-2-(*p*-$CH_3OPh$)-indole (34) |
| *n*-$C_5H_{11}CN$ | $CH_3Li$ | Ph | **4g** 3-Butyl-2-methylindole (54) |
| $CH_3CH_2CN$ | BuLi | Ph | **4h** $R^1$=2-butyl-3-methylindole (46), **4i** 2-Ethyl-3-propylindole (23) |
| $CH_3CH_2CN$ | BuMgCl | Ph | **4h** (40); **4i** (20) |
| $CH_3CH_2CN$[c] | PhMgBr | *p*-OMe-Ph | **4j** 5-Methoxy-3-methyl-2-phenylindole (32) |
| $CH_3CH_2CN$ | 3,5-Dibromo-PhLi | Ph[b] | **4k** 2-(3′,5′-Dibromophenyl)-3-methylindole (57) |

[a] The nitrile was combined with RMet in ether, followed by the addition of $ArNHNH_2 \cdot HCl$. The ether was removed in vacuo and HOAc added. The reaction mixture was then heated at 90 °C.
[b] $ArNHNH_2 \cdot HCl$ (2.6 equiv) added.
[c] Nitrile added in $C_6H_6$.




**Scheme 3.**

**Table 2**. 3-Component condensations of carboxylic acids, RLi and $ArNHNH_2$ leading to indoles **4** and indolenines[a]

| Acid | RLi | $ArNHNH_2Ar=$ | Product (% yield) |
|---|---|---|---|
| Benzoic | BuLi | Ph | **4a** 2-Phenyl-3-propylindole (72) |
| Nonanoic | $CH_3Li$ | Ph | **4l** 3-Heptyl-2-methylindole (55) |
| Isobutyric | BuLi | Ph | **6b** 2-Butyl-3,3-dimethylindolenine (66) |
| Isobutyric | BuLi | *o*-Cl-Ph | **6c** 2-Butyl-7-chloro-3,3-dimethylindolenine (48) |
| 4-Pentenoic | PhLi | Ph | **4m** 3-Allyl-2-phenylindole (52) |
| 4-Pentenoic | PhLi | *p*-OMe-Ph | **4n** 3-Allyl-5-methoxy-2-phenylindole (54) |
| 4-pentenoic | 3,5-Dibromo-PhLi | *p*-OMe-Ph | **4o** 3-Allyl-2-(3′,5′-dibromophenyl)-5-methoxyindole (29) |

[a] The acid was combined with R-Met in ether at 0 °C, followed by heating at 45–90 °C. After addition of $ArNHNH_2 \cdot HCl$ at 0 °C, the ether was removed in vacuo and HOAc added. The reaction mixture was then heated at 90 °C.

here, should prove useful in the convergent assembly of indoles from a more diverse array of available reactants. Indeed, many simple substituted indole alkaloids have significant therapeutic potential, including antibacterial, antiphosphatase, antipeptidase, anticancer and insecticidal activity.[16]

## 4. Experimental

### 4.1. Representative procedure for the synthesis of 2-arylindoles from nitriles and organolithiums

**4.1.1. Procedure A: synthesis of 2-phenyl-3-propylindole (4a).**[17] To *n*-butyllithium (hexane solution, 0.18 mL, 0.25 mmol) in anhydrous ether (0.25 mL) at 0 °C, under argon, was added a solution of benzonitrile (22 μL, 0.21 mmol) in ether (0.25 mL) by syringe over a 2 min period. The reaction mixture was stirred for 30 min under argon at 0 °C. Phenylhydrazine·HCl (73 mg, 0.55 mmol) was then added with stirring for 5 min at 0 °C, then 5 min at rt. The heterogeneous mixture was concentrated to remove ether. Glacial acetic acid (0.9 mL) was added and the reaction heated to 90 °C in an oil bath for 15 h.

The reaction mixture was diluted with ether (10 mL) and water (2 mL). The aqueous phase was extracted with ether (3×1 mL) and the combined organic layers were washed with NaOH (1 N) until basic, then with saturated NaCl (1 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to furnish an oil that was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f=0.3$), to afford an off-white solid (30 mg, 60%): mp 78–79 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.98 (br s, 1H), 7.64 (d, 1H, $J=7.6$ Hz), 7.56 (d, 2H, $J=7.1$ Hz), 7.48 (t, 2H, $J=7.4$ Hz), 7.37 (m, 2H), 7.20 (t, 1H, $J=6.8$ Hz), 7.13 (t, 1H, $J=6.8$ Hz), 2.86 (t, 2H, $J=7.8$ Hz), 1.76 (sextet, 2H, $J=7.6$ Hz), 1.00 (t, 3H, $J=7.6$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 136.07, 134.30, 133.69, 129.54, 129.02, 128.14, 127.67, 122.36, 119.63, 119.57, 114.19, 110.92, 26.92, 24.47, 14.67; IR (neat) 3408 (s), 3054 (m), 2954 (s), 1610 (w), 1465 (s), 1311 (m), 739 (s), 694 (s); CIMS (methane) *m/z*: 236 (M+H), 206.

**4.1.2. 4-Chloro-2-phenyl-3-propylindole (4b).** The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f=0.19$), to afford an off-white solid (10 mg, 19%): mp 110–112 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.04 (br s, 1H), 7.52 (d, 2H, $J=7.0$ Hz), 7.48 (t, 2H, $J=7.5$ Hz), 7.39 (t, 1H, $J=7.2$ Hz), 7.25 (d, 1H, $J=7.5$ Hz), 7.07 (m, 2H), 2.96 (t, 2H, $J=8.0$ Hz), 1.78 (sextet, 2H, $J=8.0$ Hz), 0.97 (t, 3H, $J=7.3$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 137.49, 135.73, 133.12, 129.03, 128.64, 128.15, 126.71, 125.75, 122.68, 121.06, 114.69, 109.64, 27.27, 26.70, 14.42; IR (neat) 3418 (s), 2959 (s), 1600 (m), 1485 (s), 1446 (s), 1336 (s), 1197 (s), 764 (s), 739 (s), 699 (s); CIMS (methane) *m/z*: 270 (M+H), 240, 205.

**4.1.3. 6-Chloro-2-phenyl-3-propylindole (4c).** The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f=0.31$), to afford an off-white solid (10 mg, 19%): mp 60–61 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.92 (br s, 1H), 7.51 (d, 3H, $J=8.2$ Hz), 7.46 (t, 2H, $J=7.6$ Hz), 7.36 (t, 1H, $J=7.3$ Hz), 7.31 (s, 1H), 7.08 (d, 1H, $J=7.1$ Hz), 2.80 (t, 2H, $J=7.8$ Hz), 1.71 (sextet, 2H, $J=7.8$ Hz), 0.96 (t, 3H, $J=7.3$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 136.36, 134.95, 133.18, 129.08, 128.17, 128.07, 127.92, 120.39, 120.33, 114.20, 110.84, 26.76, 24.39, 14.58; IR (neat) 3418 (s), 3064 (w), 2964 (s), 1595 (s), 1466 (s), 774 (s), 704 (s); CIMS (methane) *m/z*: 270 (M+H), 240, 234.

**4.1.4. 3-Butyl-2-phenylindole (4d).**[18] The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f=0.29$) to furnish a light orange powder (26 mg, 49%): mp 57–59 °C, lit. mp 60–62 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.97 (br s, 1H), 7.66 (d, 1H, $J=7.6$ Hz), 7.57 (d, 2H, $J=8.1$ Hz), 7.49 (t, 2H, $J=7.3$ Hz), 7.3 (t, 2H, $J=8.1$ Hz), 7.22 (t, 1H, $J=7.0$ Hz), 7.15 (t, 1H, $J=7.4$ Hz), 2.90 (t, 2H, $J=7.8$ Hz), 1.73 (p, 2H, $J=7.5$ Hz), 1.43 (sextet, 2H, $J=7.6$ Hz), 0.94 (t, 3H, $J=7.3$ Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 136.08, 134.18, 133.65, 129.49, 128.99, 128.11, 127.64, 122.35, 119.61, 119.52, 114.31, 110.94, 33.47, 24.52, 23.19, 14.21; IR (neat) 3407 (s), 3064 (m), 2925 (s), 1605 (m), 1461 (s), 1341

(m), 1311 (m), 1241 (m), 749 (s), 694 (s); CIMS (methane) *m/z*: 250 (M+H), 206.

**4.1.5. 2-(3′,5′-Dibromophenyl)-3-methylindole (4k).** 3,5-Dibromophenyllithium was prepared from 1,3,5-tribromobenzene following a literature procedure.[19] The product was purified by silica gel flash column chromatography (16:1 hexanes/ether, then 8:1 hexanes/ether), to afford a yellow powder upon cooling in the freezer overnight (29 mg, 57%): mp 100–103 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.96 (br s, 1H), 7.62 (m, 4H), 7.36 (d, 1H, $J$=8.2 Hz), 7.24 (t, 1H, $J$=8.1 Hz), 7.16 (t, 1H, $J$=8.1 Hz), 2.45 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 136.95, 136.29, 132.68, 131.05, 129.90, 129.31, 123.54, 123.49, 120.15, 119.57, 111.08, 110.95, 9.91; IR (neat) 3412 (m), 3059 (w), 2919 (w), 1595 (s), 1540 (s), 1461 (m), 863 (m), 744 (s); CIMS (methane) *m/z*: 366 (M+H), 286, 79.

**4.1.6. 3-Butyl-2-(*p*-methoxyphenyl)indole (4e).** To a solution of *p*-bromoanisole (25 μL, 0.2 mmol) in ether (0.25 mL) at 0 °C under argon was added *n*-BuLi (hexane solution, 0.12 mL, 0.2 mmol) via syringe over 1 min. The reaction mixture was warmed to rt and stirred for 1 h.[20] After cooling to 0 °C, a solution of hexanenitrile (22 μL, 0.18 mmol) in ether (0.10 mL) was added via syringe over 1 min, then stirred for 30 min. Following Method A afforded an oily solid that was purified by silica gel flash column chromatography (8:1 hexanes/ether, then 4:1 hexanes/ether), to afford a clear oil (32 mg, 64%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.91 (br s, 1H), 7.62 (d, 1H, $J$=7.8 Hz), 7.48 (d, 2H, $J$=8.0 Hz), 7.36 (d, 1H, $J$=8.0 Hz), 7.18 (t, 1H, $J$=7.9 Hz), 7.12 (t, 1H, $J$=7.8 Hz), 7.01 (d, 2H, $J$=8.1 Hz), 3.87 (s, 3H), 2.85 (t, 2H, $J$=7.8 Hz), 1.70 (p, 2H, $J$=7.7 Hz), 1.41 (sextet, 2H, $J$=7.5 Hz), 0.92 (t, 3H, $J$=7.4 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 159.25, 135.92, 134.16, 129.55, 129.38, 126.21, 122.02, 119.53, 119.31, 114.44, 113.48, 110.81, 55.56, 33.48, 24.52, 23.20, 14.23; IR (neat) 3412 (m), 2959 (s), 2940 (s), 1615 (w), 1510 (s), 1460 (s), 1251 (s), 833 (m), 744 (m); CIMS (methane) *m/z*: 280 (M+H), 265, 236, 188.

**4.1.7. 3-Butyl-7-chloro-2-(4′-methoxyphenyl)indole (4f).** Following the procedure for **4e**, the product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f$=0.29), to afford a clear oil (17 mg, 34%); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.10 (br s, 1H), 7.51 (m, 3H), 7.17 (d, 1H, $J$=7.9 Hz), 7.05 (t, 1H, $J$=7.7 Hz), 7.02 (m, 2H), 3.88 (s, 3H), 2.83 (t, 2H, $J$=7.8 Hz), 1.68 (p, 2H, $J$=7.6 Hz), 1.40 (sextet, 2H, $J$=7.5 Hz), 0.92 (t, 3H, $J$=7.4 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.56, 135.01, 133.11, 130.96, 129.53, 125.55, 121.28, 120.32, 117.89, 116.35, 114.53, 114.45, 55.59, 33.40, 24.63, 23.12, 14.20; IR (neat) 3427 (m), 2959 (s), 2934 (s), 1610 (w), 1510 (s), 1461 (s), 1252 (s), 834 (m); CIMS (methane) *m/z*: 314 (M+H), 270.

### 4.2. Representative procedure for the synthesis of aliphatic substituted indoles and indolenines from nitriles and organolithiums

**4.2.1. Procedure B: synthesis of 3-butyl-2-methylindole (4g).**[21] Methyllithium in ether (0.20 mL, 0.32 mmol) was added to a 0 °C solution of ether (0.30 mL) under argon. A solution of hexanenitrile (35 μL, 0.29 mmol) and ether (0.30 mL) was added by syringe over a 2 min period. The reaction mixture was stirred 30 min under argon at 0 °C. Phenylhydrazine·HCl (88 mg, 0.61 mmol) was added quickly and the reaction stirred 5 min at 0 °C, then 5 min at rt. The heterogeneous mixture was concentrated to remove ether. Glacial acetic acid (0.9 mL) was added and the reaction mixture was heated to 90 °C for 3 h. After following the extractive workup of procedure A, the product was purified by silica gel flash column chromatography (4:1 hexanes/ether, $R_f$=0.27), to afford a yellow oil (27 mg, 54%); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.69 (br s, 1H), 7.51 (d, 1H, $J$=7.1 Hz), 7.26 (m, 1H), 7.13–7.03 (m, 2H), 2.68 (t, 2H, $J$=7.4 Hz), 2.36 (s, 3H), 1.60 (p, 2H, $J$=7.7 Hz), 1.37 (sextet, 2H, $J$=7.2 Hz), 0.92 (t, 3H, $J$=7.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.40, 130.75, 129.02, 120.92, 119.09, 118.35, 112.65, 110.27, 33.20, 24.04, 22.86, 14.28, 11.87; IR (neat) 3407 (s), 3064 (w), 2959 (m), 2924 (s), 1461 (s), 1301 (w), 739 (s); CIMS (methane) *m/z*: 188 (M+H), 144.

**4.2.2. 2′-Butylspiro[cyclohexane-1,3′-3′H-indole] (6a):.** The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f$=0.3), to afford an off-white powder (28 mg, 56%): mp 69–71 °C; $^1$H (500 MHz, $CDCl_3$) $\delta$ 7.71 (d, 1H, $J$=7.4 Hz), 7.60 (d, 1H, $J$=7.7 Hz), 7.33 (t, 1H, $J$=7.6 Hz), 7.15 (t, 1H, $J$=7.5 Hz), 2.52 (t, 2H, $J$=7.6 Hz), 1.99–1.77 (m, 10H), 1.46 (sextet, 2H, $J$=7.8 Hz), 1.26 (m, 2H), 0.97 (t, 3H, $J$=7.4 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 191.14, 154.72, 144.70, 127.63, 124.47, 124.25, 120.41, 58.32, 31.09, 29.24, 29.16, 25.53, 23.17, 21.82, 14.20; IR (neat) 2930 (s), 2869 (m), 1580 (m), 1456 (s), 749 (s); CIMS (methane) *m/z*: 242 (M+H), 199, 144.

### 4.3. Representative procedures for the synthesis of indoles and indolenines from nitriles and Grignard reagents

**4.3.1. Procedure C: synthesis of 2-butyl-3-methylindole (4h).** A solution of butylmagnesium chloride in ether (0.15 mL, 0.29 mmol) in ether (0.25 mL) was brought to reflux under argon. A solution of propionitrile (19 μL, 0.27 mmol) in ether (0.25 mL) was added over 1 min via syringe. The reaction was heated at reflux for 4 h under argon. The reaction was then cooled to 0 °C and phenylhydrazine·HCl (81 mg, 0.56 mmol) was added. The resulting heterogeneous mixture was stirred 5 min at 0 °C, 5 min at rt, then concentrated to remove ether. Glacial acetic acid (1.0 mL) was added and the reaction was heated to 90 °C in an oil bath for 3 h before performing the extractive workup of procedure A.

**4.3.2. Procedure D:[22] synthesis of 2-butyl-3-methylindole (4h).**[23] To a solution of butylmagnesium chloride in ether, (0.15 mL, 0.29 mmol) in benzene (0.25 mL) at rt under argon was added a solution of propionitrile (19 μL, 0.27 mmol) in benzene (0.25 mL) over 1 min. The reaction was stirred at rt for 1 h. Phenylhydrazine·HCl (81 mg, 0.56 mmol) added and the mixture stirred 5 min at 0 °C, 5 min at rt, then concentrated to remove ether. Glacial acetic acid (1.0 mL) added and the reaction mixture was heated to 90 °C for 3 h. The extractive workup of procedure A was followed to afford an orange oil, which was purified by

silica gel flash column chromatography (8:1 hexanes/ether, $R_f$=0.34), to afford an orange solid upon cooling in the freezer overnight (20 mg, 40%); mp 41–43 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.69 (br s, 1H), 7.5 (d, 1H, $J$=7.5 Hz), 7.27 (d, 1H, $J$=7.0 Hz), 7.11 (m, 2H), 2.73 (t, 2H, $J$=7.5 Hz), 2.25 (s, 3H), 1.64 (p, 2H, $J$=7.5 Hz), 1.39 (sextet, 2H, $J$=7.6 Hz), 0.95 (t, 3H, $J$=7.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.49, 135.29, 129.56, 121.04, 119.11, 118.21, 110.28, 106.98, 32.05, 26.04, 22.60, 14.11, 8.69; IR (neat) 3403 (s), 2969 (s), 2924 (s), 1470 (s), 1336 (m), 1306 (m), 744 (s); CIMS (methane) *m/z*: 188 (M+H), 144.

**4.3.3. 2-Ethyl-3-propylindole (4i).** Synthesized following either procedure C or D. The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f$=0.26), to afford a waxy orange solid after standing (10 mg, 20%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (br s, 1H), 7.52 (d, 1H, $J$=6.8 Hz), 7.28 (d, 1H, $J$=7.3 Hz), 7.09 (m, 2H), 2.76 (q, 2H, $J$=7.6 Hz), 2.67 (t, 2H, $J$=7.6 Hz), 1.65 (sextet, 2H, $J$=7.5 Hz), 1.28 (t, 3H, $J$=7.6 Hz), 0.95 (t, 3H, $J$=7.4 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 136.75, 135.40, 129.02, 120.98, 119.10, 118.57, 111.60, 110.39, 26.35, 24.31, 19.54, 14.56, 14.42; IR (neat) 3402 (s), 2959 (s), 2929 (s), 1461 (s), 1321 (m), 744 (s); CIMS (methane) *m/z*: 188 (M+H), 158.

**4.3.4. 5-Methoxy-3-methyl-2-phenylindole (4j).**[24] Synthesized following procedure D. The product was purified by silica gel flash column chromatography (4:1 hexanes/ether, $R_f$=0.3), to afford a white powder (16 mg, 32%): mp 116–117 °C, lit. mp[25] 114–116 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.89 (br s, 1H), 7.57 (d, 2H, $J$=8.3 Hz), 7.47 (t, 2H, $J$=8.9 Hz), 7.35 (t, 1H, $J$=7.4 Hz), 7.27 (d, 1H, $J$=8.3 Hz), 7.04 (d, 1H, $J$=2.4 Hz), 6.87 (dd, 1H, $J$=2.4, 8.7 Hz), 3.90 (s, 3H), 2.44 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 154.32, 135.16, 133.58, 131.18, 130.60, 129.00, 127.85, 127.47, 112.62, 111.65, 108.69, 101.00, 56.16, 9.97; IR (neat) 3412 (m), 2929 (w), 1620 (m), 1585 (m), 1486 (s), 1461 (s), 1291 (m), 1217 (s), 774 (m), 699 (m); CIMS (methane) *m/z*: 238 (M+H), 223.

### 4.4. Representative procedure for the synthesis of indoles and indolenines from carboxylic acids and organolithiums

**4.4.1. Procedure E:[26] synthesis of 3-heptyl-2-methylindole (4l)** Methyllithium in ether (0.28 mL, 0.45 mmol) was added to a stirring ether (1.0 mL) solution at 0 °C, under argon. A solution of nonanoic acid (38 μL, 0.22 mmol) in ether (0.1 mL) was added over 3 min. The reaction mixture was stirred at 0 °C for 5 min, then at rt 10 min. The reaction mixture was then heated at 45 °C for 30 min. The resulting heterogeneous mixture was cooled to 0 °C and phenylhydrazine·HCl (96 mg, 0.67 mmol) quickly added. The reaction mixture was stirred 5 min at 0 °C, 5 min at rt, then concentrated to remove ether. Glacial acetic acid (0.9 mL) added and the reaction mixture was heated to 90 °C for 3 h. Following the extractive workup of procedure A, the product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f$=0.3), to afford a yellow oil (28 mg, 55%); 1H NMR (300 MHz, $CDCl_3$) $\delta$ 7.65 (br s, 1H), 7.53 (m, 1H), 7.26 (m, 1H), 7.11 (m, 2H), 2.69 (t, 2H, $J$=7.4 Hz), 2.37 (s, 3H), 1.62 (p, 2H, $J$=7.4 Hz), 1.30 (m, 8H), 0.90 (t, 3H, $J$=6.9 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 135.40, 130.73, 129.00, 120.90, 119.09, 118.35, 112.69, 110.27, 32.15, 31.01, 29.82, 29.50, 24.33, 22.92, 14.35, 11.86; IR (neat) 3407 (s), 2930 (s), 2860 (s), 1466 (s), 1306 (m), 739 (s); CIMS (methane) *m/z*: 230 (M+H), 144.

**4.4.2. 3-Allyl-2-phenylindole (4m).**[27] Synthesized following procedure E, except the reaction was heated at 90 °C for 19 h. The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f$=0.3), to afford a yellow/white powder (26 mg, 52%): mp 98–99 °C, lit. mp[28] 72–73 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.02 (br s, 1H), 7.56 (m, 3H), 7.44 (t, 2H, $J$=7.3 Hz), 7.34 (m, 2H), 7.19 (t, 1H, $J$=8.1 Hz), 7.11 (t, 1H, $J$=7.9 Hz), 6.12 (m, 1H), 5.08 (m, 2H), 3.61 (dt, 2H, $J$=1.8, 5.6 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 137.57, 136.10, 135.01, 133.16, 129.55, 129.04, 128.02, 127.86, 122.53, 119.84, 119.59, 115.38, 110.96, 110.66, 29.15; IR (neat) 3402 (s), 3078 (w), 3014 (w), 1610 (w), 1455 (s), 1306 (m), 992 (m), 928 (m), 759 (s), 700 (m); CIMS (methane) *m/z*: 234 (M+H), 206.

**4.4.3. 3-Allyl-5-methoxy-2-phenylindole (4n).** Synthesized following procedure E, except the reaction was heated at 90 °C for 15 h. The product was purified by silica gel flash column chromatography (45 mL of 8:1 hexanes/ether, then 4:1 hexanes/ether), to afford a white powder (27 mg, 54%): mp 102–104 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.95 (br s, 1H), 7.55 (d, 2H, $J$=8.1 Hz), 7.46 (t, 2H, $J$=7.9 Hz), 7.36 (t, 1H, $J$=7.4 Hz), 7.28 (d, 1H, $J$=8.7 Hz), 7.04 (sd, 1H, $J$=2.4 Hz), 6.87 (dd, 1H, $J$=2.4, 8.8 Hz), 6.13 (m, 1H), 5.11 (m, 2H), 3.87 (s, 3H), 3.60 (dt, 2H, $J$=1.8, 5.7 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 154.32, 137.44, 135.97, 133.26, 131.33, 130.06, 129.02, 127.95, 127.80, 115.37, 112.53, 111.71, 110.44, 101.52, 56.14, 29.20; IR (neat) 3402 (m), 2939 (w), 1625 (m), 1486 (s), 1456 (s), 1222 (s), 1037 (w), 763 (m), 699 (m); CIMS (methane) *m/z*: 264 (M+H), 249.

**4.4.4. 3-Allyl-2-(3′,5′-dibromophenyl)-5-methoxyindole (4o).** Synthesized following procedure E, except the reaction was heated at 90 °C for 15 h. The product was purified by silica gel flash column chromatography (4:1 hexanes/ether, $R_f$=0.3), to afford a pale yellow powder (15 mg, 29%): mp 111–114 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.89 (br s, 1H), 7.60 (s, 3H), 7.25 (d, 1H, $J$=8.8 Hz), 6.99 (sd, 1H, $J$=2.4 Hz), 6.88 (dd, 1H, $J$=2.4, 8.8 Hz), 6.07 (m, 1H), 5.08 (m, 2H), 3.84 (s, 3H), 3.55 (dt, 2H, $J$=1.8, 5.7 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 154.56, 136.77, 136.60, 132.93, 132.71, 131.55, 129.76, 129.35, 123.51, 115.91, 113.74, 112.34, 112.01, 101.37, 56.07, 29.08; IR (neat) 3408 (m), 2929 (m), 1585 (s), 1540 (m), 1490 (m), 1216 (s), 749 (s); CIMS (methane) *m/z*: 422 (M+H), 342, 264.

**4.4.5. 2-Butyl-3,3-dimethylindolenine (6b).** The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f$=0.3), to afford a yellow oil (33 mg, 66%); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.57 (d, 1H, $J$=7.6 Hz), 7.28 (m, 2H), 7.17 (t, 1H, $J$=7.3 Hz), 2.52 (t, 2H, $J$=8.2 Hz), 1.83 (p, 2H, $J$=8.0 Hz) 1.45 (sextet, 2H, $J$=7.6 Hz), 1.28 (s, 6H), 0.97 (t, 3H, $J$=7.3 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 191.36, 154.02, 145.81, 127.72, 125.16, 121.35, 120.19, 53.97, 28.89, 28.76, 23.40, 23.11,

14.17; IR (neat) 2964 (s), 2934 (s), 2869 (m), 1580 (s), 1461 (s), 1207 (w), 754 (s); CIMS (methane) *m/z*: 216 (M+$CH_3$), 202 (M+H), 146, 71.

**4.4.6. 2-Butyl-7-chloro-3,3-dimethylindolenine (6c).** The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f$=0.3), to afford an off-white powder (24 mg, 48%): mp 43–45 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.27 (dd, 1H, $J$=1.4, 7.7 Hz), 7.12 (m, 2H), 2.56 (t, 2H, $J$=7.9 Hz), 1.84 (p, 2H, $J$=7.8 Hz), 1.46 (sextet, 2H, $J$=7.5 Hz), 1.30 (s, 6H), 0.97 (t, 3H, $J$=7.4 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 192.84, 150.66, 147.78, 128.23, 126.32, 125.20, 119.72, 55.47, 29.43, 29.29, 23.22, 23.23, 14.11; IR (neat) 2964 (s), 2930 (s), 2865 (m), 1575 (s), 1461 (s), 1431 (s), 1201 (w), 963 (m), 754 (s); CIMS (methane) *m/z*: 236 (M+H), 193, 180, 157.

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