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Indole Synthesis by Controlled Carbolithiation of *o*-Aminostyrenes

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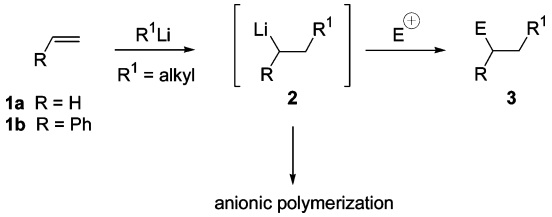
An effective synthesis of the functionalized indole ring system has been developed from substituted *o*-aminostyrene starting material. Our methodology involves a novel cascade reaction sequence of alkyllithium addition to the styrene double bond and subsequent trapping of the intermediate organolithium with a suitable electrophile, followed by an in situ ring closure and dehydration to generate the indole ring. This new reaction sequence allows for the introduction of molecular diversity at all positions on the indole scaffold. The procedure was shown to be successful with a range of both C and N substituents on the *o*-aminostyrenes. The reaction sequence was tolerant to the reactivity range of alkyllithiums such as *tert*-, *sec*-, and *n*-butyllithium. The electrophiles used were DMF, which generated indole products with C-2 unsubstituted, and nitriles, which incorporated the nitrile substituent at C-2. The *o*-aminostyrene starting materials were generated by a Pd-catalyzed cross-coupling reaction of a vinyl boronic acid equivalent with the readily available substituted *o*-bromoanilines.

Introduction

The synthetic potential of the carbolithiation of unactivated alkenes lies in the fact that both a new carbon−carbon bond and organolithium compound are generated in tandem. The newly generated organolithium species may then be exploited for further in situ transformations.[1] A drawback of this approach is that it can suffer in its application as a viable synthetic method due to the reactivity of the generated organolithium toward the starting alkene. If the generated organolithium reacts with a second molecule of the alkene an anionic polymerization process could propagate. As such, one of the earlier demonstrated applications of organolithium reactions was an anionic polymerization of styrene, which was initiated with *n*-butyllithium in THF at 20 °C (Scheme 1).[2]

The challenge in successfully exploiting the intermediate organolithium is dependent upon suppressing the anionic polymerization process in favor of generating a solution of **2** (Scheme 1). This implies that conditions are required that will facilitate the initial carbolithiation process but not favor further carbolithiation by the intermediate organolithium. This has been accomplished for the simplest unactivated carbon−carbon double bond ethene **1a**, in which controlled carbolithiation has been achieved for *tert*- and *sec*-butyllithium but not *n*-butyllithium.[3] This can be rationalized by a comparison of the stability of the starting alkyllithium and the generated

SCHEME 1. Carbolithiation of Unactivated Alkenes



alkyllithium. The rate of carbolithiation is faster for the more substituted alkyl group; thus, polymerization can be avoided for *tert*- and *sec*-butyllithium which react to generate primary alkylithiums. In comparison, when a primary alkyllithium (*n*-Bu) is used to generate an intermediate primary alkyllithium this selectivity is lost and polymerization results.

It was not until recently that the potential for the controlled organolithium addition to styrene was exploited. It was demonstrated that by employing diethyl ether as the reaction solvent and maintaining a low temperature, polymerization could be avoided and the generated organolithium product was now available for further organic transformations.[4] Use of this methodology allows for the addition of alkyl groups to the terminal carbon of the styrene **1b**, followed by trapping of the generated lithiated intermediate **2** with various electrophiles providing a viable route to alkyl-substituted aryls

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3 (Scheme 1). Styrene **1b** was shown to undergo efficient carbolithiation from −25 to −78 °C, with the reactivity of different organolithiums found to be to be tertiary > secondary > primary > methyl, phenyl. In this case, the scope of the reaction can be extended to primary alkyllithiums as the generated organolithium is a benzylic-lithium species, which is less reactive than primary alkyllithiums.

The carbolithiation of unactivated alkenes has proven very successful for the synthesis of complex polycyclic systems. This has typically been achieved by reaction sequences utilizing an intramolecular carbolithiation process to generate a variety of carbocycles[1a,5] and heterocycles.[6] To date, intermolecular carbolithiation methodology as a route to ring formation has been much more limited in its application, with the few reported examples being applied to the formation of cyclopentanes[7] and tetralins.[8]

Our goal in this work was to exploit an intermolecular carbolithiation reaction to initiate a controlled cascade reaction sequence for the generation of indole ring scaffold. To achieve this, we have expanded the synthetic utility of the styrene carbolithiation reaction for the specific case of *ortho*-substituted aminostyrenes. For these derivatives it should be possible that upon generation of the intermediate anion via organolithium addition, and subsequent reaction with specific electrophiles, a cascade reaction process could be set up between the reacted electrophile and the amine components, facilitating an in situ ring closing and dehydration to generate indole ring systems (Figure 1).[9] In this one-pot process, the carbon−nitrogen bond would be constructed from the reaction of the *o*-amino with the reacted electrophile, the carbon−carbon bond of the indole ring would be formed from the reaction of the generated organolithium with the electrophile, and uniquely, the entire process is initiated with the formation of an exocyclic carbon−carbon bond from the carbolithiation step. The formation of the bonds (ii) and (iii) is not unusual for an indole synthesis; what is unique is that the process is initiated by the formation of the exocyclic carbon−carbon bond in (i), which in the process introduces a further diversity point into the products (Figure 1).

The key biochemical roles played by the indole ring in nature ensure that this heterocyclic system maintains an intense interest from medicinal and synthetic chemists. This privileged biological scaffold continues to be a common motif for drug targets, and as such, the development of new synthetic methods is of considerable value.[10] Routes which would facilitate the introduction of molecular diversity at all positions of the indole ring in one synthetic operation would have applications for combinatorial library formation and act as an entry point into natural product synthesis. Many recent advances in indole synthesis have focused on metal-mediated procedures with copper, palladium, tin, titanium, and zirconium being the most prevalent.[11]

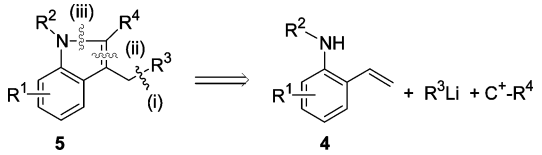

FIGURE 1. Sequence of bond formation.

Results and Discussion

Synthesis of *o*-Vinylaniline Starting Materials. The viability of our reaction sequence was tested using an array of *o*-aminostyrenes, substituted on nitrogen with a *tert*-butoxycarbonyl (Boc), an ethyl, or a benzyl group. Our ultimate starting materials were the commercially available *o*-bromoanilines **6a**−**c** and **6d**−**f**, which were prepared according to literature methods (Table 1).[12]

N-Boc protection of the 2-bromoanilines **6** was first attempted with 1 equiv of di-*tert*-butyl dicarbonate (Boc_2O) with a catalytic quantity of DMAP in THF under reflux (method A, Table 1). This procedure was successful for the conversion of **6a** and **6c** into their corresponding products **7a**,**c** albeit in poor yields of 56 and 40%, respectively (entries 1 and 5). The poor yields were due to the formation of the diarylureas **8a** and **8c** as byproducts in significant quantities. This side reaction has been previously observed for other *ortho*-substituted anilines.[13] The omission of the DMAP catalyst and the use of a 2.5 molar excess of Boc_2O in THF under reflux was successful for **6a** and **6d** leading to **7a** and **7d** in 83% and 80% yield, respectively, but the reaction failed for **6e** and **6f** possibly due to the presence of electron-withdrawing substituents on the aromatic ring and/or steric hindrance (method B, Table 1, entries 2, 6, 8, and 10). To eliminate the urea formation and overcome the lack of reactivity of some of the aniline substrates, we carried out reactions using a 2.5-fold excess of Boc_2O in the presence of catalytic DMAP (method C, Table 1).[14] This resulted in the formation of the di-Boc-protected substrates **9**, from which the selective removal of one Boc group using trifluoroacetic acid in CH_2Cl_2 could be readily achieved giving the desired products (**7a**,**b**,**d**,**e**,**f**) in high isolated yields (entries 3, 4, 7, 9, and 11).

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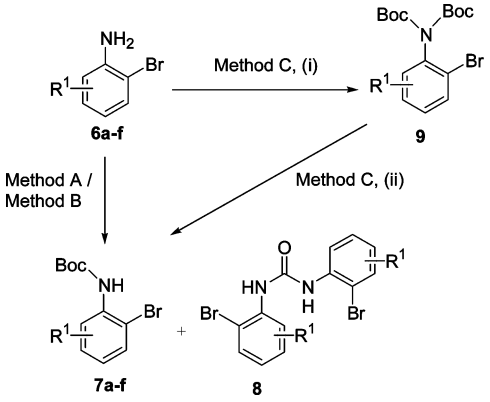
TABLE 1. Preparation of *N*-Boc-*o*-bromoanilines[a]

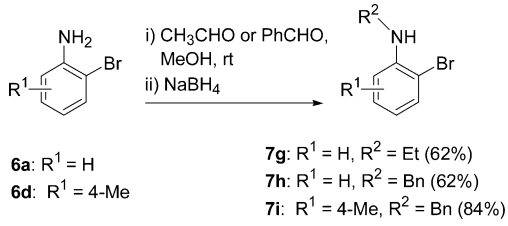


entry	substrate	R^1	method	**7** (% yield)	**8** (% yield)
1	**6a**	H	A	**7a** (56)	**8a** (17)
2	**6a**	H	B	**7a** (83)	
3	**6a**	H	C	**7a** (82)	
4	**6b**	4-F	C	**7b** (86)	
5	**6c**	4-OMe	A	**7c** (40)	**8c** (26)
6	**6d**	4-Me	B	**7d** (80)	
7	**6d**	4-Me	C	**7d** (84)	
8	**6e**	3-OMe	B	**7e** (0)	
9	**6e**	3-OMe	C	**7e** (76)	
10	**6f**	4,6-diF	B	**7f** (0)	
11	**6f**	4,6-diF	C	**7f** (88)	

[a] Method A: 1 equiv of Boc_2O, 0.1 equiv of DMAP, THF, reflux, 24 h. Method B: 2.5 equiv of Boc_2O, THF, reflux, 24 h. Method C: (i) 2.5 equiv of Boc_2O, 0.1 equiv of DMAP, THF, reflux, 24 h; (ii) CF_3COOH, CH_2Cl_2, rt, 16 h.

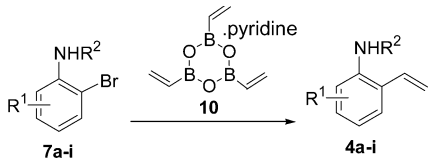
Synthesis of the *N*-ethyl- and *N*-benzyl-substituted anilines **7g**−**i** was achieved in a one-pot reductive amination reaction between **6a** or **6d** and either acetaldehyde or benzaldehyde in acceptable yields of 62−84% (Scheme 2).[15]

SCHEME 2. Preparation of the *N*-Alkylated *o*-Bromoanilines



Suzuki−Miyaura cross-coupling of **7a**−**i** with 2,4,6-trivinylcyclotriboroxane−pyridine complex **10** proved to be a very efficient and reliable method for the generation of the styrenes **4a**−**i** in high yields (Table 2). Compound **10** is bench-stable and acts as a vinylboronic acid equivalent under the reaction conditions.[16] The coupling reactions were successful using either 1.0 or 0.5 molar equiv of **10**, indicating that **10** has the potential to provide more than one of the vinyl groups for the reaction (compare entries 1 and 2; 5 and 6; 10 and 11). The procedure was tolerant to all the aryl electronic substituent variants attempted (entries 3, 4, 7, and 9) and to the three different nitrogen substituents (entries 1, 10, and 12). The steric hindrance from the *ortho* Boc-, alkyl-, or benzyl-functionalized anilines did not affect product outcome except for **7e** in which the aryl bromide atom is particularly hindered with two *ortho*-substituents (entry 7).

TABLE 2. Vinylation of 7a−i[a]



entry	substrate	R^1	R^2	equiv of **10**	product	% yield[b]
1	**7a**	H	Boc	1	**4a**	84
2	**7a**	H	Boc	0.5	**4a**	90
3	**7b**	4-F	Boc	1	**4b**	78
4	**7c**	4-OMe	Boc	1	**4c**	85
5	**7d**	4-Me	Boc	1	**4d**	80
6	**7d**	4-Me	Boc	0.5	**4d**	94
7	**7e**	3-OMe	Boc	0.5	**4e**	58
8	**7f**	4,6-diF	Boc	1	**4f**	57
9	**7f**	4,6-diF	Boc	0.5	**4f**	70
10	**7g**	H	Et	1	**4g**	77
11	**7g**	H	Et	0.5	**4g**	78
12	**7h**	H	Bn	0.5	**4h**	81
13	**7i**	4-Me	Bn	0.5	**4i**	73

[a] Conditions: $Pd(PPh_3)_4$ (5%), K_2CO_3, DME/H_2O, reflux, 20 h. [b] Isolated purified yield.

Carbolithiation of Substituted *o*-Vinylanilines. Prior to testing the scope of the indole synthesis, a survey of the carbolithiation reaction between three of the substituted *o*-vinylanilines **4a**,**b**,**h** and a number of organolithium reagents was undertaken to determine reaction conditions. The organolithium reagents examined were *tert*-butyl-, *n*-butyl-, methyl-, and phenyllithium, which were chosen to test the scope and limitations of this key step in our reaction sequence. Two sets of conditions were tested which were chosen to reflect the differing carbolithiation reactivity of each of the organolithiums. For the more reactive *tert*-butyl the reactions were examined with diethyl ether as solvent at −78 °C (method A), whereas the remainder were carried out in diethyl ether, with TMEDA additive at −25 °C (method B). Each carbolithiation reaction was quenched with 2 M HCl, and the products were isolated, purified, and characterized (Table 3). Carbolithiation of both styrenes **4a** and **4b** with *t*- or *n*-BuLi gave the expected products **11a**−**c** in high yields of 80−85% (entries 1−3). Attempts to add either methyllithium or phenyllithium to the styrene double bond of **4a** led only to recovery of the starting material and as such were not investigated further for the indole synthesis (entries 4 and 5).

Indole Synthesis. We next investigated the indole synthesis using DMF as the electrophile, which in the reaction sequence provides the unsubstituted C-2 carbon of the indole ring. For this study, a series of 1,3,4-, and 1,3,5-, and 1,3,5,7-substituted indoles were prepared (Table 4). The viability of the reaction sequence was tested using nine different *ortho*-*N*-substituted vinylanilines and three alkyllithiums as a representative sample. In a typical procedure, the organolithium reagent was added dropwise over 30 min to a solution of styrene in dry diethyl ether at −78 °C under an inert nitrogen

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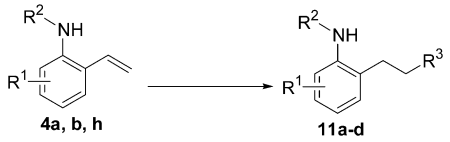
TABLE 3. Carbolithiation of *o*-Aminostyrenes[a]

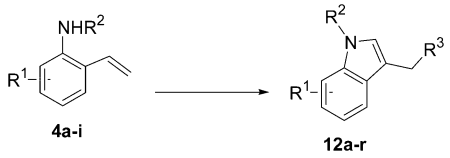


entry	styrene	method	R^1	R^2	R^3	product	% yield[b]
1	**4a**	A	H	Boc	*t*-Bu	**11a**	85
2	**4b**	A	4-F	Boc	*t*-Bu	**11b**	81
3	**4b**	B	4-F	Boc	*n*-Bu	**11c**	80
4	**4a**	B	H	Boc	Me		*c*
5	**4a**	B	H	Boc	Ph		*c*

[a] Conditions A: 2.5 equiv of R^3Li, −78 °C, Et_2O, 1.5 h. Conditions B: 4.0 equiv of R^3Li, 2 equiv of TMEDA, −78 to −25 °C, Et_2O, 2.5 h. [b] Isolated purified yield. [c] Recovered starting material.

atmosphere. The reaction mixture was then stirred for another 1 h at −78 °C or, in the case of less reactive primary alkyllithium, the additive TMEDA was included and the reaction temperature allowed to warm to −25 °C and maintained for 2 h at this temperature. The electrophile, DMF, was then added at −78 °C, and after 10 min the reaction was acidified with 2 M HCl.

TABLE 4. Synthesis of 1,3,4-, 1,3,5-, and 1,3,5,7-Substituted Indoles[a]

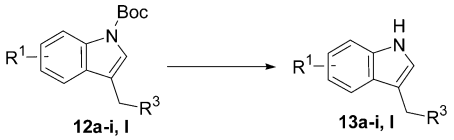


entry	substrate	R^1	R^2	R^3	indole	% yield[b]
1	**4a**	H	Boc	*t*-Bu	**12a**	75
2	**4a**	H	Boc	*s*-Bu	**12b**	62
3	**4a**	H	Boc	*n*-Bu	**12c**	84
4	**4b**	5-F	Boc	*t*-Bu	**12d**	70
5	**4b**	5-F	Boc	*s*-Bu	**12e**	43
6	**4b**	5-F	Boc	*n*-Bu	**12f**	71
7	**4c**	5-OMe	Boc	*t*-Bu	**12g**	77
8	**4c**	5-OMe	Boc	*n*-Bu	**12h**	80
9	**4d**	5-Me	Boc	*t*-Bu	**12i**	71
10	**4d**	5-Me	Boc	*s*-Bu	**12j**	74
11	**4d**	5-Me	Boc	*n*-Bu	**12k**	59
12	**4e**	4-OMe	Boc	*t*-Bu	**12l**	48
13	**4f**	5,7-di-F	Boc	*t*-Bu	**12m**	34
14	**4g**	H	Et	*t*-Bu	**12n**	67
15	**4g**	H	Et	*s*-Bu	**12o**	55
16	**4g**	H	Et	*n*-Bu	**12p**	27
17	**4h**	H	Bn	*t*-Bu	**12q**	86
18	**4i**	5-Me	Bn	*t*-Bu	**12r**	70

[a] Conditions: (i) R^3Li, −78 °C 1.5 h *or* −25 °C with TMEDA, 2.5 h, Et_2O; (ii) DMF, −78 °C, 10 min; (iii) 2 M HCl, THF, 5 h. [b] Isolated purified yield.

The reaction sequence was shown to be successful in generating the indole ring with a wide distribution of substituents in the 1, 3, 4, 5, and 7 positions (Table 4). The reaction sequence was tolerant of varying substituents (Me, OMe, F) in the *meta* position to the vinyl group of the aminostyrene substrates **4b**−**d** with the isolated yields varying from moderate to excellent (Table 4, entries 4−11). Substitution of a methoxy group *ortho* to the vinyl as in **4e** gave the 4-methoxy-substituted indole **12l** (entry 12), and the 5,7-difluoro substitution pattern on the indole **12m** was also achieved from the corresponding vinylaniline **4f** (entry 13).

TABLE 5. Deprotection of *N-tert*-Butoxycarbonyl-Substituted Indoles[a]



entry	substrate	R^1	R^3	product	% yield[b]
1	**12a**	H	*t*-Bu	**13a**	88
2	**12b**	H	*s*-Bu	**13b**	83
3	**12c**	H	*n*-Bu	**13c**	97
4	**12d**	5-F	*t*-Bu	**13d**	87
5	**12e**	5-F	*s*-Bu	**13e**	70
6	**12f**	5-F	*n*-Bu	**13f**	90
7	**12g**	5-OMe	*t*-Bu	**13g**	85
8	**12h**	5-OMe	*n*-Bu	**13h**	65
9	**12i**	5-Me	*t*-Bu	**13i**	67
10	**12l**	4-OMe	*t*-Bu	**13l**	71

[a] Conditions: 12 M HCl, EtOAc, 1−12 h. [b] Isolated purified yield.

The mild acidification conditions chosen allowed the retention of the Boc group on the indole nitrogen, which could be advantageous for further synthetic transformation of these products (entries 1−13). The *N*-ethyl- or benzyl-substituted substrates **4g**−**i** also yielded their corresponding nitrogen substituted indoles demonstrating a complementary direct route to *N*-alkyl- or benzylindoles (entries 14−18). The reaction was tolerant for the tested series of *tert*-, *sec*-, or *n*-butyl with each of the alkyllithiums resulting in good yields with few exceptions.

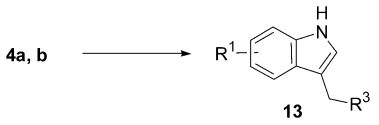
The deprotection of *N*-Boc-substituted indoles was readily accomplished by stirring at room temperature with 12 M HCl in ethyl acetate, generating **13a**−**i**,**l** in excellent yields (Table 5). This deprotection methodology is complementary with our synthetic approach as it can be employed as part of the reaction acidification following the carbolithiation/electrophile reaction sequence. If required, this allows the *N*-deprotected indole to be directly isolated simply by changing the acidification conditions. This avoids an additional synthetic operation with reagents such as aluminum chloride,[17] boron trifluoride etherate,[18] ceric ammonium nitrate,[19] or tetrabutylammonium fluoride.[20]

To demonstrate this versatile approach, following carbolithiation of two examples **4a**,**b** and treatment with electrophile (DMF) the intermediates were directly converted to deprotected indoles **13a**,**d** by changing the reaction acidification conditions from 2 M HCl to the 12 M HCl. This resulted in the isolation of the deprotected indoles **13a** and **13d** in satisfactory yields (Table 6).

A proposed reaction sequence for the indole formation is as follows: the aniline nitrogen is deprotonated upon the addition of the first equivalent of organolithium, and a second equivalent carbolithiates the vinyl double bond leading to a new benzylic lithiated species. This reacts with the electrophile DMF to give an aldehyde precursor,

(17) Bose, D. S.; Lakshminarayana, V. *Synthesis* **1999**, 66.
(18) Evans, E. F.; Lewis, N. J.; Kapfer, I.; Macdonald, G.; Taylor, R. J. K. *Synth. Commun*. **1997**, *27*, 1819.
(19) Hwu, J. R.; Jain, M. L.; Tsay, S.-C.; Hakimelahi, G. H. *Tetrahedron Lett*. **1996**, *37*, 2035.
(20) Routier, S.; Saugé, L.; Ayerbe, N.; Coudert, G.; Mérour, J.-Y. *Tetrahedron Lett*. **2002**, *43*, 589.

TABLE 6. Direct Synthesis of *N*-Unsubstituted Indoles[a]



entry	substrate	R^1	R^3	product	% yield[b]
1	**4a**	H	*t*-Bu	**13a**	75
2	**4b**	5-F	*t*-Bu	**13d**	68

[a] Conditions: (i) R^3Li, −78 °C, 1.5 h, Et_2O; (ii) DMF, −78 °C, 10 min; (iii) 12 M HCl, EtOAc, 5 h. [b] Isolated purified yield.

which after acidification undergoes a ring closure to a 2-hydroxy-2,3-dihydro-2-hydroxyindole **14**, which dehydrates to generate the final indole products. Using milder acidification conditions, one derivative of **14** (R^1 = H, R^2 = Boc, R^3 = *t*-Bu) was isolated and characterized (Figure 2).

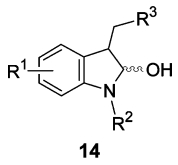


FIGURE 2. Substituted 2-hydroxy-2,3-dihydroindole intermediates.

The use of DMF as an electrophile precludes the direct introduction of a substituent at the C-2 of the indole ring. The inclusion of functionality at this position can be achieved by a change of the electrophile to a substituted nitrile. Consequently, we repeated our carbolithiation methods but treated the lithiated intermediates with a range of substituted nitriles. The reaction of nitriles is slower than that of DMF, and an efficient reaction was achieved by stirring at −25 °C for 2 h. Subsequent treatment of the reaction mixture with 12 M HCl in ethyl acetate was successful for the direct generation of the *N*-unsubstituted 2,3,5-substituted indoles **15a**−**h** in acceptable yields (Table 7). Incorporation of an indole *N*-benzyl substitutient was achieved for the 1,2,3,5-substituted derivatives **15i** and **15j** (entries 9 and 10).

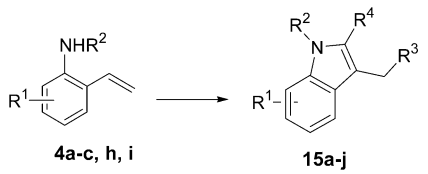
The nitrile electrophile methodology was capable of introducing a range of C-2 substituents, including phenyl, thiophene, and sterically bulky *tert*-butyl groups (entries 1, 2, and 3). It was also successful when using 2,2-diethoxypropionitrile as an electrophile, which in addition to going through the complex reaction cascade sequence also underwent a further in situ deprotection of the acetal protecting group, thereby generating the 2-keto-substituted indoles **15d** and **15i** (entries 4 and 9).

If milder acidification conditions are employed in the reaction, the intermediate ketones of type **16** can be isolated indicating a similar reaction pathway as for the DMF electrophile examples (Figure 3). Isolation of one intermediate was carried out for the specific case of R^1 = 4-F; R^2 = Boc; R^3 = *t*-Bu; R^4 = Ph).

Conclusion

The combination of a robust vinylation procedure using the coupling of a vinyl boronic acid equivalent with aryl bromides and an organolithium addition−cyclization methodology provides a new entry into the functionalized indole ring system. The methodology is diversity tolerant, facilitating the introduction of aryl, hetroaryl, alkyl, keto, halo, and ether substituents around the indole scaffold. The use of organolithiation as the key step for the assembly of cascade reaction sequences to generate other heterocyclic systems is currently under investigation.

TABLE 7. Synthesis of 2,3,5- and 1,2,3,5-Substituted Indoles[a]



entry	substrate	R^1	R^2	R^3	R^4	indole	% yield
1	**4a**	H	H	*t*-Bu	Ph	**15a**	65
2	**4a**	H	H	*n*-Bu	C_4H_3S	**15b**	60
3	**4a**	H	H	*t-Bu*	*t*-Bu	**15c**	67
4	**4a**	H	H	*n*-Bu	$COCH_3$	**15d**	44
5	**4b**	5-F	H	*t*-Bu	Ph	**15e**	40
6	**4b**	5-F	H	*n*-Bu	*t*-Bu	**15f**	54
7	**4c**	5-OMe	H	*t*-Bu	Ph	**15g**	57
8	**4c**	5-OMe	H	*n*-Bu	Ph	**15h**	68
9	**4h**	H	Bn	*t*-Bu	$COCH_3$	**15i**	36
10	**4i**	5-Me	Bn	*t*-Bu	Ph	**15j**	51

[a] Conditions: (i) R^3Li, −78 °C *or* −25 °C with TMEDA, 1.5 h, Et_2O; (ii) R^4CN, −25 °C, 2 h; (iii) 12 M HCl, EtOAc, 16 h.

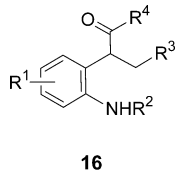


FIGURE 3. Isolatable reaction intermediates using nitrile electrophiles.

Experimental Section

All reactions were performed under nitrogen atmosphere. Solvents were distilled and dried according to standard procedures. *t*-BuLi was purchased as 1.7 M in pentane, *s*-BuLi 1.4 M in cyclohexane, and *n*-BuLi 2.5 M in hexanes. Exact concentration of organolithiums were determined by titration in THF with diphenylacetic acid as an indicator prior to use. All nitriles used were anhydrous. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ (internal Me_4Si) or DMSO-d_6. Column chromatography was carried out on silica gel 60 (230−400 mesh ASTM). Melting points are uncorrected.

3-(2,2-Dimethylpropyl)indolecarboxylic Acid *tert*-Butyl Ester 12a. Compound **4a** (0.42 g, 1.91 mmol) was dissolved in dry diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (4.5 mL, 1.7 M in pentane, 7.6 mmol) was added dropwise via syringe over 30 min. The orange-red solution was stirred for a further 1 h at −78 °C. DMF (1.6 mL, 20 mmol) was added and stirring continued for 10 min. HCl (2 M, 25 mL) was added and the solution warmed to room temperature. Diethyl ether was evaporated, THF added (25 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (2 × 20 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow oil. Flash chromatography eluting with hexane/diethyl ether (7:3) gave the product as a colorless oil (0.40 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (s, 9H), 1.59 (s, 9H), 2.49 (s, 2H), 7.13−7.15

(m, 2H), 7.26 (s, 1H), 7.44 (d, J = 7.0 Hz, 1H), 8.05 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.2, 28.7, 30.9, 37.6, 82.3, 114.0, 117.6, 118.8, 121.1, 122.8, 123.2, 131.1, 134.1, 148.9. IR (NaCl plate, neat): 2951, 1729 cm^{-1}. EI-MS: *m/z* 287.3. HRMS $(M)^+$: 287.1884, $C_{18}H_{25}NO_2$ requires 287.1885. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 74.95; H, 9.07; N 4.66.

3-(2-Methylbutyl)indole-1-carboxylic Acid *tert*-Butyl Ester 12b. Compound **4a** (0.43 g, 1.96 mmol) was dissolved in dry diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *s*-BuLi (10 mL, 0.78 M in cyclohexane, 7.8 mmol) was added dropwise via syringe over 30 min. The orange-red solution was stirred for a further 1 h at −78 °C. DMF (1.5 mL, 19 mmol) was added and stirring continued for 10 min. HCl (2 M, 25 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (25 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (2 × 20 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow oil. Flash chromatography eluting with hexane/diethyl ether (4:1) gave the product as a colorless oil (0.32 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90−0.95 (m, 6H), 1.15−1.29 (m, 1H), 1.40−1.54 (m, 1H), 1.66 (s, 9H), 1.71−1.82 (m, 1H), 2.43 (dd, J = 8.05, 14.3 Hz, 1H), 2.68 (dd, J = 6.0, 14.3 Hz, 1H), 7.18−7.33 (m, 3H), 7.50 (d, J = 7.0 Hz, 1H), 8.10 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.8, 19.7, 28.5, 29.8, 32.5, 35.1, 83.5, 115.4, 119.5, 120.4, 122.4, 123.3, 124.4, 131.5, 136.1, 150.2. IR (NaCl plate, neat): 2956, 1736 cm^{-1}. EI-MS: *m/z* 287.2. HRMS: $(M + Na)^+$ 310.1780, $C_{18}H_{25}NO_2Na$ requires 310.1783. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 74.97; H, 8.67; N, 4.80.

3-Pentylindole-1-carboxylic Acid *tert*-Butyl Ester 12c. Compound **4a** (0.39 g, 1.77 mmol) and TMEDA (0.5 mL, 3.2 mmol) were dissolved in dry diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *n*-BuLi (3.5 mL, 2.0 M in pentane, 7.0 mmol) was added dropwise via syringe over 30 min. The temperature was warmed to −25 °C with stirring for 2 h during which time an orange-red color developed. The solution was cooled to −78 °C, DMF (1.4 mL, 18 mmol) was added, and stirring was continued for 10 min. HCl (2 M, 25 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (20 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (4 × 20 mL) and dried over sodium sulfate, and the solvent evaporated to give a pale yellow oil. Flash chromatography eluting with hexane/diethyl ether (4:1) gave the product as a colorless oil (0.42 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95−1.00 (m, 3H), 1.42−1.47 (m, 4H), 1.72 (s, 9H), 1.74−1.79 (m, 2H), 2.72 (t, J = 7.8 Hz, 2H), 7.28−7.41 (m, 3H), 7.57 (d, J = 6.8 Hz, 1H), 8.16 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 22.8, 25.2, 28.5, 29.2, 32.0, 83.4, 115.5, 119.3, 121.8, 122.5, 124.1, 124.4, 131.2, 135.9, 150.2. IR (NaCl plate, neat) cm^{-1}: 2957, 1731. EI-MS: *m/z* 287.2. HRMS $(M)^+$: 287.1881, $C_{18}H_{25}NFO_2$ requires 287.1885. Anal. Calcd for $C_{18}H_{25}NFO_2$: C, 75.22; H, 8.77; N, 4.87. Found C, 75.55; H, 8.98; N, 4.63.

3-(2,2-Dimethylpropyl)-5-fluoroindole-1-carboxylic Acid *tert*-Butyl Ester 12d. Compound **4b** (0.40 g, 1.69 mmol) was dissolved in dry diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (6.7 mL, 1.0 M in pentane, 6.7 mmol) was added dropwise via syringe over 30 min. The orange-red solution was stirred for a further 1 h. DMF (1.3 mL, 17 mmol) was added and stirring continued for 10 min. HCl (2 M, 25 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (25 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (3 × 30 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow solid. Purification by chromatography eluting with hexane/diethyl ether (95:5) gave the product as a pale yellow solid (0.36 g, 70%). Mp: 70−71 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 9H), 1.66 (s, 9H), 2.51 (s, 2H), 6.95−7.05 (m, 1H), 7.16 (d, J = 9.2 Hz, 1H), 7.36 (s, 1H), 8.10 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.1, 28.6, 30.9, 37.6, 82.5, 104.3 (d, J_{CF} = 23.6 Hz), 110.5 (d, J_{CF} = 25.2 Hz), 114.9 (d, J_{CF} = 9.2 Hz), 117.3 (d, J_{CF} = 4.6 Hz), 124.7, 130.5, 132.3 (d, J_{CF} = 9.9 Hz) 148.6, 156.6 (d, J_{CF} = 238.8 Hz). IR (KBr disk): 2966,1732 cm^{-1}. EI-MS: *m/z* 305.4. HRMS $(M)^+$: 305.1787, $C_{18}H_{24}FNO_2$ requires 305.1791. Anal. Calcd for $C_{18}H_{24}FNO_2$: C, 70.79; H, 7.92; F, 6.22; N, 4.59. Found: C, 70.49; H, 7.94; F, 6.48; N, 4.52. (Note: Compound **11b** was also isolated in 13% yield as a reaction byproduct.)

5-Fluoro-3-(2-methylbutyl)indole-1-carboxylic Acid *tert*-Butyl Ester 12e. Compound **4b** (0.40 g, 1.69 mmol) was dissolved in dry diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *s*-BuLi (6.2 mL, 1.2 M in cyclohexane, 7.4 mmol) was added dropwise via syringe over 30 min. The orange solution was stirred for a further 1 h at −78 °C. DMF (1.5 mL, 20 mmol) was added and stirring continued for 10 min. HCl (2 M, 25 mL) was added, and the solution was warmed to room temperature. The diethyl ether was evaporated, THF added (25 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (3 × 30 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow liquid. Flash chromatography on silica gel eluting with hexane/diethyl ether (4:1) gave the product as colorless oil (0.24 g, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90−0.96 (m, 6H), 1.14−1.26 (m, 1H), 1.39−1.52 (m, 1H), 1.66 (s, 9H), 1.69−1.87 (m, 1H), 2.40 (dd, J = 8.05, 14.4 Hz, 1H), 2.64 (dd, J = 6.1, 14.4 Hz, 1H), 6.97−7.04 (m, 1H), 7.15 (d, J = 8.9 Hz, 1H), 7.36 (s, 1H), 8.05 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.8, 19.6, 28.4, 29.7, 32.4, 35.1, 83.7, 105.0 (d, J_{CF} = 23.6 Hz), 111.9 (d, J_{CF} = 25.3 Hz), 116.3 (d, J_{CF} = 9.2 Hz), 120.1 (d, J = 4.0 Hz), 124.8, 132.0, 132.3 (d, J = 9.7 Hz), 149.8, 159.3 (d, J = 238.7 Hz). IR (NaCl plate, neat): 2968, 1741 cm^{-1}. EI-MS: *m/z* 305.3. HRMS $(M + Na)^+$: 328.1696, $C_{18}H_{25}NO_2Na$ requires 328.1689. Anal. Calcd for $C_{18}H_{24}NO_2$: C, 70.79; H, 7.92; F, 6.22; N, 4.59. Found: C, 71.04; H, 7.97; F, 6.62; N, 4.34.

5-Fluoro-3-pentylindole-1-carboxylic Acid *tert*-Butyl Ester 12f. Compound **4b** (0.41 g, 1.73 mmol) and TMEDA (0.5 mL, 3.2 mmol) were dissolved in dry diethyl ether (20 mL) and cooled to −78 °C under nitrogen. *n*-BuLi (3.8 mL, 1.8 M in pentane, 6.8 mmol) was added dropwise via syringe over 30 min. The temperature was warmed to −25 °C with stirring for 2 h during which time a red color developed. The solution was cooled −78 °C, DMF (1.4 mL, 18 mmol) was added, and stirring was continued for 10 min. HCl (2 M, 25 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (25 mL), and the solution stirred at room temperature for 5 h. The THF was evaporated, the residue extracted with diethyl ether (3 × 50 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow solid. Flash chromatography eluting with hexane/diethyl ether (95:5) gave the product as a pale yellow solid (0.37 g, 71%). Mp: 40−41 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89−0.94 (m, 3H), 1.35−1.39 (m, 4H), 1.66 (s, 9H), 1.70−1.73 (m, 2H), 2.60 (t, J = 7.7 Hz, 2H), 6.97−7.04 (m, 1H), 7.15 (d, J = 8.9 Hz, 1H), 7.36 (s, 1H), 8.05 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.7, 25.0, 28.4, 29.0, 31.9, 83.7, 104.9 (d, J_{CF} = 23.7 Hz), 111.9 (d, J_{CF} = 25.2 Hz), 116.4 (d, J_{CF} = 9.2 Hz), 121.5 (d, J_{CF} = 4.6 Hz), 124.0, 132.1 (d, J_{CF} = 9.1 Hz), 149.9, 157.8 (d, J_{CF} = 239.5 Hz). IR (KBr disk): 2929, 1726 cm^{-1}. EI-MS: *m/z* 305.3. HRMS $(M)^+$: 305.1786, $C_{18}H_{24}FNO_2$ requires 305.1791. Anal. Calcd for $C_{18}H_{24}FNO_2$: C, 70.79; H, 7.92; F, 6.22; N, 4.59. Found: C, 70.74; H, 7.88; F, 6.39; N, 4.60.

3-(2,2-Dimethylpropyl)-5-methoxyindole-1-carboxylic Acid *tert*-Butyl Ester 12g. Compound **4c** (0.4 g, 1.6 mmol) was dissolved in dry diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (6.3 mL, 1.0 M in pentane, 6.3 mmol) was added dropwise via syringe over 30 min. The red solution was stirred for a further 1 h at −78 °C. DMF (1.3 mL, 17 mmol)

was added and stirring continued for 10 min. HCl (2 M, 25 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (20 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (3 × 50 mL) and dried over sodium sulfate, and the solvent evaporated to give a brown oil. Flash chromatography eluting with hexane/diethyl ether (95:5) gave the product as a colorless oil (0.39 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (s, 9H), 1.66 (s, 9H), 2.53 (s, 2H), 3.85 (s, 3H), 6.87−6.98 (m, 2H) 7.31 (s, 1H), 8.05 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.5, 29.9, 32.2, 38.9, 55.9, 83.4, 103.2, 112.4, 115.9, 118.6, 125.2, 130.1, 133.2, 150.1, 155.8. IR (NaCl plate, neat): 2945, 1735 cm^{-1}. EI-MS: *m/z* 317.2. HRMS $(M)^+$: 317.1993, $C_{19}H_{27}NO_3$ requires 317.1990. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found C, 72.0; H, 8.57; N, 4.35.

5-Methoxy-3-pentylindole-1-carboxylic Acid *tert*-Butyl Ester 12h. Compound **4c** (0.40 g, 1.60 mmol) and TMEDA (0.5 mL, 3.2 mmol) were dissolved in dry diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *n*-BuLi (3.3 mL, 2.0 M in pentane, 6.6 mmol) was added dropwise via syringe over 30 min. The temperature was warmed to −25 °C with stirring for 2 h during which time a red color developed. The solution was cooled to −78 °C, DMF (1.5 mL, 20 mmol) was added, and stirring was continued for 10 min. HCl (2 M, 25 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (25 mL), and the solution stirred at room temperature under nitrogen for 5 h. The THF was evaporated, the residue extracted with diethyl ether (2 × 30 mL) and dried over sodium sulfate, and the solvent evaporated. Flash chromatography eluting with hexane/diethyl ether (9:1) to give the product as a white solid (0.40 g, 80%). Mp: 54−55 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88 (t, J = 7.0 Hz, 3H), 1.24−1.37 (m, 4H), 1.61 (s, 9H), 1.62−1.68 (m, 2H), 2.62 (t, J = 7.3 Hz, 2H), 3.80 (s, 3H), 6.93 (dd, J = 2.5, 8.9 Hz, 1H), 7.06 (d, J = 2.5 Hz, 1H), 7.38 (s, 1H), 7.90 (d, J = 8.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.7, 25.1, 28.5, 29.0, 32.0, 56.0, 83.2, 102.3, 112.6, 116.1, 118.6, 125.3, 130.1, 133.2, 150.1, 155.9. IR (KBr disk): 2998, 1721 cm^{-1}. EI-MS: *m/z* 317.3. HRMS $(M + H)^+$: 318.2080, $C_{19}H_{28}NO_3$ requires 318.2069. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found C, 71.94; H, 8.60; N, 4.33.

5-Methyl-3-(2,2-dimethyl-propyl)-indole-1-carboxylic acid *tert*-butyl ester 12i: Compound **4d** (150 mg, 0.64 mmol) was dissolved in dry diethyl ether (8.0 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (1.0 mL, 1.6M in pentane, 1.6 mmol) was added dropwise via syringe over 30 min. The red solution was stirred for a further 1 h at −78 °C. DMF (0.5 mL, 6.4 mmol) was added and stirring continued for 10 min. 2M HCl (8.0 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (8.0 mL) and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (2 × 10 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow oil. Flash chromatography eluting with hexane/diethyl ether (4:1) gave the product as a colorless oil which crystallize on standing (136 mg, 71%). Mp: 59−61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (s, 9H), 1.59 (s, 9H), 2.36 (s, 3H), 2.46 (s, 2H), 7.01 (d, J = 8.5 Hz, 1H), 7.22 (s, 2H), 7.96 (d, J = 6.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 28.5, 30.0, 32.2, 38.8, 83.4, 114.9, 118.6, 119.9, 124.5, 125.4, 131.8, 132.6, 133.5, 150.1. IR (KBr disk): 2948, 1724 cm^{-1}. EI-MS: *m/z* 301.3. HRMS $(M + H)^+$: 302.2127, $C_{19}H_{28}NO_2$ requires 302.2120. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.45; H, 8.82; N, 4.75.

5-Methyl-3-(2-methylbutyl)indole-1-carboxylic Acid *tert*-Butyl Ester 12j. Compound **4d** (150 mg, 0.64 mmol) was dissolved in dry diethyl ether (8.0 mL) and cooled to −78 °C under nitrogen. *s*-BuLi (2.0 mL, 1.3 M in cyclohexane, 2.6 mmol) was added dropwise via syringe over 30 min. The orange solution was stirred for a further 1 h at −78 °C. DMF (0.5 mL, 6.4 mmol) was added and stirring continued for 10 min. HCl (2 M, 8.0 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (8.0 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (2 × 10 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow oil. Flash chromatography eluting with hexane/diethyl ether (4:1) gave the product as a colorless oil (143 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86−0.96 (m, 6H), 1.14−1.32 (m, 1H), 1.40−1.52 (m, 1H), 1.66 (s, 9H), 1.70−1.79 (m, 1H), 2.41 (dd, J = 6.0 Hz, 13.3 Hz, 1H), 2.44 (s, 3H), 2.65 (dd, J = 6.0 Hz, 14.3 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 7.28 (s, 2H), 7.96 (d, J = 6.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.8, 19.6, 21.6, 28.5, 29.8, 32.5, 35.0, 83.4, 115.1, 119.4, 120.1, 123.3, 125.7, 131.8, 136.0, 160.3. IR (NaCl plates): 2962, 1730 cm^{-1}. EI-MS: *m/z* 301.3. HRMS $(M + H)^+$: 302.2119, $C_{19}H_{28}NO_2$ requires 302.2120. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.71; H, 9.00; N, 4.57.

5-Methyl-3-pentylindole-1-carboxylic Acid *tert*-Butyl Ester 12k. Compound **4d** (150 mg, 0.64 mmol) and TMEDA (0.2 mL, 1.3 mmol) were dissolved in dry diethyl ether (8.0 mL) and cooled to −78 °C under nitrogen. *n*-BuLi (1.4 mL, 1.9 M in pentane, 2.6 mmol) was added dropwise via syringe over 30 min. The temperature was warmed to −25 °C with stirring for 2 h during which time an orange color developed. The solution was cooled to −78 °C, DMF (0.5 mL, 6.4 mmol) was added, and stirring was continued for 10 min. HCl (2 M, 8.0 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (8.0 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (4 × 10 mL) and dried over sodium sulfate, and the solvent evaporated to give a pale yellow oil. Flash chromatography eluting with hexane/diethyl ether (9:1) gave the product as a colorless oil (114 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 3H), 1.23−1.41 (m, 6H), 1.65 (s, 9H), 2.44 (s, 3H), 2.63 (t, J = 7.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 1H), 7.29 (s, 2H), 7.96 (d, J = 7.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.1, 21.4, 22.6, 24.9, 28.3, 29.0, 31.8, 83.1, 114.9, 119.0, 121.3, 122.3, 125.5, 131.1, 131.7, 133.8, 150.0. IR (NaCl plates): 2929, 1730 cm^{-1}. EI-MS: *m/z* 301.3. HRMS $(M + H)^+$: 302.2121, $C_{19}H_{28}NO_2$ requires 302.2120. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.32; H, 9.13; N, 4.50.

4-Methoxy-3-(2,2-dimethylpropyl)indole-1-carboxylic Acid *tert*-Butyl Ester 12l. Compound **4e** (98 mg, 0.39 mmol) was dissolved in dry diethyl ether (6.2 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (0.6 mL, 1.8 M in cyclohexane, 1.0 mmol) was added dropwise via syringe over 30 min. The orange solution was stirred for a further 1 h at −78 °C. DMF (0.3 mL, 3.9 mmol) was added and stirring continued for 10 min. HCl (2 M, 6.2 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (6.2 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (2 × 10 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow oil. Flash chromatography eluting with hexane/diethyl ether (4:1) gave the product as a colorless oil which crystallize on standing (60 mg, 48%). Mp: 74−76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (s, 9H), 1.66 (s, 9H), 2.79 (s, 2H), 3.89 (s, 9H), 6.63 (d, J = 8.0 Hz, 1H), 7.15−7.21 (m, 2H), 7.74 (d, J = 8.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 29.4, 31.9, 38.9, 54.9, 83.3, 103.3, 108.2, 118.6, 121.2, 123.1, 124.6, 136.7, 149.9, 154.5. IR (NaCl plates): 2951, 1734 cm^{-1}. ES$^+$-MS: *m/z* 318.2. HRMS $(M + H)^+$: 318.2068, $C_{19}H_{28}NO_3$ requires 318.2069. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.71; H, 8.62; N, 4.30.

5,7-Difluoro-3-(2,2-dimethylpropyl)indole-1-carboxylic Acid *tert*-Butyl Ester 12m. Compound **4f** (127 mg, 0.5 mmol) was dissolved in dry diethyl ether (6.2 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (0.9 mL, 1.4 M in cyclohex-

ane, 1.2 mmol) was added dropwise via syringe over 15 min. The orange solution was stirred for a further 1 h at −78 °C. DMF (0.4 mL, 5.2 mmol) was added and stirring continued for 10 min. HCl (2 M, 6.2 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (6.2 mL), and the solution stirred at room temperature for 60 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (2 × 10 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow oil. Flash chromatography eluting with hexane/diethyl ether (4:1) gave the product as a pale yellow oil (55 mg, 34%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 9H), 1.71 (s, 9H), 2.56 (s, 2H), 6.80−6.85 (m, 1H), 7.03 (dd, J = 2.4, 8.4 Hz, 1H), 7.49 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.0, 29.6, 32.0, 38.5, 84.2, 100.4 (dd, J_{CF} = 26.4, 28.7 Hz), 101.2 (dd, J_{CF} = 4.2, 23.1 Hz), 118.5 (dd, J_{CF} = 1.9, 4.6 Hz), 118.6 (d, J_{CF} = 2.0 Hz), 128.2, 136.4 (dd, J_{CF} = 4.9, 10.4 Hz), 148.9, 149.5 (dd, J_{CF} = 13.5, 255.4 Hz), 158.6 (dd, J_{CF} = 10.3, 241.0 Hz). IR (NaCl plates): 1737 cm^{-1}. ES$^+$-MS: *m/z* 324.0. HRMS (M + H)$^+$: 324.1773, $C_{18}H_{24}FNO_2$ requires 324.1175.

3-(2,2-Dimethylpropyl)-1-ethyl-1*H*-indole 12n. Compound **4g** (147 mg, 1.00 mmol) was dissolved in dry diethyl ether (12.5 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (1.7 mL, 1.5 M in cyclohexane, 2.5 mmol) was added dropwise via syringe over 30 min. The orange solution was stirred for a further 1 h at −78 °C. DMF (0.8 mL, 10.0 mmol) was added and stirring continued for 10 min. HCl (2 M, 12.5 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (12.5 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (3 × 20 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow oil. Flash chromatography eluting with hexane/diethyl ether (9:1) gave the product as a colorless oil (145 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 9H), 1.44 (t, J = 7.2 Hz, 3H), 2.62 (s, 2H), 4.14 (q, J = 7.2 Hz, 2H), 6.87 (s, 1H), 7.07 (t, J = 8.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.7, 29.9, 32.4, 39.3, 40.9, 109.2, 112.9, 118.6, 120.1, 121.1, 126.4, 129.8, 135.9. IR (NaCl plates): 2949 cm^{-1}. EI-MS: *m/z* 215.3. HRMS (M + H)$^+$: 216.1754, $C_{15}H_{22}N$ requires 216.1752. Anal. Calcd for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50. Found: C, 82.90; H, 9.77; N, 6.35.

1-Ethyl-3-(2-methylbutyl)-1*H*-indole 12o. Compound **4g** (100 mg, 0.68 mmol) was dissolved in dry diethyl ether (8.5 mL) and cooled to −78 °C under nitrogen. *s*-BuLi (1.4 mL, 1.2 M in cyclohexane, 1.7 mmol) was added dropwise via syringe over 30 min. The orange solution was stirred for a further 1 h at −78 °C. DMF (0.5 mL, 6.4 mmol) was added and stirring continued for 10 min. HCl (2 M, 8.5 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (8.5 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (3 × 15 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow oil. Flash chromatography eluting with hexane/diethyl ether (9:1) gave the product as a colorless oil (80 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86−0.95 (m, 6H), 1.14−1.32 (m, 1H), 1.40−1.54 (m, 1H), 1.43 (t, J = 7.1 Hz, 3H), 1.67−1.79 (m, 1H), 2.51 (dd, J = 7.7, 14.2 Hz, 1H), 2.75 (dd, J = 6.1, 14.2 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 6.86 (s, 1H), 7.07 (m, 1H), 7.18 (m, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9, 15.7, 19.7, 29.7, 32.7, 36.0, 40.9, 109.3, 114.6, 118.6, 119.6, 121.3, 125.2, 128.8, 136.2. IR (NaCl plates): 2959 cm^{-1}. EI-MS: *m/z* 215.4. HRMS (M + H)$^+$: 216.1762, $C_{15}H_{22}N$ requires 216.1752.

1-Ethyl-3-pentyl-1*H*-indole 12p. Compound **4g** (100 mg, 0.68 mmol) and TMEDA (0.2 mL, 1.3 mmol) were dissolved in dry diethyl ether (8.5 mL) and cooled to −78 °C under nitrogen. *n*-BuLi (1.3 mL, 2.1 M in pentane, 2.7 mmol) was added dropwise via syringe over 30 min. The temperature was warmed to −25 °C with stirring for 2 h during which time a yellow-orange color developed. The solution was cooled to −78 °C, DMF (0.5 mL, 6.4 mmol) was added, and stirring continued for 10 min. HCl (2 M, 8.5 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (8.5 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (3 × 15 mL) and dried over sodium sulfate, and the solvent evaporated to give a pale yellow oil. Flash chromatography eluting with hexane/diethyl ether (4:1) gave the product as a colorless oil (39 mg, 27%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88−0.93 (m, 3H), 1.35−1.40 (m, 4H), 1.43 (t, J = 7.2 Hz, 3H), 1.70 (m, 2H), 2.73 (t, J = 7.6 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 6.88 (s, 1H), 7.07 (m, 1H), 7.18 (m, 1H), 7.30 (d, J = 8.1 Hz), 7.59 (d, J = 7.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 15.7, 22.8, 25.4, 30.3, 32.2, 40.9, 109.3, 116.0, 118.6, 119.4, 121.4, 124.3, 128.5, 136.2. IR (NaCl plates): 2926 cm^{-1}. EI-MS: *m/z* 215.4. HRMS (M + H)$^+$: 216.1757, $C_{15}H_{22}N$ requires 216.1752.

1-Benzyl-3-(2,2-dimethylpropyl)-1*H*-indole 12q. Compound **4h** (129 mg, 0.61 mmol) was dissolved in dry diethyl ether (6.2 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (1.0 mL, 1.5 M in cyclohexane, 1.5 mmol) was added dropwise via syringe over 30 min. The orange solution was stirred for a further 1 h at −78 °C. DMF (0.5 mL, 6.4 mmol) was added and stirring continued for 10 min. HCl (2 M, 6.2 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (6.2 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (3 × 15 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow oil. Flash chromatography eluting with hexane/diethyl ether (9:1) gave the product as a white solid. Mp: 96−99 °C (148 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 9H), 2.63 (s, 2H), 5.30 (s, 2H), 6.89 (s, 1H), 7.06−7.15 (m, 4H), 7.22−7.37 (m, 4H), 7.61 (d, J = 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.8, 32.2, 39.1, 49.8, 109.4, 113.4, 118.8, 119.9, 121.3, 126.7, 127.4, 127.5, 128.8, 129.6, 136.3, 138.2. IR (KBr disk): 2954 cm^{-1}. EI-MS: *m/z* 277.4. ES$^+$-MS: *m/z* 278.4. HRMS (M + H)$^+$: 278.1913, $C_{21}H_{24}N$ requires 278.1909. Anal. Calcd for $C_{20}H_{23}N$: C, 86.59; H, 8.36; N, 5.05. Found: C, 86.37; H, 8.54; N, 4.99.

1-Benzyl-3-(2,2-dimethylpropyl)-5-methyl-1*H*-indole 12r. Compound **4i** (100 mg, 0.45 mmol) was dissolved in dry diethyl ether (5.6 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (0.7 mL, 1.6 M in cyclohexane, 1.1 mmol) was added dropwise via syringe over 30 min. The orange solution was stirred for a further 1 h at −78 °C. DMF (0.4 mL, 5.1 mmol) was added and stirring continued for 10 min. HCl (2 M, 5.6 mL) was added and the solution warmed to room temperature. The diethyl ether was evaporated, THF added (5.6 mL), and the solution stirred at room temperature for 5 h under nitrogen. The THF was evaporated, the residue extracted with diethyl ether (3 × 10 mL) and dried over sodium sulfate, and the solvent evaporated to give a yellow oil. Flash chromatography eluting with hexane/diethyl ether (9:1) gave the product as a pale yellow oil (90 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 9H), 2.44 (s, 3H), 2.60 (s, 2H), 5.26 (s, 2H), 6.85 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.05−7.12 (m, 3H), 7.20−7.30 (m, 3H), 7.38 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 29.8, 32.1, 39.1, 49.9, 109.1, 112.8, 119.6, 122.9, 126.6, 127.4, 127.5, 127.9, 128.7, 129.8, 134.7, 138.1. IR (NaCl plates): 2948 cm^{-1}. EI-MS: *m/z* 291.5. ES$^+$-MS: 291.9. HRMS (M + H)$^+$: 292.2065, $C_{21}H_{26}N$ requires 292.2065. Anal. Calcd for $C_{21}H_{25}N$: C, 86.55; H, 8.65; N, 4.81. Found: C, 86.09; H, 8.53; N, 4.59.

3-(2,2-Dimethylpropyl)-2-phenyl-1*H*-indole 15a. Compound **4a** (0.50 g, 2.3 mmol) was dissolved in diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (6.3 mL, 1.44 M in hexane, 9.12 mmol) was added dropwise via syringe over 30 min. The orange-red solution was stirred for a further 1 h at −78 °C. Benzonitrile (2.3 mL, 23 mmol) was added and the solution warmed to −25 °C with stirring continued for 2

h. The reaction was cooled to −78 °C, 2 M HCl (25 mL) added, and the solution warmed to room temperature. The reaction mixture was extracted with ethyl acetate (3 × 30 mL), the organic layer dried over sodium sulfate, and the solvent evaporated. The residue was dissolved in a solution of ethyl acetate (8.4 mL)/12 M HCl (3.6 mL) and stirred at room temperature for 16 h under nitrogen. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), washed with sodium hydrogen carbonate (1 M, 2 × 50 mL), and dried over sodium sulfate and the solvent evaporated. Flash chromatography on silica eluting with a gradient of hexane/diethyl ether (9:1 to 3:7) gave the product as a white solid (0.39 g, 65%). Mp: 94−95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74 (s, 9H), 2.86 (s, 2H), 7.07−7.17 (m, 2H), 7.24−7.33 (m, 2H), 7.37−7.42 (m, 2H), 7.48−7.52 (m, 2H), 7.60−7.65 (m, 1H), 7.83 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.3, 34.5, 37.6, 110.9, 111.6, 119.6, 120.6, 122.1, 127.8, 129.0, 129.1, 130.8, 135.1, 135.9, 136.2. IR (KBr disk): 3396 cm^{-1}. EI-MS: *m/z* 263.3. HRMS $(M)^+$: 263.1670, $C_{19}H_{21}N$ requires 263.1673. Anal. Calcd for $C_{19}H_{21}N$: C, 86.65; H, 8.04; N, 5.32. Found C, 86.36; H, 8.14; N, 5.27.

3-Pentyl-2-thiophene-2-yl-1*H*-indole 15b. Compound **4a** (0.40 g, 1.8 mmol) and TMEDA (0.54 mL, 3.6 mmol) were dissolved in dry diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *n*-BuLi (3.1 mL, 2.35 M in hexane, 7.2 mmol) was added dropwise via syringe over 30 min. The temperature was warmed to −25 °C with stirring for 2 h during which time a red-orange solution developed. The mixture was cooled to −78 °C, 2-thiophenecarbonitrile (1.68 mL, 18.0 mmol) added, the temperature raised to −25 °C, and stirring continued for 2 h. The solution developed a deep red-brown color and a black solid precipitated. The reaction was cooled to −78 °C, 2 M HCl (25 mL) added, and the solution warmed to room temperature. The solution was filtered to remove the black solid, the filtrate extracted with ethyl acetate (3 × 30 mL), the organic layer dried over sodium sulfate, and the solvent evaporated. The residue was dissolved in a solution of ethyl acetate (8.4 mL)/12 M HCl (3.6 mL) and stirred at room temperature for 16 h under nitrogen. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), washed with sodium hydrogen carbonate (1 M, 2 × 50 mL), and dried over sodium sulfate and the solvent evaporated. Flash chromatography eluting with a gradient of hexane/diethyl ether (9:1 to 7:3) gave the product as a yellow oil (0.29 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 7.1 Hz, 3H), 1.31−1.44 (m, 4H), 1.54−1.75 (m, 2H), 2.92 (t, J = 7.8 Hz, 2H), 7.07−7.17 (m, 4H), 7.18−7.31 (m, 2H), 7.59 (m, 1H), 7.95 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 22.9, 25.1, 30.7, 32.4, 110.9, 115.4, 119.5, 119.9, 122.9, 124.4, 125.2, 127.8, 128.2, 129.6, 135.4, 136.2. IR (NaCl plate, neat): 3055, 2987 cm−^{1}. EI-MS: *m/z* 269.2. HRMS $(M)^+$: 269.1223, $C_{17}H_{19}NS$ requires 269.1238.

2-*tert*-Butyl-3-(2,2-dimethylpropyl)-1*H*-indole 15c. Compound **4a** (0.40 g, 1.8 mmol) was dissolved in dry diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (5.8 mL, 1.3 M in pentane, 7.5 mmol) was added dropwise via syringe over 30 min. The orange-red solution was stirred for a further 1 h at −78 °C. Trimethylacetonitrile (2 mL, 18 mmol) was added and the solution warmed to −25 °C with stirring continued for 2 h. The reaction was cooled to −78 °C, 2 M HCl (25 mL) added, and the solution warmed to room temperature. The reaction mixture was extracted with ethyl acetate (3 × 30 mL), the organic layer dried over sodium sulfate, and the solvent evaporated. The residue was dissolved in a solution of solution of ethyl acetate (8.4 mL)/12 M HCl (3.6 mL) and stirred at room temperature for 16 h under nitrogen. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), washed with sodium hydrogen carbonate (1 M, 2 × 50 mL), and dried over sodium sulfate and the solvent evaporated. Flash chromatography on silica eluting with a gradient of hexane/diethyl ether (95:5 to 1:1) gave the product as a white solid (0.29 g, 67%). Mp: 61−62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (s, 9H), 1.34 (s, 9H), 2.87 (s, 2H), 6.92−6.99 (m, 2H), 7.08−7.10 (m, 1H), 7.46−7.50 (m, 1H), 7.83 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.5, 31.8, 33.6, 34.1, 37.7, 109.2, 109.9, 118.6, 120.7, 121.1, 130.9, 134.8, 142.6. IR (KBr disk): 3147, 2960 cm^{-1}. EI-MS: *m/z* 243.2. HRMS $(M)^+$: 243.1982, $C_{17}H_{25}N$ requires 243.1986. Anal. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.35; N, 5.75. Found: C, 83.51; H, 10.15; N, 5.42. (Note: 2,3-dialkylsubstituted indoles are prone to oxidative ring opening of the five-membered ring in the presence of air.)

1-(3-Pentyl-1*H*-indol-2-yl)ethanone 15d. Compound **4a** (0.40 g, 1.8 mmol) and TMEDA (0.5 mL, 3.3 mmol) were dissolved in dry diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *n*-BuLi (3.7 mL, 2.0 M in pentane, 7.4 mmol) was added dropwise over 30 min. The temperature was warmed to −25 °C with stirring for 2 h during which time an orange-red color developed. The mixture was cooled to −78 °C, 2,2-diethoxypropionitrile (2.8 mL, 18 mmol) added, the temperature raised to −25 °C, and stirring continued for 2 h. The reaction was cooled to −78 °C, saturated NH_4Cl (25 mL) added, and the solution warmed to room temperature for 1 h. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), the organic layer dried over sodium sulfate, and the solvent evaporated. The residue was dissolved in a solution of ethyl acetate (8.4 mL)/12 M HCl (3.6 mL) and stirred at room temperature for 16 h under nitrogen. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), washed with sodium hydrogen carbonate (1 M, 2 × 50 mL), and dried over sodium sulfate and the solvent evaporated. Flash chromatography eluting with hexane/diethyl ether (2:1) gave the product as a white solid (0.182 g, 44%). Mp: 77−78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 (t, J = 7.1 Hz, 3H), 1.25−1.47 (m, 4H), 1.66−1.76 (m, 2H), 2.65 (s, 3H), 3.09 (t, J = 8.0 Hz, 2H), 7.10−7.15 (m, 1H), 7.30−7.37 (m, 2H), 7.70 (d, J = 8.1 Hz, 1H), 8.91 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.7, 25.7, 28.5, 31.7, 32.3, 112.0, 120.2, 121.6, 124.5, 126.6, 129.1, 132.2, 136.3, 190.6. IR (KBr disk): 3332, 2951, 1637 cm^{-1}. EI-MS: *m/z* 229.3. HRMS $(M)^+$: 229.1465, $C_{15}H_{19}NO$ requires 229.1466. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.44; H, 8.35; N, 6.10.

3-(2,2-Dimethylpropyl)-5-fluoro-2-phenyl-1*H*-indole 15e. Compound **4b** (0.42 g, 1.8 mmol) was dissolved in dry diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (6.4 mL, 1.1 M in hexane, 7.0 mmol) was added dropwise via syringe over 30 min. The orange-red solution was stirred for a further 1 h at −78 °C. Benzonitrile (1.8 mL, 18 mmol) was added and the solution warmed to −25 °C with stirring continued for 2 h. The reaction was cooled to −78 °C, 2 M HCl (25 mL) added, and the solution warmed to room temperature. The reaction mixture was extracted with ethyl acetate (3 × 30 mL), the organic layer dried over sodium sulfate, and the solvent evaporated. The residue was dissolved in a solution of ethyl acetate (8.4 mL)/12 M HCl (3.6 mL) and stirred at room temperature for 16 h under nitrogen. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), washed with sodium hydrogen carbonate (1 M, 2 × 50 mL), and dried over sodium sulfate and the solvent evaporated. Flash chromatography on silica eluting with hexane/ethyl acetate (19:1) gave the product as a pale yellow solid (0.2 g, 40%). Mp: 100−101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.73 (s, 9H), 2.8 (s, 2H), 6.86−6.92 (m, 1H), 7.18−7.36 (m, 2H), 7.39−7.52 (m, 5H), 7.9 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.1, 34.4, 37.6, 105.3 (d, J_{CF} = 23.6 Hz), 110.2, (d, J_{CF} = 25.9 Hz), 111.4 (d, J_{CF} = 9.9 Hz), 111.8 (d, J_{CF} = 4.5 Hz), 128.0, 128.9, 129.0, 131.2 (d, J_{CF} = 9.9 Hz), 132.3, 134.6, 138.0, 158.1 (d, J_{CF} = 233.4 Hz). IR (KBr disk): 3429, 2960 cm^{-1}. EI-MS: *m/z* 281.3. HRMS $(M)^+$: 281.1577, $C_{19}H_{20}FN$ requires 281.1579. Anal. Calcd for $C_{19}H_{20}FN$: C, 81.11; H, 7.16; F, 6.75; N, 4.98. Found: C, 81.0; H, 7.45; F, 6.48; N, 4.90. (Note: Compound **11b** was also isolated in 10% yield as a reaction byproduct.)

2-*tert*-Butyl-5-fluoro-3-pentyl-1*H*-indole 15f. Compound **4b** (0.50 g, 2.1 mmol) and TMEDA (0.6 mL, 4.2 mmol) were dissolved in dry diethyl ether (30 mL) and cooled to −78 °C under nitrogen. *n*-BuLi (3.6 mL, 2.3 M in hexane, 8.3 mmol)

was added dropwise via syringe over 30 min. The temperature was warmed to −25 °C with stirring for 2 h during which time an orange-red color developed. The mixture was cooled to −78 °C, trimethylacetonitrile (2.3 mL, 21 mmol) added, the temperature raised to −25 °C, and stirring continued for 2 h. The reaction was cooled to −78 °C, 2 M HCl (25 mL) added, and the solution warmed to room temperature. The reaction mixture was extracted with ethyl acetate (3 × 30 mL) and dried, the organic layer dried over sodium sulfate, and the solvent evaporated. The residue was dissolved in a solution of ethyl acetate (8.4 mL)/12 M HCl (3.6 mL) and stirred at room temperature for 16 h under nitrogen. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), washed with sodium hydrogen carbonate (1 M, 2 × 50 mL), and dried over sodium sulfate and the solvent evaporated. Flash chromatography on silica eluting with hexane/diethyl ether (4:1) gave the product as a colorless oil (0.29 g, 54%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, J = 7.0 Hz, 3H), 1.37−1.43 (m, 4H), 1.44 (s, 9H), 1.57−1.67 (m, 2H), 2.77 (t, J = 8.0 Hz, 2H), 6.79−6.86 (m, 1H), 7.10−7.22 (m, 2H), 7.67 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 22.8, 25.8, 30.7, 31.3, 32.7, 33.2, 103.3 (d, J_{CF} = 23.6 Hz), 109.1 (d, J_{CF} = 25.9 Hz), 111.0 (d, J_{CF} = 9.8 Hz), 111.9 (d, J_{CF} = 4.5 Hz), 130.6 (d, J_{CF} = 9.9 Hz), 143.2, 143.5, 158.3 (d, J_{CF} = 233.2 Hz). IR (NaCl plate, neat): 3477, 2958 cm^{-1}. EI-MS *m/z*: 261.3. HRMS $(M + H)^+$: 262.1927, $C_{17}H_{25}FN$ requires 262.1971. (Note: 2,3-dialkyl-substituted indoles are prone to oxidative ring opening of the five-membered ring in the presence of air.)

3-(2,2-Dimethylpropyl)-5-methoxy-2-phenyl-1*H*-indole 15g. Compound **4c** (0.5 g, 2.0 mmol) was dissolved in dry diethyl ether (30 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (7.2 mL, 1.2 M in pentane, 8.6 mmol) was added dropwise via syringe over 30 min. The orange-red solution was stirred for a further 1 h at −78 °C. Benzonitrile (2 mL, 20 mmol) was added and the solution warmed to −25 °C with stirring continued for 2 h. The reaction was cooled to −78 °C, 2 M HCl (25 mL) added, and the solution warmed to room temperature. The reaction mixture was extracted with ethyl acetate (3 × 30 mL), the organic layer dried over sodium sulfate, and the solvent evaporated. The residue was dissolved in a solution of ethyl acetate (8.4 mL)/12 M HCl (3.6 mL) and stirred at room temperature for 16 h under nitrogen. The reaction mixture was washed with sodium hydrogen carbonate (1 M, 2 × 50 mL), extracted with ethyl acetate (3 × 20 mL), and dried over sodium sulfate and the solvent evaporated. Flash chromatography on silica eluting with hexane/diethyl ether (4:1) gave the product as a yellow solid (0.33 g, 57%). Mp: 116−117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (s, 9H), 2.85 (s, 2H), 3.87 (s, 3H), 6.85 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 2.3 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.33−7.36 (1H, m), 7.40−7.45 (m, 2H), 7.54 (m, 2H), 7.88 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.2, 34.3, 37.5, 56.2, 102.7, 111.4, 111.5, 112.0, 127.7, 128.8, 128.9, 131.1, 131.2, 135.8, 137.8, 154.0. IR (KBr disk): 3424, 2954 cm^{-1}. EI-MS *m/z*: 293.4. HRMS: $(M + H)^+$ 294.1851, $C_{20}H_{24}NO$ requires 294.1858. Anal. Calcd for $C_{20}H_{23}NO$: 81.87; H, 7.90; N, 4.77. Found: C, 81.48; H, 7.89; N, 4.62.

5-Methoxy-3-pentyl-2-phenyl-1*H*-indole 15h. Compound **4c** (0.4 g, 1.6 mmol) and TMEDA (0.5 mL, 3.3 mmol) were dissolved in dry diethyl ether (25 mL) and cooled to −78 °C under nitrogen. *n*-BuLi (4.4 mL, 1.5 M, 6.6 mmol) was added dropwise via syringe over 30 min. The red solution was stirred for a further 1 h at −78 °C. Anhydrous benzonitrile (1.6 mL, 16 mmol) was added and the solution warmed to −25 °C with stirring continued for 2 h. The reaction was cooled to −78 °C, 2 M HCl (25 mL) added, and the solution warmed to room temperature. The reaction mixture was extracted with ethyl acetate (3 × 30 mL), the organic layer dried over sodium sulfate, and the solvent evaporated. The residue was dissolved in a solution of ethyl acetate (8.4 mL)/12 M HCl (3.6 mL) and stirred at room temperature for 16 h under nitrogen. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), washed with sodium hydrogen carbonate (1 M, 2 × 50 mL), and dried over sodium sulfate and the solvent evaporated. Flash chromatography on silica eluting with hexane/diethyl ether (4:1) gave the product as a white solid (0.32 g, 68%). Mp: 65−66 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 7.3 Hz, 3H), 1.30−1.41 (m, 4H), 1.66−1.74 (m, 2H), 2.83 (t, J = 8.0 Hz, 2H), 3.89 (s, 3H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 7.24−7.56 (m, 6H,), 7.85 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.6, 22.6, 24.7, 30.8, 32.1, 56.1, 101.1, 112.1, 112.5, 112.7, 127.7, 128.2, 129.3, 129.7, 131.9, 134.0, 135.2, 153.8. IR (KBr disk): 3383, 2957 cm^{-1}. EI-MS: *m/z* 293.3. HRMS $(M)^+$: 293.1773, $C_{20}H_{23}NO$ requires 293.1779.

1-Benzyl-3-(2,2-dimethylpropyl)-2-acetyl-1*H*-indole 15i. Compound **4h** (67 mg, 0.32 mmol) was dissolved in dry diethyl ether (4.0 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (0.5 mL, 1.7 M in hexanes, 0.8 mmol) was added dropwise over 30 min. The yellow-orange solution was stirred for a further 1 h at −78 °C. 2,2-Ethoxypropionitrile (0.5 mL, 3.2 mmol) was added, the temperature raised to −25 °C, and stirring continued for 2 h. The reaction mixture was cooled to −78 °C, 2 M HCl (4.0 mL) added, and the solution warmed to room temperature. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), the organic layer dried over sodium sulfate, and the solvent evaporated. The residue was dissolved in a solution of ethyl acetate (1.4 mL)/12 M HCl (0.6 mL) and stirred at room temperature for 16 h under nitrogen. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), washed with 1 M sodium hydrogen carbonate (2 × 20 mL), and dried over sodium sulfate and the solvent evaporated. Flash chromatography eluting with cyclohexane/diethyl ether (9:1) gave the product as a yellow oil, (37 mg, 36%). Mp: 78−80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 9H), 2.51 (s, 3H), 3.03 (s, 2H), 5.60 (s, 2H), 6.91−6.94 (m, 2H), 7.10−7.33 (m, 6H), 7.69−7.72 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.1, 31.1, 33.9, 38.3, 47.9, 110.5, 120.0, 120.2, 122.1, 125.2, 126.2, 127.1, 128.3, 128.5, 138.2, 138.5, 195.5. IR (KBr disk): 2963, 1660 cm^{-1}. ES$^+$-MS: *m/z* 320. HRMS $(M + H)^+$: 320.2022, $C_{22}H_{26}NO$ requires 320.2014.

1-Benzyl-3-(2,2-dimethylpropyl)-5-methyl-2-phenyl-1*H*-indole 15j. Compound **4i** (85 mg, 0.38 mmol) was dissolved in dry diethyl ether (4.1 mL) and cooled to −78 °C under nitrogen. *t*-BuLi (0.6 mL, 1.7 M in hexanes, 1.0 mmol) was added dropwise over 30 min. The yellow-orange solution was stirred for a further 1 h at −78 °C. Benzonitrile (0.4 mL, 4.0 mmol) was added, the temperature raised to −25 °C, and stirring continued for 2 h. The reaction mixture was cooled to −78 °C, 2 M HCl (4.1 mL) added, and the solution warmed to room temperature. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), the organic layer dried over sodium sulfate, and the solvent evaporated. The residue was dissolved in a solution of ethyl acetate (1.4 mL)/12 M HCl (0.6 mL) and stirred at room temperature for 16 h. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), washed with 1 M sodium hydrogen carbonate (2 × 10 mL), and dried over sodium sulfate and the solvent evaporated. Flash chromatography eluting with cyclohexane/diethyl ether (9:1) gave the product as a yellow oil (71 mg, 51%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.67 (s, 9H), 2.38 (s, 3H), 2.67 (s, 2H), 5.24 (s, 2H), 6.76 (m, Hz, 2H), 6.91 (m, 1H), 7.14−7.20 (m, 4H), 7.33−7.45 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.2, 33.8, 37.8, 47.4, 109.7, 111.3, 120.1, 123.0, 126.0, 129.9, 127.8, 128.3, 128.4, 128.5, 129.7, 131.2, 133.1, 134.8, 138.7, 139.5. IR (NaCl plates): 2948 cm^{-1}. ES$^+$-MS: *m/z* 368.2. HRMS $(M + H)^+$: 368.2387, $C_{27}H_{30}N$ requires 368.2378.

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Supporting Information Available: Literature references for known compounds. Experimental procedures and characterization data for **4c**−**i**, **7a**−**i**, **11a**−**c**, **13a**−**i**, **13l**, **14**, and **16**. ^{1}H and ^{13}C NMR spectra for new compounds **4d**−**i**, **12a**−**r**, and **15a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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