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Synthesis of indoles via domino reaction of 2-fluorotoluenes and nitriles

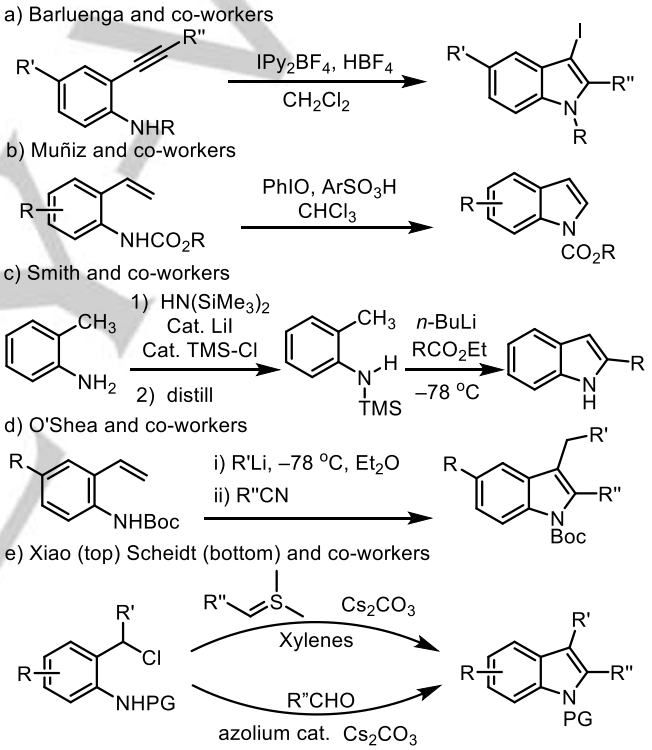
Jianyou Mao,* Zhiting Wang,‖ Xinyu Xu,‖ Guoqing Liu,‖ Runsheng Jiang, Haixing Guan, Zhipeng, Zheng, and Patrick J. Walsh*

Abstract: Indoles are essential heterocycles in medicinal chemistry and, therefore, novel and efficient approaches to their synthesis are in high demand. Among indoles, 2-aryl indoles have been described as privileged scaffolds. Advanced herein is a straightforward, practical and transition metal-free assembly of 2-arylindoles. Simply combining readily available 2-fluorotoluenes, nitriles, $LiN(SiMe_3)_2$ and CsF enables generation of a diverse array of indoles (38 examples, 48–92% yield). A range of substituents can be introduced into each position of the indole backbone (C-4 to C-7, and aryl groups at C-2), providing handles for further elaboration.

Indole and its derivatives are widely distributed in natural products and are universal structural motifs in pharmaceuticals.[1] Their diverse and potent biological activity has resulted in their classification as "privileged" heterocycles in medicinal chemistry.[2] Due to their significance, the synthesis of indoles continues to attract great interest, where demand remains high for more selective, straightforward, economical, and environmentally benign syntheses.

Early routes to access indoles include the Bischler–Möhlau synthesis[3] and the renowned Fischer indole synthesis.[4] The harsh reaction conditions and challenges associated with hydrazines have inspired more practical and flexible approaches toward the preparation of indoles. Many contemporary indole syntheses (i.e., Hegedus,[5] Larock,[6] etc.) and indole functionalization reactions involve the use of transition metal catalysts[7] that exhibit excellent control over selectivity and high efficiency.[8] The stringent limitations for trace metal contaminants in active pharmaceutical ingredients, however, have driven the demand for transition metal-free syntheses of functionalized indoles from readily accessible materials.

Advances in transition metal-free indole syntheses have been considerable. Emulating the Larock and Hegedus indole syntheses, but employing IPy_2BF_4 in place of Pd, Barluenga and co-workers developed an intramolecular annulation of 2-ethynyl aniline derivatives (Scheme 1a).[9] Muñiz and co-workers employed PhIO with vinyl aniline derivatives and bulky aryl sulfonic acids to afford indoles (Scheme 1b).[10] The teams of Smith and O'Shea employed organolithium reagents to generate carbanions that underwent addition to esters and nitriles, respectively, at –78 °C to afford a variety of indoles (Scheme 1c and d).[11] Xiao and co-workers developed cascade annulations of sulfur ylides with *N*-(ortho-chloromethyl)aryl amides (Scheme 1e, top),[12] while Scheidt and co-workers introduced an *N*-heterocyclic carbene-*catalyzed* synthesis of 2-aryl indoles with aldehydes (Scheme 1e, bottom).[13] The syntheses in Scheme 1 employ highly functionalized precursors or low temperatures that are difficult to access on scale.



Scheme 1. Transition metal-free synthesis of indoles.

Our team has been interested in the use of common feedstocks for the synthesis of value added fine chemicals of pharmaceutical interest. Our strategy to facilitate the use of toluene derivatives relies on cation-π interactions[14] between group(I) metal cations and the π-system of toluenes to acidify the benzylic hydrogens (pK_a ~43[15] in DMSO) to the extent that they can be reversibly deprotonated with relatively mild $MN(SiMe_3)_2$ bases [$HN(SiMe_3)_2$ $pK_a \approx 26$[16] in THF]. As proof of concept (Scheme 2a), reaction of toluene derivatives with $NaN(SiMe_3)_2$ in the presence of Cs^+ salts initially results in the formation of the *N*-$SiMe_3$ imine. The key finding is that under the reaction conditions (40–110 °C), toluene derivatives could be reversibly deprotonated. Although the equilibrium presumably lies very far to the left, the benzylic organometallic was efficiently trapped by the imine, providing

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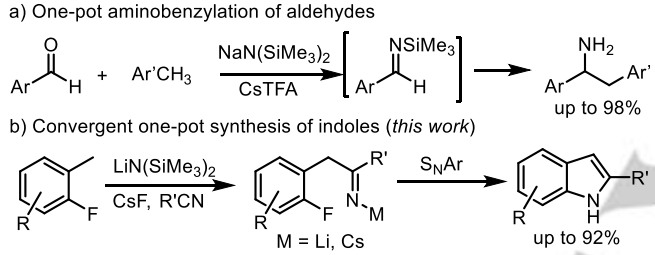
biologically important 1,2-diarylethylamine derivatives upon workup (36 examples, 56–98% yield).[17]

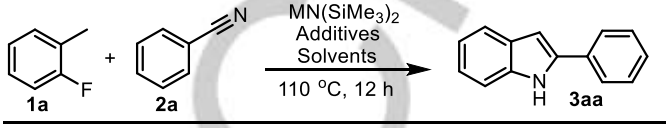
Our ongoing interest in the synthesis of biologically active compounds inspired us to ask if other electrophiles would undergo selective reaction with the transiently generated benzyl organometallic intermediates in a similar fashion to Scheme 2a. From our past experience, we knew that $MN(SiMe_3)_2$ bases add to nitriles with a relatively high barrier,[17a] and thus we envisioned the benzylation of benzonitriles as a path forward. Further, we desired to exploit the reactivity of the metallated imine intermediate to form an N–C bond. To avoid transition metal coupling reactions, we targeted 2-fluorotoluene derivatives, which could undergo nucleophilic aromatic substitution reactions (S_NAr)[17b, 18] potentially providing a convergent and straightforward route to a diverse array of indoles. Herein, we disclose a novel one-pot route to 2-arylindoles via CsF assisted conversion of 2-fluorotoluenes and benzonitriles to functionalized 2-aryl indoles (Scheme 2b). 2-Arylindoles of the type prepare herein exhibit a wide range of biological activities[19] and have been characterized as promising candidates for drug development.[20]



Scheme 2. a) Aminobenzylation of aldehydes and b) Novel route to indoles.

To initiate the optimization of the tandem reaction with 2-fluorotoluene (**1a**) and benzonitrile (**2a**), we examined three different bases [$LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$] using CPME (cyclopentyl methyl ether) as the solvent at 110 °C for 12 h (Table 1). None of the three commercially available bases promoted indole formation (entries 1–3). Based on our discovery that $NaN(SiMe_3)_2$/CsTFA mediated the amine formation in Scheme 2a, we next tested a variety of cesium salts in combination with $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$. This screen led to the identification of $LiN(SiMe_3)_2$ and CsF as a promising combination, affording the desired 2-phenylindole in 46% AY (entry 4, AY = assay yield determined by ^1H NMR integration of the unpurified reaction mixture against an internal standard). Other combinations either gave low AY of **3aa** (entries 5–6) or didn't promote the reaction at all (see Supporting Information for details). O'Hara and co-workers demonstrated that $CsN(SiMe_3)_2$ could be obtained via metathesis between $LiN(SiMe_3)_2$ and CsF.[21] We ascribe the success of this indole synthesis to the enhanced reactivity of $CsN(SiMe_3)_2$ over $LiN(SiMe_3)_2$. The conditions in entry 4 were next used to probe the impact of substrate stoichiometry. Increasing the loading of $LiN(SiMe_3)_2$ from 1 to 2 equiv improved the AY of **3aa** to 64% (entry 7). Further increasing the loading to 3 equiv however, had a detrimental impact on the AY (entry 8). Increasing the amount of **1a** to 2 equiv improved the AY to 86% (entry 9). Further screening revealed that the concentration had a significant impact on the AY, as exemplified in entries 10 (0.5 M, 98% yield) and 11 (1.0 M, 98% yield) vs. entry 9 (0.1 M, 86% yield). Other ethereal solvents (CPME vs. DME, THF, TBME, and $^iPr_2O$) were also examined under the conditions of entry 11. The reaction in CPME exhibited the highest AY (entry 10 vs. 11–14). Finally, decreasing the temperature from 110 to 90 °C had a detrimental impact on the AY of **3aa** (49%, entry 15). Therefore, the optimized conditions employed 3 equiv of 2-fluorotoluene (**1a**), 1 equiv of benzonitrile (**2a**), 2 equiv of $LiN(SiMe_3)_2$, and 1 equiv CsF in CPME (0.5 M or 1.0 M) at 110 °C for 12 h.[22]

Table 1. Optimization studies.[a]



entry	bases	additives	**1a**:**2a**:base	solvent	AY[b]
1	$LiN(SiMe_3)_2$	--	1.5:1:1	CPME	0
2	$NaN(SiMe_3)_2$	--	1.5:1:1	CPME	0
3	$KN(SiMe_3)_2$	--	1.5:1:1	CPME	0
4	$LiN(SiMe_3)_2$	CsF	1.5:1:1	CPME	46
5	$LiN(SiMe_3)_2$	Cs_2CO_3	1.5:1:1	CPME	35
6	$LiN(SiMe_3)_2$	CsTFA	1.5:1:1	CPME	2
7	$LiN(SiMe_3)_2$	CsF	1.5:1:2	CPME	64
8	$LiN(SiMe_3)_2$	CsF	1.5:1:3	CPME	0
9	$LiN(SiMe_3)_2$	CsF	3:1:2	CPME	86
10	$LiN(SiMe_3)_2$	CsF	3:1:2	CPME	98[c]
11	$LiN(SiMe_3)_2$	CsF	3:1:2	CPME	98[d]
12	$LiN(SiMe_3)_2$	CsF	3:1:2	DME	90[d]
13	$LiN(SiMe_3)_2$	CsF	3:1:2	THF	90[d]
14	$LiN(SiMe_3)_2$	CsF	3:1:2	TBME	92[d]
15	$LiN(SiMe_3)_2$	CsF	3:1:2	$^iPr_2O$	78[d]
16	$LiN(SiMe_3)_2$	CsF	3:1:2	CPME	49[e]

[a]Reaction performed on a 0.1 mmol scale in 1 mL solvent (0.1 M). [b] AY determined by integration of the ^1H NMR of the unpurified reaction mixture. [c] Reaction performed in 0.2 mL solvent (0.5 M). [d] Reaction performed in 0.1 mL solvent (1 M). [e] Reaction performed at 90 °C.

With the optimized conditions in hand, we next examined the scope of 2-fluorotoluene derivatives with benzonitrile (**2a**, Table 2). 2-Fluorotoluenes containing halogens situated ortho to the methyl group, including fluoro (**1b**), chloro (**1c**), bromo (**1d**), and iodo (**1e**), exhibited good to excellent reactivity, producing indoles substituted at the C-4 position (**3ba**–**3ea**) in 63–87% isolated yields. It's noteworthy that these 4-halo derivatives can be easily elaborated. Likewise, 2-fluorotoluenes possessing electron-donating groups located ortho to the methyl, including Me (**1f**), OMe (**1g**), and NMe_2 (**1h**), afforded the corresponding C-4 substituted indoles in 60, 72 and 81% yield, respectively (**3fa**–**3ha**). For substrate **1f**, mixed base $LiN(SiMe_3)_2$ (1 equiv) and $KN(SiMe_3)_2$ (1 equiv) was used. Substituents on the 2-fluorotoluenes located *meta* to the methyl (F, Cl, OMe, Ph) or *para* (F, Ph), or *ortho* to the fluoro (F, Cl, Me) substituents were also compatible under our conditions, as exemplified by the generation of **3ia**–**3qa** in 60–81% yield (entries 9–17). Our method enables positioning of substituents at C-4 to C-7 of the indole backbone. For reasons that are unclear, 2-fluorotoluenes with Cl or Br groups (located para to the fluoro) were not viable substrates under conditions examined (with the starting aryl halides recovered). It is noteworthy that **3ka** exhibited significant bioactivity against the grampositive pathogen *Bacillus cereus*.[20] In general,

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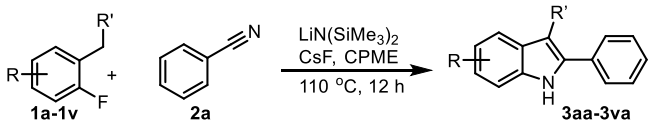
polyfluorotoluenes were also viable substrates affording the corresponding indoles in 90, 78, and 87% yield (**3ra**–**3ta**), respectively (entries 18–20). Some substrates were found to be sensitive to the conditions and required additional optimization (see Supporting Information for details). For example, **1i**, **1j**, **1m**, **1r**, and **1s** required excess benzonitrile (4 equiv benzonitrile to 2-fluorotoluenes, entries 9, 10, 13, 18, and 19). In some cases the barrier to toluene deprotonation/addition to the nitrile appears comparable to addition of the amide base to the nitrile carbon, which has a detrimental impact on the yield when the nitrile is the limiting reagent.

We were also interested in preparing 2,3-disubstituted indoles. The popular annulation reactions of anilines with alkynes to give 2,3-disubstituted indoles usually suffer from low regioselectivity with unsymmetrical alkynes.[8k, 23] To our delight, 2,3-disubstituted indoles (**3pa** and **3qa**) were generated under our conditions, which provide an alternative route to access these compounds (entries 21 and 22).

Table 2. Substrate scope of 2-fluorotoluene derivatives[a]

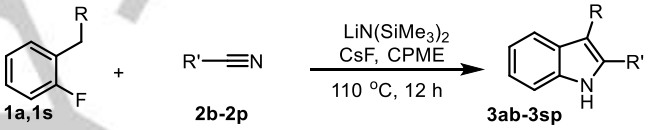


Entry	R	R'	Product	Y [%]
1	H	H (**1a**)	**3aa**	90
2	6-F	H (**1b**)	**3ba** (4-F)	81
3	6-Cl	H (**1c**)	**3ca** (4-Cl)	87
4	6-Br	H (**1d**)	**3da** (4-Br)	63
5	6-I	H (**1e**)	**3ea** (4-I)	74
6	6-Me	H (**1f**)	**3fa** (4-Me)	60[b]
7	6-OMe	H (**1g**)	**3ga** (4-OMe)	72
8	6-NMe_2	H (**1h**)	**3ha** (4- NMe_2)	81[c]
9	5-F	H (**1i**)	**3ia** (5-F)	80[d]
10	5-Cl	H (**1j**)	**3ja** (5-Cl)	76[d]
11	5-OMe	H (**1k**)	**3ka** (5-OMe)	63
12	5-Ph	H (**1l**)	**3la** (5-Ph)	76[e]
13	4-F	H (**1m**)	**3ma** (6-F)	60[f]
14	4-Ph	H (**1n**)	**3na** (6-Ph)	69[g]
15	3-F	H (**1o**)	**3oa** (7-F)	81
16	3-Cl	H (**1p**)	**3pa** (7-Cl)	70[g]
17	3-Me	H (**1q**)	**3qa** (7-Me)	67[e]
18	3,6-F_2	H (**1r**)	**3ra** (4,7-F_2)	90[d]
19	3,4-F_2	H (**1s**)	**3sa** (6,7-F_2)	78[d]
20	3,4,5,6-F_4	H (**1t**)	**3ta** (4,5,6,7-F_4)	87[g]
21	H	Ph (**1u**)	**3ua**	92[h]
22	H	2-Tol (**1v**)	**3va**	67[h]

[a] Reactions performed on a 0.2 mmol scale with 3 equiv 2-fluorotoluenes, 1-equiv benzonitrile, 2 equiv $LiN(SiMe_3)_2$, 1 equiv CsF in 0.4 mL CPME. Yield is that of the isolated product. [b]1 equiv $LiN(SiMe_3)_2$ and 1 equiv $KN(SiMe_3)_2$ were used. [c]0.2 mL CPME was used. [d]Reaction performed with 0.2 mmol 2-fluorotoluene derivatives and 0.8 mmol **2a** in 0.2 mL DME. [e]0.2 mL DME was used. [f]Reaction performed with 1 equiv $LiN(SiMe_3)_2$, 1 equiv $KN(SiMe_3)_2$ and 1.5 equiv CsF in 0.5 mL DME. [g]Reaction performed with 0.2 mmol 2-fluorotoluene derivatives and 0.8 mmol **2a** in 0.2 mL CPME. [h]Reaction performed with 3 equiv $KN(SiMe_3)_2$ and 1.5 equiv CsF in 0.4 mL $^iPr_2O$.

We next turned our attention to the scope of the nitrile coupling partner. We found that our indole synthesis tolerates a range of substitution patterns and functional groups on the nitrile (Table 3). Benzonitriles bearing electron-donating, electron-withdrawing and electron-neutral groups in the 4-position, such as 4-methyl (**2b**), 4-*tert*-butyl (**2c**), 4-methoxy (**2d**), 4-trifluoromethyl (**2e**), 4-fluoro (**2f**), and 4-phenyl (**2g**), exhibited good reactivity, affording **3ab**–**3ag** in 51–80% yield. Benzonitriles with substituents at the 3-position, such as 3-OMe (**2h**), 3,5-di(OMe) (**2i**) and 3-F (**2j**) afforded the desired indoles in 80, 73, and 69% yields, respectively. Nitriles with extended π-systems, such as 2-naphthonitrile (**2k**), furnished the product (**3ak**) in 88% yield. Indoles with heteroaryl substituents at the 2-position could be prepared from the corresponding heterocyclic nitriles. For example, 5-cyano *N*-methyl indole and 4- or 2-cyanopyridines afforded **3al**–**3an** in 60–71% yields. Pivalonitrile was a competent partner, affording 2-*tert*-butyl indole (**3ao**) in 48% yield. Nitriles bearing acidic α-C–H's are not viable substrates, most likely a result of deprotonation of the nitrile. 2,3-Disubstituted indoles possessing heteroaryl groups at the C-3 position could be prepared under our conditions in 61–64% yields (entries 15–16).

Table 3. Substrate scope of nitriles[a]



Entry	R	R'	Product	Y [%]
1	H(**1a**)	4-C_6H_4-Me (**2b**)	**3ab**	51[b]
2	H(**1a**)	4-C_6H_4-^{t}Bu (**2c**)	**3ac**	89
3	H(**1a**)	4-C_6H_4-OMe(**2d**)	**3ad**	76[c]
4	H(**1a**)	4-C_6H_4-CF_3 (**2e**)	**3ae**	68[c]
5	H(**1a**)	4-C_6H_4-F (**2f**)	**3af**	66[c]
6	H(**1a**)	4-C_6H_4-Ph (**2g**)	**3ag**	80[d]
7	H(**1a**)	3-C_6H_4-OMe (**2h**)	**3ah**	80[d]
8	H(**1a**)	3,5-C_6H_4-$(OMe)_2$ (**2i**)	**3ai**	73
9	H(**1a**)	3-C_6H_4-F (**2j**)	**3aj**	69[c]
10	H(**1a**)	2-Naphthyl (**2k**)	**3ak**	88[e]
11	H(**1a**)	5-(*N*-Me-indoly) (**2l**)	**3al**	61[g]
12	H(**1a**)	4-pyridyl (**2m**)	**3am**	60[c]
13	H(**1a**)	2-pyridyl (**2n**)	**3an**	70
14	H(**1a**)	^{t}Bu (**2o**)	**3ao**	48[f]
15	Ph (**1s**)	2-pyridyl (**2n**)	**3sn**	61[h]
16	Ph (**1s**)	3-pyridyl (**2p**)	**3sp**	64[h]

[a]Reactions performed on a 0.2 mmol scale with 2 equiv $LiN(SiMe_3)_2$, 1 equiv CsF in 0.2 mL CPME. Yield of isolated product. [b]Dioxane was used. [c]Reaction performed with 3 equiv $LiN(SiMe_3)_2$, 2 equiv CsF in 0.1 mL THF. [d]0.4 mL DME was used. [e]0.1 mL DME was used. [f]0.2 mL THF was used. [g]0.4 mL CPME was used. [h]3 equiv $KN(SiMe_3)_2$, 1.5 equiv CsF in 0.4 mL $^iPr_2O$.

To test the scalability of our indole synthesis, we performed the synthesis of **3ca**, **3ga**, **3ja** and **3ta** on a 5 mmol scale. Under our conditions, the desired indoles were obtained in 80–84%. Very good yield can also be afforded on 25 mmol scale (**3ca** and **3ja**, Scheme 3). Additionally, the product **3ca** could be elaborated via Suzuki-Miyaura cross-coupling (**4a** and **4b**),[24] cyanation (**4c**),[25] Buchwald-Hartwig amination (**4d**),[26] and alkynalation (**4e**)[27] (see Supporting Information for details).

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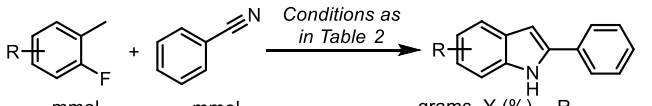


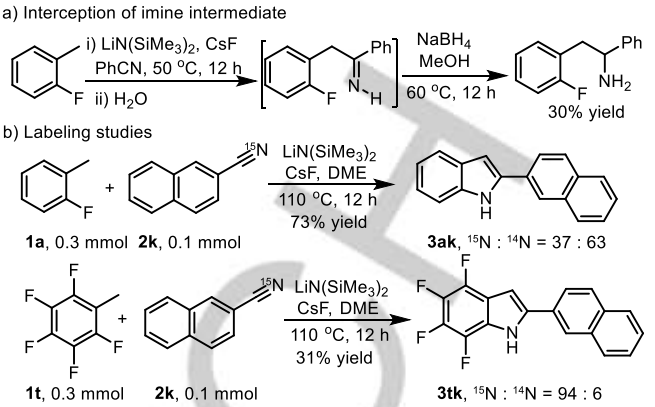
	mmol		mmol		grams	Y (%)	R
1c	15	**2a**	5	**3ca**	0.92	81	4-Cl
1g	15		5	**3ga**	0.90	81	4-OMe[a]
1j	5		20	**3ja**	0.91	80	5-Cl
1t	5		25	**3ta**	1.11	84	4,5,6,7-F_4[b]
1c	75		25	**3ca**	4.44	78	4-Cl
1j	25		100	**3ja**	4.33	76	5-Cl

Scheme 3. Gram-scale transformation with benzonitrile. [a]Reaction performed at 1.0 M. [b]5.0 equiv of benzonitrile was used.

We next desired to gain insight into the mechanism of this tandem process, first exploring the role of the base. We anticipated that $CsN(SiMe_3)_2$ was formed in situ via salt metathesis between $LiN(SiMe_3)_2$ and CsF. Thus, under the standard conditions, $LiN(SiMe_3)_2$ (2 equiv) did not promote indole formation. In contrast, independently prepared $CsN(SiMe_3)_2$ (2 equiv) afforded the indole in 88% yield. The mix $LiN(SiMe_3)_2$ (1 equiv) and $CsN(SiMe_3)_2$ (1 equiv) afforded a similar yield of indole (90%) compared to the standard reaction conditions with $LiN(SiMe_3)_2$ and CsF. These data support the enhanced reactivity of $CsN(SiMe_3)_2$ over $LiN(SiMe_3)_2$.

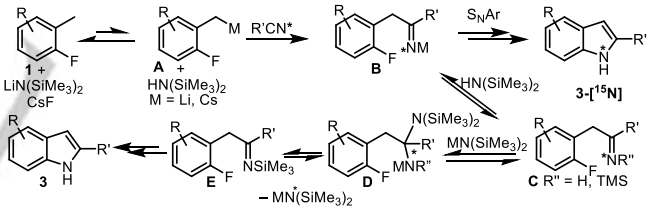
Two mechanisms were envisioned for generation of indoles, one similar to the abbreviated mechanism shown in Scheme 2b and one involving S_NAr between the silyl amide base and 2-fluoro toluene in the first step (generating an aniline and paralleling the Smith indole synthesis, Scheme 1c). In the absence of the nitrile, neither 2-methylaniline nor indole were generated, suggesting direct amination of 2-fluorotoluene with $Li/CsN(SiMe_3)_2$ is not operable. When the indole synthesis was conducted at 50 °C (vs. 110 °C) for 12 h, worked up with water, and quickly subjected to reduction with $NaBH_4$, the amine product was obtained in 30% yield (Scheme 4a). This result supports the mechanism in Scheme 2b and suggests that intermolecular S_NAr is slower than deprotonation of toluene and addition to the nitrile.

We next explored the origin of the nitrogen atom in the indole by employing ^{15}N labeled 2-naphthonitrile.^1H NMR analysis of the indole N–H (singlet for ^{14}N, doublet for ^{15}N), indicated only 37% of the nitrogen in the indole was from the nitrile [63% from the $LiN(SiMe_3)_2$, Scheme 4b, top]. We hypothesize that the ^{14}N-indole does not arise from direct S_NAr with $MN(SiMe_3)_2$, but that an interesting exchange of the labeled ^{15}N for ^{14}N occurs via intermediates **C**, **D**, and **E** (Scheme 5).[28] For this to be true, transimination would need to be faster than S_NAr. We hypothesized that use of electron withdrawing groups on the toluene would increase the rate of S_NAr and raise the level of incorporation with the labeled nitrogen. Consistent with this hypothesis, use of pentafluorotoluene resulted in 94% of the ^{15}N product (Scheme 4b, bottom).



Scheme 4. a) Isolation of intermediates and b) ^{15}N labeling experiment.

Based on the experiments above, we propose a possible reaction pathway (Scheme 5). In the presence of $LiN(SiMe_3)_2$ and CsF, 2-fluorotoluene is deprotonated reversibly to afford an alkali metal complex **A**, which could be η^1- or η^3-bound.[29] Intermediate **A** then attacks the nitrile to give the metallated imine intermediate **B**. **B** can be either protonated [proton transfer from $HN(SiMe_3)_2$] or silylated [silyl transfer from $HN(SiMe_3)_2$], generating the imine **C**.[30] In the presence of the $Li/CsN(SiMe_3)_2$, the imine **C** undergoes reversible transimination (addition, silyl-migration, elimination) to furnish nitrogen exchanged intermediate **E**,[28a] which can undergo silyl transfer and S_NAr. It is noteworthy that the addition, silyl-migration and elimination processes are often found in organometallic complexes.[30-31]



Scheme 5. Key steps in the proposed reaction pathway for indole synthesis (see Chart S4 for more details).

In conclusion, 2-arylindoles represent privileged molecular scaffolds with wide-ranging biological activities.[20] Herein, a highly efficient, tandem and transition-metal-free approach to 2-arylindoles has been introduced. A wide array of 2-arylindoles is generated with very good functional group tolerance (33 examples, 60–92% yields). 2,3-Diaryl/heteroaryl substituted indoles are also readily formed using 2-fluorodiarylmethane coupling partners. Our method enables preparation of indoles bearing substituents at each position on the indole backbone. This novel method for indole synthesis complements classic routes to 2-substituted indoles, such as the Fischer,[4] Gassman,[32] Hegedus,[5c] Madelung,[33] and Reissert[34] indole syntheses.[35] Among these our synthesis stands out for its conciseness, convergent nature, and avoidance of low temperatures that are difficult to access on scale.

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Keywords: indoles • domino reaction • 2-fluorotoluenes • nitrogen heterocyclos

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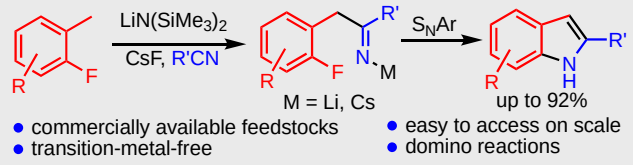

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Jianyou Mao, Zhiting Wang, Xinyu Xu, Guoqing Liu, Runsheng Jiang, Haixing Guan, Zhipeng, Zheng, and Patrick J. Walsh**

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Synthesis of indoles via domino reaction of 2-fluorotoluenes and nitriles

Indoles galore: One of the world's easiest syntheses of indoles is introduced. Simply combining 2-fluorotoluenes, benzonitriles, base, and CsF and heating results in the formation of 2-aryl indoles with diverse substitution patterns.