Base-Promoted Tandem Synthesis of 2-Substituted Indoles and *N*-Fused Polycyclic Indoles

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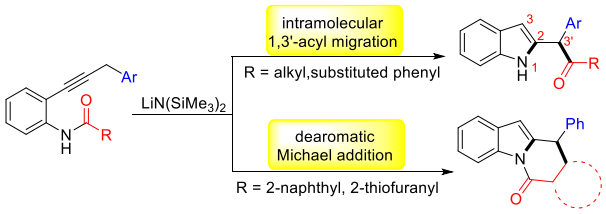
Supporting Information Placeholder



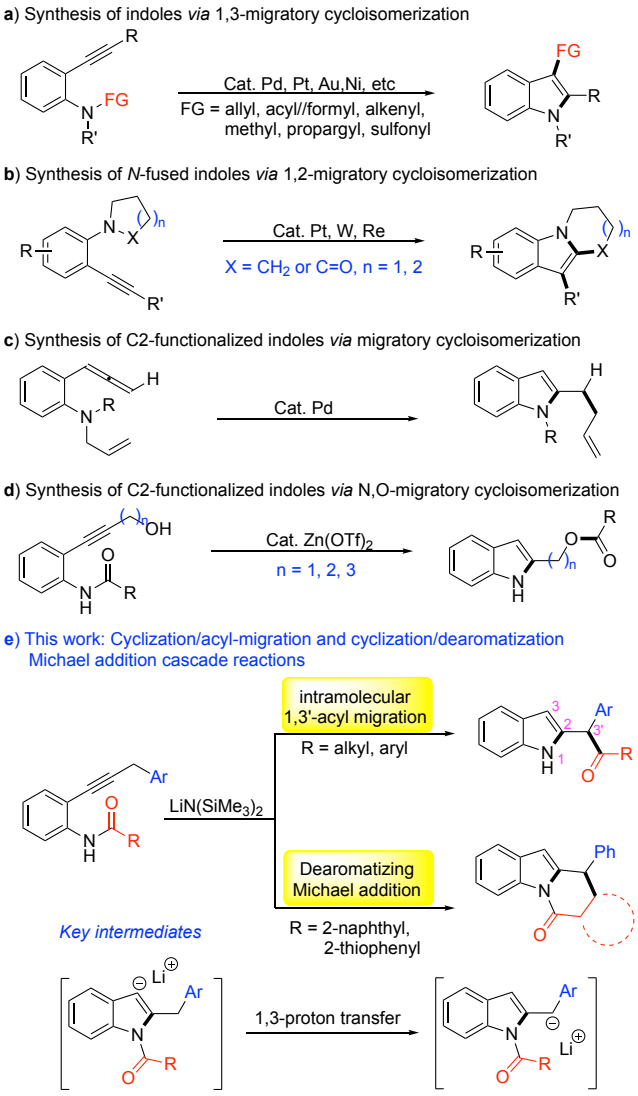
ABSTRACT: Herein is developed a base-promoted approach for the synthesis of C2-substituted indoles and *N*-fused polycyclic indoles *via* 5-*endo*-*dig* cyclization of 2-alkynyl anilines followed by a 1,3'-acyl migration or a dearomatizing Michael addition process. A range of N–H free indoles and 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one scaffolds were synthesized in good to excellent yields with broad scope.

Indoles represent a ubiquitous structural unit found in natural products, biologically active molecules, and pharmaceuticals.[1,2] Consequently, numerous synthetic approaches for the synthesis of these privileged heterocycles have been introduced. Traditional routes include the Fischer indole synthesis,[3] Bartoli indole synthesis,[4] Bischler indole synthesis[5,6] and Fukuyama indole synthesis.[7] Recently, the transition metal-catalyzed cyclization of 2-alkynylaniline derivatives has become a popular method to access functionalized indoles.[8-11] This approach has the additional benefit that it enables functionalization of the *C*3-position of the indole via *N* to *C*3 migration. Examples of migrating groups include allyl,[12,13] acyl/formyl,[14,15] alkenyl,[16,17] methyl,[18] propargyl[19,20] and sulfonyl groups.[21] These migrations usually proceed *via* alkenyl–transition metal intermediates (Pd, Pt, Au, Ni, etc.) (Scheme 1a). In contrast, examples of *N* to *C*2 migration are known but rare and proceed through metal carbene intermediates. In this regard, pioneering studies by the Zhang[22] and Iwasawa[23] groups described efficient methods for the synthesis of *N*-fused tricyclic indoles *via* tandem 5-*endo*-*dig* cyclization/1,2-migration reactions of *N*-(2-alkynylphenyl)lactams and 2-alkynylphenyl pyrrolidines or piperidines (Scheme 1b). Migration of non-tethered groups to the *C*2-position has proven more challenging. Another strategy is *N* to *C* migration of groups to a substituent bound to the indole *C*2-position (called the *C*3' position herein). In 2019, Arisawa and co-workers reported such a Pd-catalyzed migratory cycloisomerization of *N*-allyl-2-allenylaniline derivatives to elaborate the *C*3' position via C–C bond-formation (Scheme 1c).[24] Recently, Wang's group demonstrated a $Zn(OTf)_2$ catalyzed preparation of *C*2-alkyl substituted indoles from *o*-benzamido alkynols by cycloisomerization/*N*- to *O*-acyl migratory to install esters at various positions on the *C*2-substituent (Scheme 1d).[25]

Based on our long-standing interests in the functionalization of weakly acidic benzylic C–H bonds,[26-30] herein we present a novel transition metal-free method for the synthesis of 2-substituted indoles and *N*-fused polycyclic indoles with broad substrate scope. As shown in Scheme 1e, *N*-acyl-2-arylpropargyl anilines bearing weakly acidic benzylic sp^3 C–H bonds are employed as starting materials. Thus, 5-*endo*-*dig* cyclization leads to a *C*3-lithiated intermediate. Proton transfer from the more acidic benzylic site generates a *C*3' lithiated intermediate. The formation of the benzylic carbanion triggers an intramolecular *N* to *C*3'-acyl migration to furnish the final ketone product (we cannot rule out isomerization of the alkyne to an allene followed by cyclization). A divergent reaction pathway was observed with amide bound aryl rings of reduced aromaticity, such as 2-naphthyl and thiophenyl groups. In these cases, a conjugate addition of the *C*3' benzylic anion onto *N*-fused amide ensues leading to polycyclic indoles with loss of aromaticity in the Michael accepting aryl group and

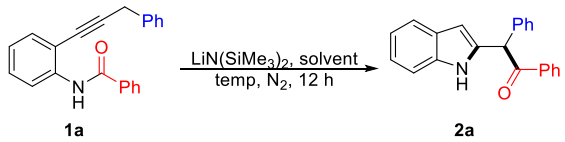
establishment of three new stereogenic centers with very high diastereoselectivity.

Scheme 1 Synthesis of Indoles *via* Cycloisomerization/Migration



As shown in Table 1, the tandem reaction was explored with *N*-(2-(3-phenylprop-1-yn-1-yl)phenyl)benzamide **1a** as substrate. Various solvents (THF, CPME, DME, 1,4-dioxane, and toluene) were screened at 60 °C with 4 equiv of $LiN(SiMe_3)_2$ (entries 1–5, Table 1). The target product **2a** was generated in good to excellent assay yields (entries 1–5, 81–92% assay yield, AY, as measured by ^1H NMR spectroscopy) with toluene the best choice (entry 5, 92% AY). Different $MN(SiMe_3)_2$ base counterions have a profound impact on their reactivity.[31] In this case, $KN(SiMe_3)_2$ and $NaN(SiMe_3)_2$ showed reduced proficiency for the desired cyclization/rearrangement (entry 6–7 vs 5, 57–68% *vs* 92% AY). Next, we examined the influence of reaction temperature. Comparable reactivity was observed at 40 °C, while 87% AY was observed at room temperature. At 80 °C, the indole product **2a** was obtained in 96% AY and 91% isolated yield (entry 10). Notably, excess base was critical for the reaction yield. Lowering the $LiN(SiMe_3)_2$ to 3 equiv gave 90% AY and 82% isolated yield, while only 65% and 12% AY were obtained with 2 and 1 equiv of $LiN(SiMe_3)_2$, respectively. We reasoned that one equivalent is needed to deprotonate the amide and initiate the reaction, ultimately giving the N-deprotonated indole, and another equivalent deprotonates the ketone product to afford the enolate. The excess base likely reacts with any trace water in the solvent or starting alkyne. Workup results in protonation of both the enolate and the indole nitrogen. Overall, the optimized reaction conditions are those in entry 10 and afford the desired *C*2-functional indole **2a** in 91% isolated yield.

Table 1 Reaction Optimization[a]



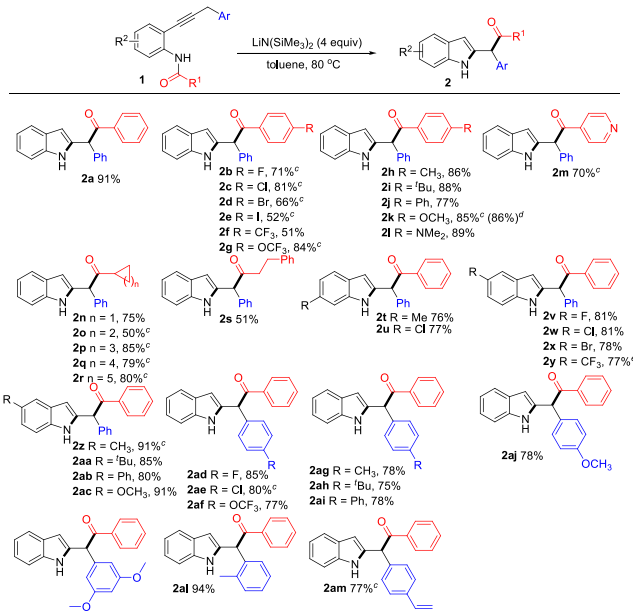
1a **2a**

entry	solvent	$MN(SiMe_3)_2$	T(°C)	Yield[b] (%)
1	THF	$LiN(SiMe_3)_2$	60	85
2	CPME	$LiN(SiMe_3)_2$	60	86
3	DME	$LiN(SiMe_3)_2$	60	90
4	1,4-dioxane	$LiN(SiMe_3)_2$	60	81
5	toluene	$LiN(SiMe_3)_2$	60	92
6	toluene	$NaN(SiMe_3)_2$	60	68
7	toluene	$KN(SiMe_3)_2$	60	57
8	toluene	$LiN(SiMe_3)_2$	25	83
9	toluene	$LiN(SiMe_3)_2$	40	92
10	toluene	$LiN(SiMe_3)_2$	80	96(91[c])
13[d]	toluene	$LiN(SiMe_3)_2$	80	90(82[c])
12[e]	toluene	$LiN(SiMe_3)_2$	80	65
11[f]	toluene	$LiN(SiMe_3)_2$	80	12

[a]Reaction conditions: **1a** (0.1 mmol), $MN(SiMe_3)_2$ (0.4 mmol), solvent (1 mL), 12 h. [b]Determined by ^1H NMR analysis of crude reaction mixture with CH_2Br_2 as internal standard. [c]Isolated yield. [d]$LiN(SiMe_3)_2$ (0.3 mmol). [e]$LiN(SiMe_3)_2$ (0.2 mmol). [f]$LiN(SiMe_3)_2$ (0.1 mmol).

With the optimized conditions in hand, we investigated the substrate scope of the reaction (Table 2). *N*-Acyl-2-alkynylanilines bearing electronegative or electron-withdrawing substituents on the *N*-benzoyl (4-F, **2b**; 4-Cl, **2c**; 4-Br, **2d**; 4-I, **2e**; 4-CF_3, **2f**; 4-OCF_3, **2g**) were all tolerated in this tandem reaction, giving the corresponding products in 51–84% yields. Additionally, substrates bearing alkyl (4-Me, 4-^{t}Bu), 4-phenyl, and electron-donating groups (4-OMe, 4-NMe_2) on the *N*-benzoyl group provided the desired products (**2h**–**2l**) in 77–89% yields. Product **2k** was obtained in 86% yield on a 3.22 mmol scale. Heterocyclic 4-pyridyl was also tolerated in this protocol, affording **2m** in 70% yield. Aliphatic amide substrates bearing cycloalkyl groups of different sizes (**1n**–**1r**) were all suitable in this tandem reaction, furnishing the products (**2n**–**2r**) in 50–85%. Additionally, a phenylethyl (**1s**) group on the *N*-benzoyl was also tolerated, affording the product **2s** in 51% yield.

Table 2 Scope of the synthesis of C2-functionalized indoles



[a]Reaction conditions: **1** (0.1 mmol), $LiN(SiMe_3)_2$ (0.4 mmol), toluene (1 mL), 80 °C, 12 h. [b]Isolated yields. [c]DME (1 mL). [d]Reaction performed on 3.22 mmol. [e]**1y** (0.1 mmol), $KN(SiMe_3)_2$ (0.4 mmol), 18-crown-6 (0.8 mmol), DME (1 mL), 80 °C, 12 h.

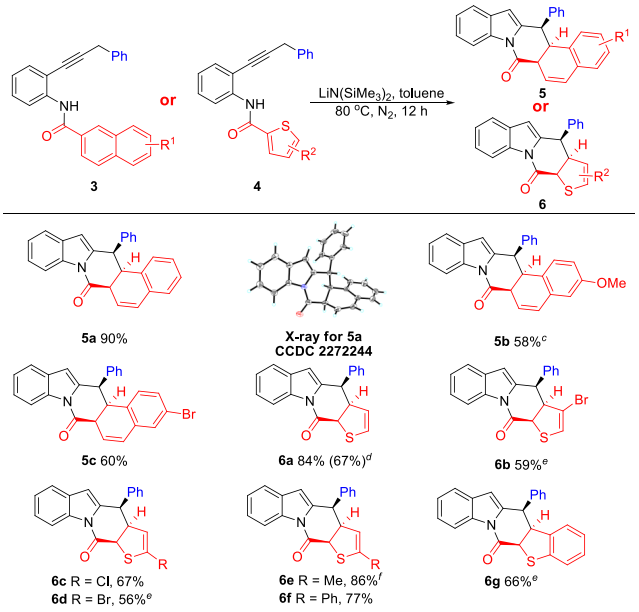
Next, we focused on the diversity of the aniline aryl moiety. 2-Alkynylanilines bearing a 5-Me or a 5-Cl group on the *N*-Ar ring gave products **2t** and **2u** in 76–77% yields. In addition, electronegative or electron-withdrawing groups (F, **2v**; Cl, **2w**; Br, **2x**; CF_3, **2y**) on the *para* position of aniline reacted well under the optimized conditions, affording the indole products in 77–81% yields. In the case of **2y**, with a 4-CF_3 group, no product was observed with $LiN(SiMe_3)_2$ possibly due to elimination of fluoride. In contrast, $KN(SiMe_3)_2$ with excess 18-crown-6 gave the desired product in 77% yield. Moreover, substrates possessing alkyl (4-Me, 4-^{t}Bu), 4-phenyl or electron donating (4-OMe) groups performed well in this transformation, giving the cyclization/rearrangement products **2z**–**2ac** in 80–91% yields.

The scope of aryl propargyl groups was next explored. As shown in Table 2, various substituents on the benzoyl ring were tolerated to provide the target products in 75–94% yields. Alkynyl derivatives bearing electronegative groups on the phenyl ring, including 4-F, 4-Cl and 4-OCF_3, were compatible with this protocol to give the cyclized products (**2ad**–**2af**) in 77–85%, yields. Alkyl (4-Me, 4-^{t}Bu) and 4-phenyl groups were also tolerated, resulting in the generation of indoles **2ag**–**2ai** in 75–78% yields. In addition, substrates with methoxy groups (4-OMe, **1aj**; 3,5-diOMe, **1ak**) on the aryl ring of the aryl propargyl moiety readily reacted to afford the desired indoles in 78% and 93% yields, respectively. A sterically demanding substrate bearing a 2-tolyl propargyl group was also found to be suitable, providing the desired product **2al** in 94% yield. It is noteworthy that 4-styryl on the propargyl moiety was applicable in this reaction, giving **2am** in 77% yield.

Interestingly, 2-alkynylanilines bearing naphthalene-2-carbonyl or thiofuran-2-carbonyl groups followed a different pathway under the standard conditions. With these substrates, the *C*3'-benzylic anion underwent a Michael addition onto the aromatic moiety to afford the dearomatized 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one scaffolds as single diastereomers after protonation. The *N*-fused polycyclic indoles **5a** and **6a** were isolated in 90% and 84% yields, respectively. Crystals of **5a** were obtained by crystallization from CH_2Cl_2 by slow evaporation and the structure was determined by X-ray crystallography (CCDC 2272244). As shown in Table 3, the Michael reaction generated 3 new stereocenters giving a *cis*-fused ring. Indole **6a** was generated in 67% yield when 3.47 mmol alkyne was used.

A brief study of the scope of the synthesis of *N*-fused indoles was investigated using representative substrates with reduced aromaticity. As shown in Table 3, 2-alkynylanilines bearing electron-donating (6-OMe) and electronegative (6-Br) substituents on the naphthyl ring produced *N*-fused indoles **5b** and **5c** in 58–60% yields, again as single diastereomers. Similarly, substrates possessing electronegative (4-Br, 5-Cl, 5-Br), alkyl (5-Me), and 5-phenyl on the thiofuranyl moiety were all compatible with this cascade reaction, affording the corresponding *N*-fused indoles **6b**–**6f** in 56–86% yield. Employing benzo[*b*]thiophene-2-carboxamide (**5g**), the *N*-fused indole **6g** was isolated in 66% yield.

Table 3 Scope of the synthesis of *N*-fused indoles

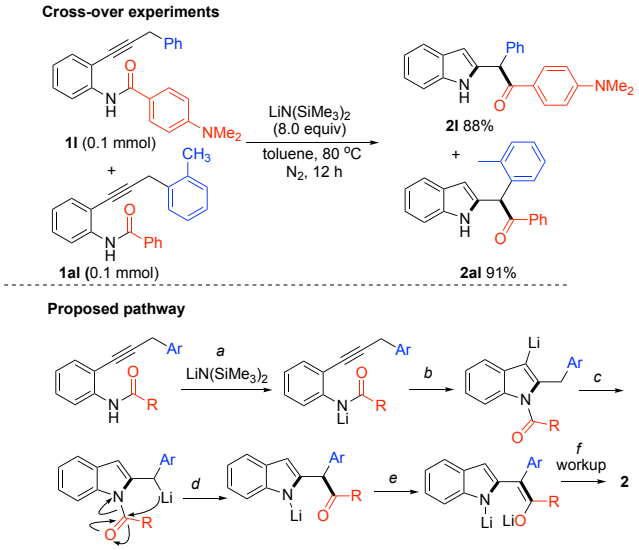


[a]Reaction conditions: **3** or **4** (0.1 mmol), $LiN(SiMe_3)_2$ (0.4 mmol), toluene (1 mL), 80 °C, 12 h. [b]Isolated yields. [c]CPME (1 mL). [d]Reaction performed on 3.47 mmol scale. [e]DME (1 mL). [f]1,4-Dioxane(1 mL).

Finally, a crossover experiment was conducted to clarify the rearrangement reaction pathway. As shown in Scheme 2, a reaction between **1l** and **1al** under the

optimized conditions was conducted in a single reaction vessel. Only indole products **2l** and **2al** were observed and isolated in 88% and 91% yields respectively, with no crossover products detected. Thus, the acyl-migration pathway is exclusively an intramolecular process. A proposed mechanism (Scheme 2) involves deprotonation followed by cyclization in (*b*) and isomerization in (*c*). In step (*d*) acyl migration gives a ketone that is deprotonated in (*e*) with subsequent workup with water in (*f*) to afford **2**.

Scheme 2 Cross-over Study and proposed pathway.



The indole derivatives were subjected to evaluation for cytotoxicity against Hela cancer cells. Compound **2f**, **2w**, and **2ai** were found to be cytotoxic (see Supporting Information for details). A more comprehensive analysis is needed to explore the specific anti-proliferative mechanisms of activity.

In summary, we have developed a novel transition metal-free method for the synthesis of 2-substituted indole ketones and *N*-fused polycyclic indoles. The reactions proceed *via* tandem 5-*endo-dig* cyclization/1,3'-acyl migration or 5-*endo-dig* cyclization/Michael addition with loss of aromaticity. The reactions are simple, efficient and atom-economical. A crossover experiment illustrates that the acyl migration is an intramolecular process. Among the evaluation of the indole compounds prepared in this study, three compounds showed strong anti-proliferative affects against Hela cancer cells. Further studies toward the development of methods for the synthesis of diverse indole scaffolds are currently underway in our laboratories.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, NMR spectra (PDF), and Crystal Data.

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Notes

The authors declare no competing financial interest.

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