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Article

Base-Promoted Tandem Synthesis of Indolo[1,2-*b*]isoquinolines from 2-Alkynylaniline and Nitroarenes

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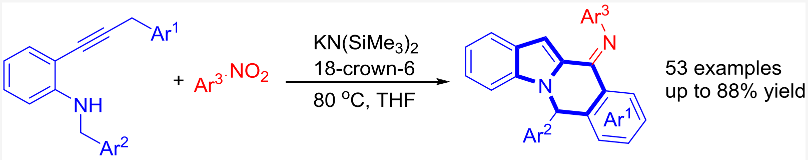

■ transition metal-free ■ cascade process ■ operationally simple
■ direct activation of nitroarenes ■ two heterocycles formed

ABSTRACT: Polycyclic fused indoles have many applications in medicinal chemistry. Using 2-alkynylanilines, $KN(SiMe_3)_2$, and nitroarenes, a tandem method for the synthesis of various indolo[1,2-*b*]isoquinolines is presented (53 examples, yields up to 88%). A key feature of this strategy is the construction of fused indole and isoquinoline heterocycles with the generation of three new bonds in one pot. In addition, nitroarenes are used as electrophiles to install *N*-aryl moieties.

Polycyclic fused indole derivatives are privileged scaffolds that are present in numerous natural products and biologically active compounds.[1−3] Consequently, considerable effort has been devoted to developing more practical and efficient methods for the synthesis of such indole-based structures.[4−8] The subclass of indolo[1,2-*b*]isoquinolines has a unique tetracyclic scaffold with fused indole and isoquinoline rings that share two nitrogen centers and two carbon centers. In contrast to their structural isomers indolo[2,1-*a*]isoquinolines,[9−15] the synthesis of indolo[1,2-*b*]isoquinolines has been rarely reported in the literature. The Greaney group reported a Pd-catalyzed tandem indole C−H alkenylation/arylation process (Scheme 1a),[16] while the Nanduri group disclosed a Lewis acid-catalyzed intramolecular Friedel−Crafts alkylation route for the synthesis of these fused heterocyclic compounds (Scheme 1b).[17] An interesting cobalt-catalyzed [2 + 2 + 2] cyclotrimerization was reported by Ramana and co-workers for the synthesis of several indolo[1,2-*b*]isoquinolines.[18] Iwasawa's team reported a single example of the tungsten-mediated synthesis of this ring system via a tandem [1,2]-Stevens-type rearrangement of metalated ammonium ylides. This example is particularly noteworthy as it simultaneously generates both the indole core and tetrahydroisoquinoline rings in one operation.[19] As illustrated in Scheme 1, the predominant strategies previously employed for constructing indolo[1,2-*b*]isoquinoline have predominantly relied on functionalized indoles, limiting the substitution patterns of the tetracyclic products. Moreover, stoichiometric or catalytic transition metals[16,19−22] or harsh reaction conditions have been employed.[18] Therefore, efficient approaches that assemble the indole and isoquinoline motifs in a single operation would offer enhanced synthetic efficiency and potentially greater atom economy.

A theme of our research is the deprotonation of substrates bearing weakly acidic C−Hs mediated by silyl amide bases,[23] which are proposed to be facilitated by cation−π interactions.[24] We have applied this approach to the synthesis of heterocycles (pyrroles,[25,26] indoles,[27−30] and isoquinolines[31]), including from alkynylaniline substrates.[27,28] We have also been interested in the application of nitroarenes to install N−Ar substituents.[32,33] Herein, we present a one-pot transition-metal-free method for the synthesis of indolo[1,2-*b*]isoquinolines from 2-alkynylanilines and nitroarenes. This novel tandem process assembles the two heterocyclic cores with the formation of three new bonds. Key features of this reaction are the employment of readily available nitroarenes and their use without the need for an external reductant. These features render the present strategy attractive, especially considering that the direct activation of nitroarenes remains challenging and underutilized in organic synthesis.[34−40]

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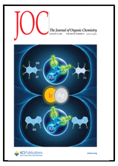

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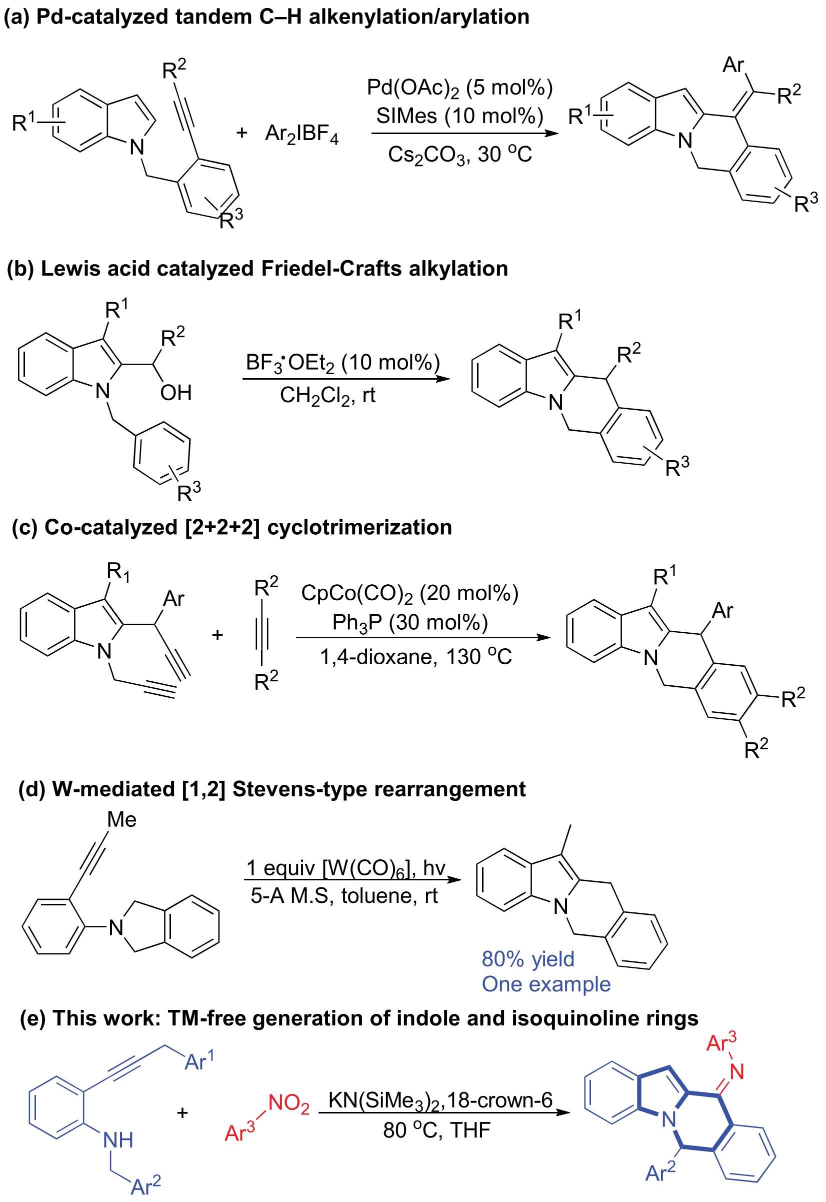
Scheme 1. Methods for Synthesis of Indolo[1,2-*b*]isoquinoline



(a) Pd-catalyzed tandem C–H alkenylation/arylation

(b) Lewis acid catalyzed Friedel-Crafts alkylation

(c) Co-catalyzed [2+2+2] cyclotrimerization

(d) W-mediated [1,2] Stevens-type rearrangement

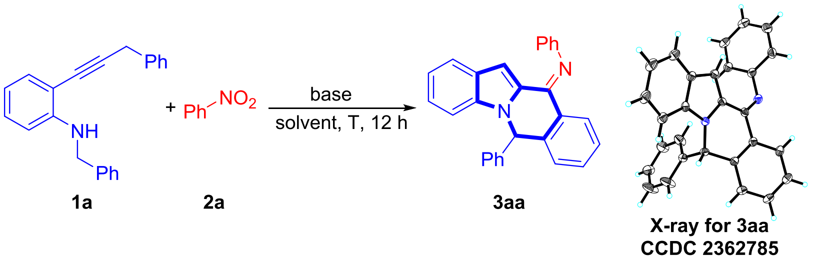
(e) This work: TM-free generation of indole and isoquinoline rings

RESULTS AND DISCUSSION

Initially, the tandem reaction was explored with *N*-benzyl-2-(3-phenylprop-1-ynyl)aniline (**1a**) and nitrobenzene (**2a**) as the model substrates using 1,2-dimethoxyethane (DME) as a solvent at 80 °C for 12 h (Table 1). Screening of bases [LiO^{t}Bu, NaO^{t}Bu, KO^{t}Bu, LiN(SiMe$_3$)$_2$, NaN(SiMe$_3$)$_2$, KN(SiMe$_3$)$_2$] indicated that only KN(SiMe$_3$)$_2$ provided the desired polycyclic product **3aa** in 30% yield (entry 6 vs entries 1–5). Among the five solvents tested [DME, toluene, cyclopentylmethyl ether (CPME), 1,4-dioxane, and tetrahydrofuran (THF)], THF and DME were identified as suitable solvents (entries 6–10) with THF slightly better than DME. Temperature evaluation indicated 80 °C was the best choice (entries 10–12). Increasing the amount of **1a** was beneficial to the transformation, with 2.0 equiv of **1a** providing a 34% yield (entry 13) and 3.0 equiv of **1a** providing a 46% yield (entry 14). Additionally, the yield of **3aa** was improved significantly upon the addition of 1.5 equiv of 18-crown-6. The increased reactivity in the presence of the crown ether is in line with our previous studies in the functionalization of carbanions derived from reversible deprotonation of toluene derivatives for the formation of heterocyclic compounds.[27,28,31] Interestingly, the volume of the solvent has a profound influence on this reaction. Slightly decreasing the amount of THF from 1 to 0.7 mL improved the yield of **3aa** to 88%, while 1.7 mL of THF provided the fused indole in 55% yield (entry 17). Overall, the optimized reaction conditions were established in entry 16 and were used to explore the scope of the substrates. The structure of **3aa** was verified by X-ray crystallography and found to have the *Z* configuration. An ORTEP depiction of the structure is shown in Table 1.

With the optimized conditions established, the scope of nitroarenes with *N*-benzyl-2-(3-phenylprop-1-ynyl)aniline **1a** was investigated (Table 2). Nitroarenes bearing alkyl groups (4-Me, 4-^{t}Bu, and 3-Me) afforded the corresponding products **3ab**–**3ad** in 56–65% yields. In addition, both

Table 1. Reaction Optimization[a]



entry	solvent	base	T(°C)	1a/2a	yield[b] (%)
1	DME	LiO^{t}Bu	80	1:1	
2	DME	NaO^{t}Bu	80	1:1	
3	DME	KO^{t}Bu	80	1:1	
4	DME	$LiN(SiMe_3)_2$	80	1:1	
5	DME	$NaN(SiMe_3)_2$	80	1:1	
6	DME	$KN(SiMe_3)_2$	80	1:1	30
7	toluene	$KN(SiMe_3)_2$	80	1:1	19
8	CPME	$KN(SiMe_3)_2$	80	1:1	20
9	DIO	$KN(SiMe_3)_2$	80	1:1	12
10	THF	$KN(SiMe_3)_2$	80	1:1	32
11	THF	$KN(SiMe_3)_2$	60	1:1	19
12	THF	$KN(SiMe_3)_2$	100	1:1	23
13	THF	$KN(SiMe_3)_2$	80	2:1	34
14	THF	$KN(SiMe_3)_2$	80	3:1	46
15[c]	THF	$KN(SiMe_3)_2$	80	3:1	62
16[c,d]	THF	$KN(SiMe_3)_2$	80	3:1	88
17[c,e]	THF	$KN(SiMe_3)_2$	80	3:1	55

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), base (0.3 mmol), solvent (1 mL), 12 h. [b] Isolated yield. [c] 0.15 mmol of 18-crown-6. [d] 0.7 mL of THF. [e] 1.7 mL of THF.

electron-donating (4-OMe, 4-OPh, 4-NMe_2) and electronegative (4-F, 4-Cl) groups were tolerated in this protocol, giving the *N*-fused indole products (**3ae**−**3ai**) in 52−72% yields. Interestingly, nitroarenes possessing heterocyclic groups, such as furan, thiophene, and morpholine, all worked well in this reaction, providing the desired products (**3aj**−**3al**) in 47−82% yields. In addition to monosubstituted nitroarenes, disubstituted substrates, including 1,2-dimethyl-4-nitrobenzene **2m**, 2-methoxy-1-methyl-4-nitrobenzene **2n**, 1-methoxy-2-methyl-4-nitrobenzene **2o**, and 2-fluoro-1-methoxy-4-nitrobenzene **2p**, led to the polycyclic indoles **3am**−**3ap** in 51−57% yields.

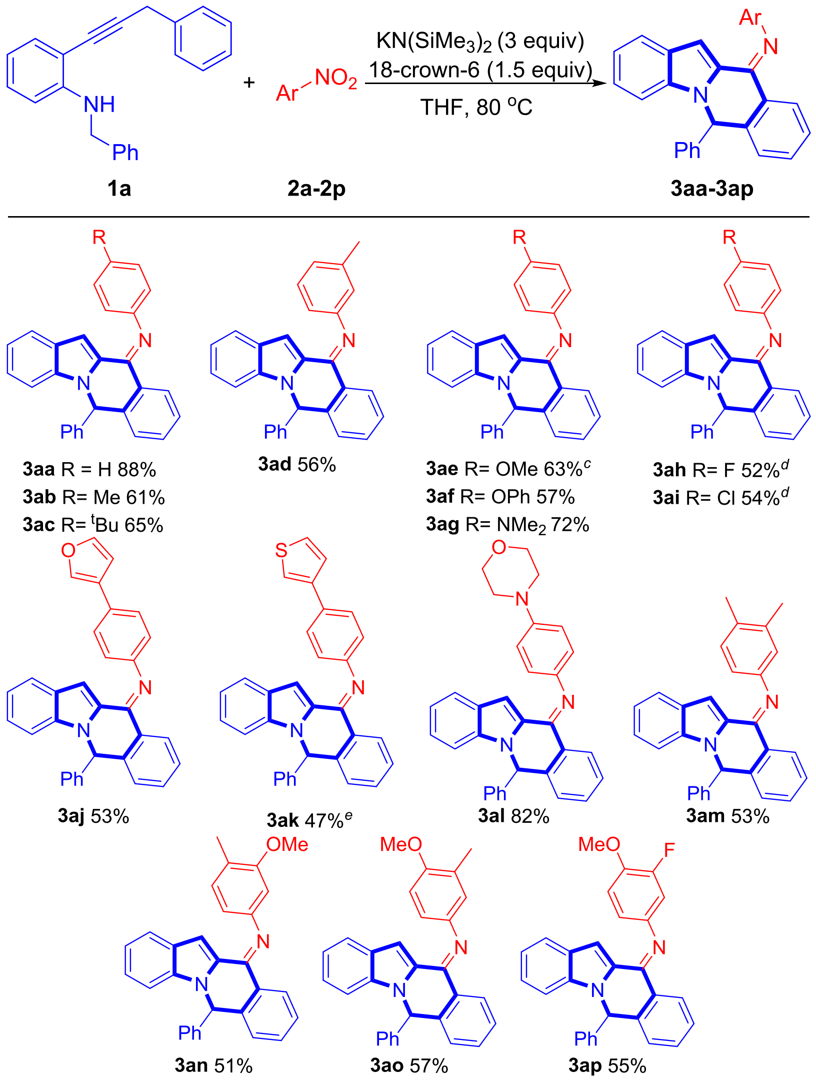
Next, substitution on the aniline moiety was explored with nitrobenzene (**2a**) (Table 3) beginning with *N*-benzyl-2-arylpropargyl anilines bearing alkyl (4-Me, 4-^{t}Bu), benzyl (4-Bn), and phenyl (4-Ph) groups on the aniline core. These substrates worked well in this reaction, giving the corresponding products **3ba**−**3ea** in 74−82% yields. Additionally, substrates possessing electronically diverse substituents, including electron-donating (4-OMe) and electron-withdrawing substituents (4-F, 4-Cl, 4-Br, 4-CF_3, 4-OCF_3), were all well tolerated in this protocol, affording the *N*-fused indole products **3fa**−**3ka** in 60−82% yields.

With respect to the scope of arylpropargyl groups, a series of substrates containing alkyl (4-Me, **1l**; 4-^{t}Bu, **1m**), phenyl (**1n**), electron-donating (4-OMe, **1o**), and electronegative and electron-withdrawing (4-F, **1p**; 4-Cl, **1q**; 4-OCF_3, **1r**) groups on the para positions of the aryl ring reacted with nitrobenzene readily under the optimal reaction conditions providing the tetracyclic products (**3la**−**3ra**) in 45−81% yields.

Finally, the scope of the aryl group on the *N*-benzyl portion of the substrates was investigated. *N*-Benzyl-2-alkynylanilines bearing alkyl (4-Me, **1s**; 4-^{t}Bu, **1t**), 4-phenyl (**1u**), electron-donating (4-OMe, **1v**; 4-OPh, **1w**; 4-NMe_2, **1x**; 4-SMe, **1y**), and electronegative or electron-withdrawing (4-F, **1z**; 4-CN, **1A**; 4-OCF_3, **1B**) groups on the *N*-benzyl group were all well tolerated in this protocol, resulting in the formation of the products **3sa**−**3Ba** in 48−82% yields. In addition, heterocyclic substituents on the *N*-benzyl groups, such as 2-pyridinyl and morpholino groups, were both tolerated, giving the annulated product (**3Ca**, **3Da**) in 77 and 69% yields, respectively. Notably, *N*-benzyl groups with *ortho*-substituents, including 2-F, 2-Cl, and the sterically hindered 2-Me groups, were acceptable in the tandem process, furnishing the products **3Ea**−**3Ga** in 68−77% yields. Moreover, heterocyclic 2-furanyl (**1H**), 2-thiophenyl (**1I**), 2-pyridyl (**1J**), 2-quinolyl (**1K**), and 3-methylenedioxyphenyl (**1L**) substituents were compatible, providing the indole products (**3Ha**−**3La**) in 56−66% yields.

To test the practicality of this tandem reaction, a gram-scale procedure was carried out with 12 mmol of **1a** and 4 mmol of **2a** under the standard conditions (Scheme 2a). The desired product **3aa** was isolated in an 84% yield (1.29 g). The products synthesized herein can be hydrolyzed to access ketones. Specifically, hydrolysis of **3aa** with 1 M HCl provides **4** in 82% yield (Scheme 2b). We next sought to gain insight into the reaction mechanism of this tandem process. As shown in Scheme 2c, we prepared the indole intermediate **5** without the addition of nitrobenzene. Next, subjecting **5** to nitro-

Table 2. Scope of Nitroarenes[a,b]



[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.1 mmol), $KN(SiMe_3)_2$ (1.0 mol/L in THF, 0.3 mL, 0.3 mmol), 18-crown-6 (0.15 mmol), THF (0.7 mL), 80 °C, 12 h. [b]Isolated yield. [c]0 °C. [d]1,4-Dioxane (0.7 mL), $KN(SiMe_3)_2$ (0.6 mmol). [e]40 °C.

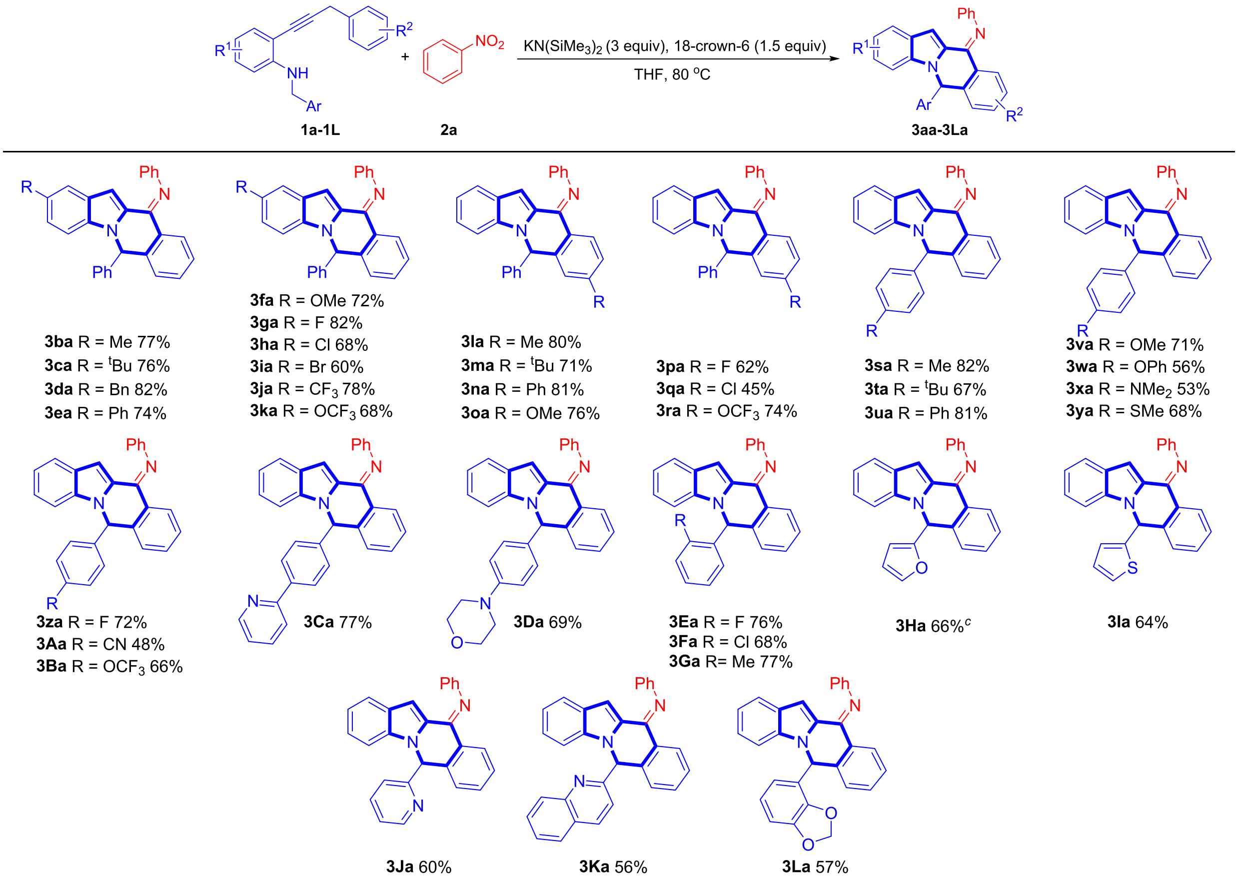
benzene under the optimal reaction conditions (entry 16 in Table 1) gave indolo[1,2-*b*]isoquinoline **3aa** in 73% yield. These results indicate that (1) indole **5** is a viable intermediate in the tandem reaction and (2) the crown-ether-coordinated K^+ plays a role in the second part of the reaction.

A working mechanism is proposed in Scheme 3 (the crown ether is not included for clarity but likely serves to bind K^+ to break up aggregates or generate carbanions that are solvent separated). Deprotonation of the N–H bond of **1a** by the $KN(SiMe_3)_2$ generates the amide **A**. The nucleophilic nitrogen of **A** adds to the triple bond to form the C–N bond and generate an sp^2 carbanion **B**. Carbanion **B** undergoes proton transfer to form resonance-stabilized carbanion **C**. This process may be mediated by the conjugate acid of the base, $HN(SiMe_3)_2$. We propose that carbanion **C** reacts with nitroarene to give **D**. This step is drawn as a two-electron addition but may well be a stepwise radical process with single electron transfer (SET) from carbanion **C** to the nitroarene, followed by radical–radical coupling. Either way, intermediate **D** is proposed to undergo silyl transfer from $HN(SiMe_3)_2$ driven by the formation of a strong Si–O bond. Base-promoted elimination of the weak base $KOSiMe_3$ from intermediate **E** results in the formation of the electrophilic imine-*N*-oxide in **F**. A second silylation event is proposed to generate a silyloxy leaving group. Reversible deprotonation of the *N*-benzyl methylene affords a new carbanion (**G**) that can add to the electron-deficient phenyl ring to generate the C–C bond and break the aromaticity. Subsequent base-promoted elimination of the remaining $KOSiMe_3$ is proposed to regenerate the aromaticity to form the product **3aa**.

CONCLUSIONS

In conclusion, we have developed a novel base-promoted protocol for the synthesis of indolo[1,2-*b*]isoquinolines from 2-alkynylanilines and nitroarenes. In this cascade process, the *5-endo-dig* cyclization to the indole, tautomerization to the benzylic carbanion, and addition to the nitroarene are proposed. The annulation is proposed to be promoted by the activation of the N–O bonds by silyl

Table 3. Scope of 2-Alkynylanilines[a,b]



1a-1L **2a** **3aa-3La**

3ba R = Me 77%
3ca R = ^{t}Bu 76%
3da R = Bn 82%
3ea R = Ph 74%

3fa R = OMe 72%
3ga R = F 82%
3ha R = Cl 68%
3ia R = Br 60%
3ja R = CF_3 78%
3ka R = OCF_3 68%

3la R = Me 80%
3ma R = ^{t}Bu 71%
3na R = Ph 81%
3oa R = OMe 76%

3pa R = F 62%
3qa R = Cl 45%
3ra R = OCF_3 74%

3sa R = Me 82%
3ta R = ^{t}Bu 67%
3ua R = Ph 81%

3va R = OMe 71%
3wa R = OPh 56%
3xa R = NMe_2 53%
3ya R = SMe 68%

3za R = F 72%
3Aa R = CN 48%
3Ba R = OCF_3 66%

3Ca 77%

3Da 69%

3Ea R = F 76%
3Fa R = Cl 68%
3Ga R= Me 77%

3Ha 66%[c]

3Ia 64%

3Ja 60%

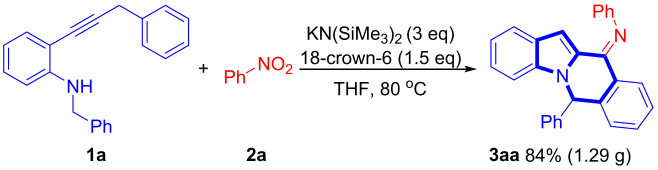
3Ka 56%

3La 57%

[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.1 mmol), $KN(SiMe_3)_2$ (1.0 mol/L in THF, 0.3 mL, 0.3 mmol), 18-crown-6 (0.15 mmol), THF (0.7 mL), 80 °C, 12 h. [b] Isolated yield. [c] 60 °C.

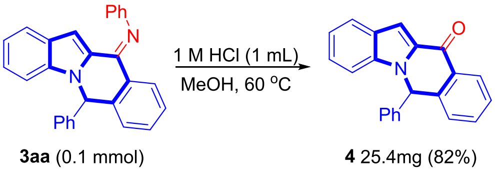
Scheme 2. (a) Scale-Up Synthesis of 3aa; (b) Hydrolysis of 3aa; (c) Probing Reaction Intermediates

(a) Gram-scale synthesis of 3aa



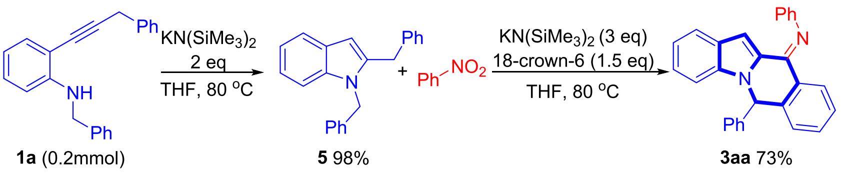
1a **2a** **3aa** 84% (1.29 g)

(b) Hydrolysis of 3aa



3aa (0.1 mmol) **4** 25.4mg (82%)

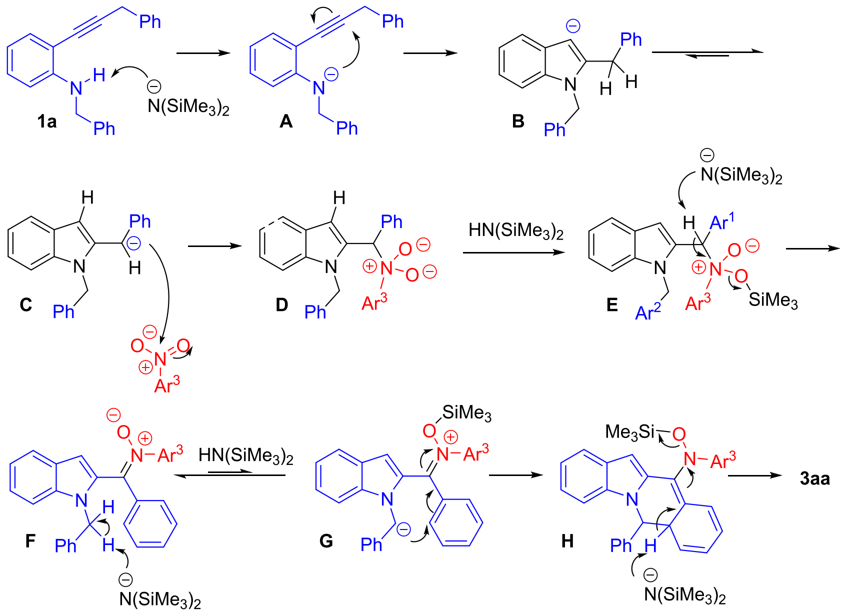
(c) Step-wise reaction



1a (0.2mmol) **5** 98% **3aa** 73%

transfer from $HN(SiMe_3)_2$. Compared to previously reported methods for the synthesis of indolo[1,2-*b*]-isoquinolines, the approach presented herein is operationally simple, general, and conducted without the addition of transition metals. The broad scope and good functional group compatibility of this reaction make it attractive for the generation of a host of indolo[1,2-*b*]isoquinolines.

Scheme 3. Working Mechanism for the Base-Mediated Tandem Reaction to Form Indolo[1,2-*b*]isoquinolines



ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.5c01270.

Experimental procedures, characterization data, NMR spectra, and crystal data (PDF)

Accession Codes

Deposition Number 2362785 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version.

Notes

The authors declare no competing financial interest.

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