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Cis-3-Azido-2-Methoxyindolines as Safe and Stable Precursors to Overcome the Instability of Fleeting 3-Azidoindoles †

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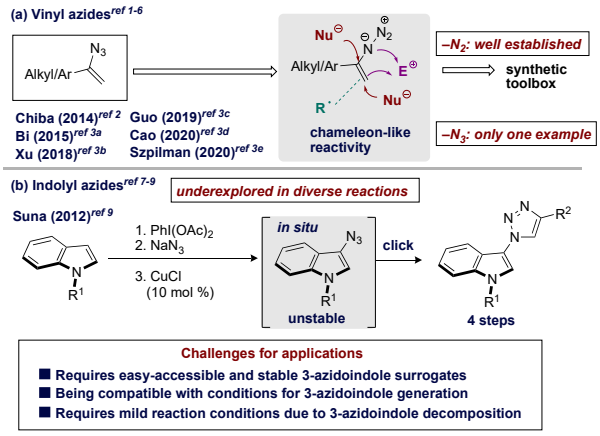
Use of 3-azidoindoles in organic synthesis remains difficult task owing to their instabilities. Herein, we report a general and concise approach for tackling this problem by using 3-azidoindole surrogates. The surrogates are bench-stable presumably due to the observed intramolecular O–N$_\beta$ bonding. The resultant fleeting intermediate undergo capturing *in situ* to afford 3-substitued indoles through formal *ipso*-substitution of the azide group by nucleophiles. In these investigations, we found that the fleeting 3-azidoindoles show C3-electrophilic character for the first time.

Vinyl azides has been used as versatile synthons for diverse transformations due to its chameleonic properties (Scheme 1a).[1-3] They serve as precursor to vinyl nitrene or azirines with a release of N_2 as a driving force.[4] Recently, metal-mediated or radical methods been enlisted to generate imines[5] and imino radicals[6] with newly formed C–C bonds driven by a loss of N_2. Because of the dominant denitrogenation reactions of vinyl azides, nucleophilic substitution reactions triggered by a release of N_3 moiety, which is so-called *ipso*-substitutions of the azide group, is still very challenging.[3e] Although the chemistry of an indolyl azide has considerably less attention, the structural resemblance with the vinyl azide would be a potential candidate for the substrate of the *ipso*-substitution. The classical "click" reaction occupies a central role in indolyl azide,[7] although there are exceptions.[8] In 2012, Suna and co-workers have pioneered an alternative approach involving an *in situ* generated indolyl azide from hypervalent iodine with NaN_3 for the "click" reaction, affording the triazoles through 4 steps (Scheme 1b).[9] In the report, it is found that the indolylazide decomposed during attempted purification due to their instability. Existing utilization of unstable indolyl azides require multi-step protocol and offer limited to triazole products. The lack of efficient access to them and their instabilities has limited the progress in the azidoindole chemistry. Consequently, a design and synthesis of a more stable surrogate of the indolyl azide is largely needed to overcome the limitations associated with the state-of-the-art. If easily accessing 3-azidoindoles from their stable surrogates in hand, it can be used as a novel synthetic linchpin that shows a diverse reactivity due to their structural resemblance with vinyl azides.



Scheme 1 State-of-the-art of vinyl azides and indolyl azides.

Recently, we introduced a new class of bench-stable indoline-type reagents that serve as an umpoled indole synthon for formal cross-nucleophile coupling.[10] In this line, we envisioned that an azide indoline derivative would afford 3-azidoindole *in situ* through the elimination of methoxy group by Lewis acids, thereby allowing an *ipso*-substitution of the azide moiety by nucleophiles (Scheme 2).[11] We also hypothesized that the instability of 3-azidoindole might render them intrinsically reactive, thus affording the complementary or high reactivity to the vinyl azides. Herein, we demonstrate the utility of 3-azido-

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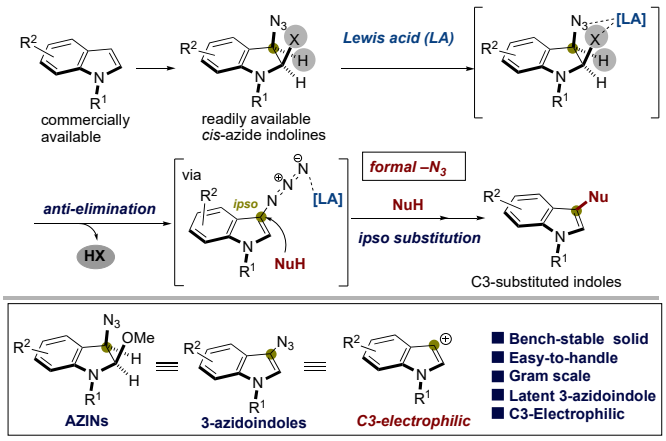
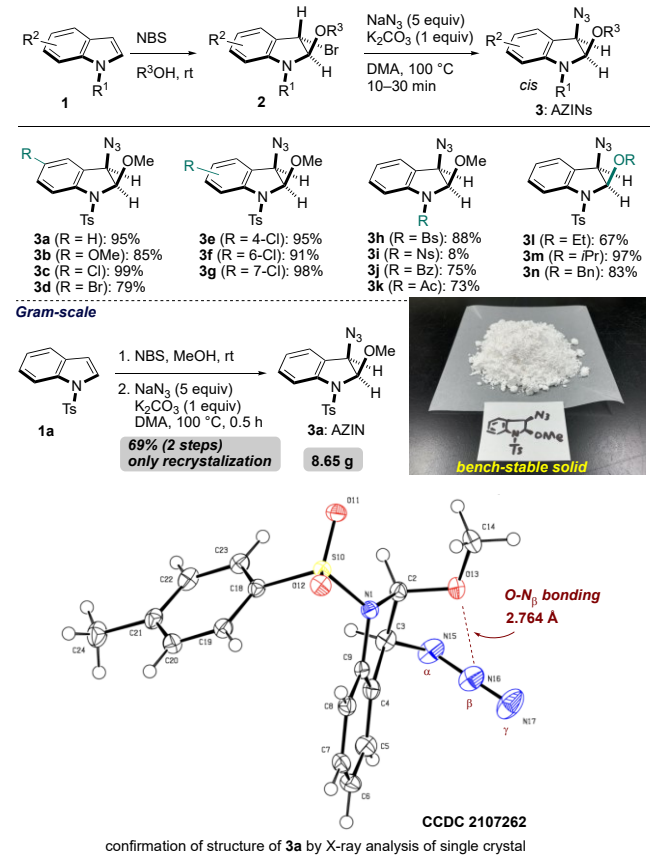
2-methoxyindoline (AZIN) as 3-azidoindole surrogates to afford 3-substituted indoles through *ipso*-substitutions along with a formal release of N_3 moiety. The AZIN is a bench-stable solid that reacts with a wide variety of electron-rich heteroarene/arene, and thiol in the presence of Lewis acids. High stability against a variety of reaction conditions makes this a useful reagent to access diverse indole derivatives that are difficult to make using previous methods.



Scheme 2 Our designed 3-azidoindole surrogates

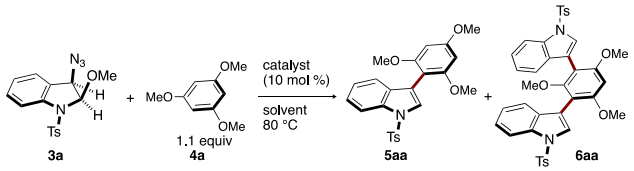


confirmation of structure of **3a** by X-ray analysis of single crystal

Scheme 3 Synthesis of AZINs[a,b]: [a] **2** (1 mmol), NaN_3 (5 mmol), K_2CO_3 (1 mmol), DMF (5 mL). [b] Isolated yields.

Our first challenge was to develop a synthetic route to the stable 3-azidoindole surrogates. Alkyl azides were generally accessed through nucleophilic substitutions of the corresponding alkyl bromides with NaN_3.[12] Therefore, we focused on using 3-bromo-2-methoxy indolines **2**, which were prepared by bromoetherifications of indoles **1** using NBS in MeOH (see S. I., Scheme S1),[13] as an alkyl bromide. To our surprise, 3-azido-2-methoxyindoline (**3a**, AZIN) could be prepared by *cis*-selective azidation using K_2CO_3/NaN_3. Using this azidation protocol, a variety of novel AZINs could be obtained in good to excellent yields. This novel protocol performed on gram-scale to afford 8.65 g of **3a** in a single-batch by only recrystallization. Recently, Sureshan, Werz and co-workers have demonstrated a series of the compounds with the azide and oxygen groups orient syn to each other with a short O–N_β contact (O–N bonding).[14b] By X-ray crystallographic analysis of **3a**, the central nitrogen of the azide group and the oxygen atom of the methoxy group were within the sum of their van der Waals radii (2.76 Å *vs*.1.64 Å + 1.58 Å = 3.22 Å), suggesting the presence of intramolecular oxygen-nitrogen (O–N_β) bonding (donor: lone pair of O; acceptor: N^+).[14] Due to the O–N_β bonding, AZIN **3a** would be a thermally stable and non-explosive solid with relatively high melting point 97-100 °C (3-azidoindole: 60 °C, decomposition[7d]). This thermal stability allows for easy application in the reaction screening as well as its storage and handling. Indeed, the AZINs has been shown to be bench-stable under ambient conditions without degradation over one year.

Table 1 Optimization of reaction conditions[a]

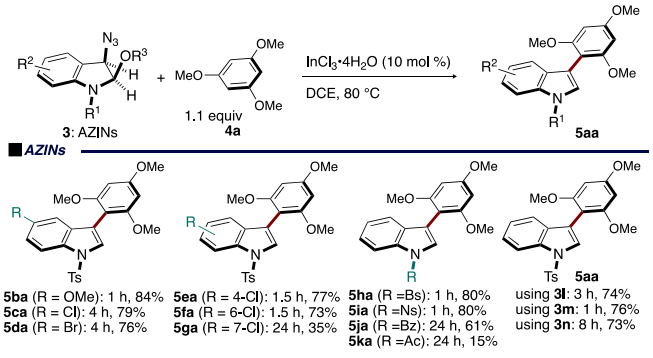


Run	Catalyst	Solvent	Time (h)	Yield (%) of **5aa**[b]	Yield (%) of **6aa**[b]
1	$In(OTf)_3$	DCE	2	18	8
2	$InF_3•3H_2O$	DCE	2	trace	0
3	**$InBr_3$**	**DCE**	**1**	**79**	**21**
4	**$InCl_3•4H_2O$**	**DCE**	**1**	**77**	**17**
5	$AlCl_3$	DCE	2	42	3
6	$LaCl_3•7H_2O$	DCE	2	trace	0
7	$FeCl_3$	DCE	1	73	20
8	$InCl_3•4H_2O$	toluene	2	48	0
9	$InCl_3•4H_2O$	ClC_6H_5	2	54	3
10	$InCl_3•4H_2O$	$CF_3C_6H_5$	2	67	13
11	$InCl_3•4H_2O$	HFIP	1	72	8
12[c]	$InCl_3•4H_2O$	DCE	1	21	58
13	---	DCE	16	nr	nr

[a] **3a** (0.3 mmol), **4a** (0.33 mmol), and catalyst (0.03 mmol) in solvent (3 mL). [b] Isolated yields. [c] **3a** (0.3 mmol), and **4a** (0.15 mmol), and $InCl_3•4H_2O$ (0.03 mmol) in DCE (3 mL).

Having the 3-azidoindole precursor in hand, we first explored its efficacy in promoting S_N2 reactions between *in situ* generated 3-azidoindole and trimethoxybenzene **4a** in the presence of catalyst (Table 1). It was established in our previous studies that $In(OTf)_3$ is crucial for high reactivity in S_NAr reactions at the indole 3-position with a release of MeOH.[11] Thus, we started with acidic $In(OTf)_3$ in DCE. We are pleased to observed that the use of $In(OTf)_3$ enabled the proposed reactivity, leading to 3-arylindole **5aa** in 18% yield, albeit with

unexpected diindolylarene **6aa** in 8% yield (entry 1). Among the indium salts, notable progress was achieved by using more basic $InBr_3$ as a catalyst, affording **5aa** in 79% yield (entries 2–3). Pleasingly, replacement of expensive $InBr_3$ with inexpensive $InCl_3•4H_2O$ provided **5aa** without a noticeable decrease of the yield (77% yield, entry 4). Other metal salts like $AlCl_3$ and $LaCl_3•7H_2O$ proved ineffective (entries 5–6), while $FeCl_3$ was found to be effective giving 73% yield (entry 7). The solvent effect significantly influenced this transformation, and the use of toluene, ClC_6H_5, $CF_3C_6H_5$, and HFIP afforded the desired product **5aa** in 48%, 54%, 67% and 72% yields, respectively (entries 8–11). It was found that the yield of **6aa** could be improved by increasing the ratio of **3a**/**4a** (entry 12). Reaction in the absence of $InCl_3•4H_2O$ returned the unreactive substrate (entry 13).

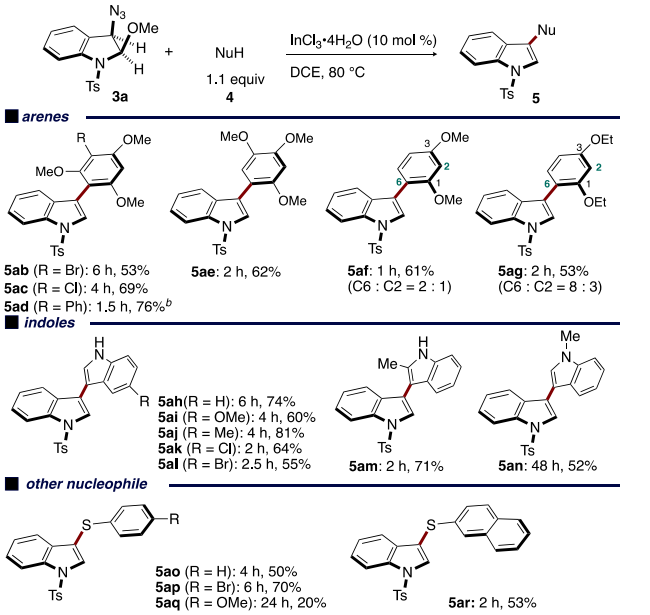


Scheme 4 Substrate scope with respect to AZINs[a,b]: [a] **3** (0.3 mmol), **4a** (0.33 mmol) in DCE (1.5 mL). [b] Isolated yields.

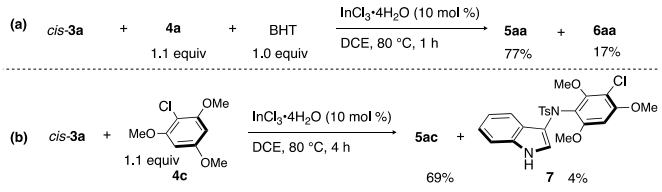
With the optimized reaction conditions in hand, the scope of the *ipso*-substitution was next investigated (Scheme 4). A variety of substituted AZINs proved to be amenable to this transformation. The benzene ring bearing both electron-donating (**5ba**) and -withdrawing (**5ca**–**da**) groups participated to give the desired products. Substituents on the benzene ring at different positions including 4-Cl, 6-Cl and 7-Cl were well tolerated (**5ea**, **5fa**, and **5ga**). The protecting group, such as Bs, Ns, Bz, and Ac performed, and low to good yields were obtained (**5ha**, **5ia**, **5ja** and **5ka**). A series of 2-alkoxy AZINs (**3l**, **3m**, and **3n**) resulted in slow formation of **5aa**.

Subsequently, the scope of nucleophiles was evaluated (Scheme 5). The electron density on arene was demonstrated to have remarkable effect on the reaction efficiency (**5ab**, **5ac**, and **5ad**). 1,3-Alkoxybenzenes also exhibited good reaction efficiency with low regioselectivity (**5af** and **5ag**). Our protocol could also be extended to indoles as a nucleophile without any further modifications (**5ah**–**5an**). Furthermore, thiophenols also exhibited good reaction efficiency with complete regioselectivity (**5ao**–**5ar**). 3-Arylindoles are ubiquitous in pharmaceuticals and natural products and is considered to be a privileged scaffold in medicinal chemistry.[15] However, the synthetic route for 3-arylindoles is limited;[16] our protocol provides a straightforward access to these motifs.

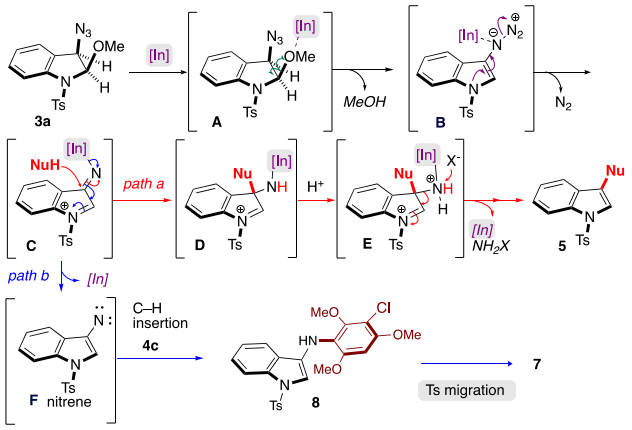
In order to obtain mechanistic insights, control experiments were conducted. When a radical scavenger BHT was added the reaction mixture, the formation of **5aa** was not suppressed (Scheme 6a). These results suggest that radical initiation step may be not involved in the reaction.[17] During the screening of nucleophiles, we encountered 3-aminoindole **7** (Scheme 6b). This result suggests that a nitrene intermediate generate in situ under the reaction conditions.



Scheme 5 Substrate scope with respect to nucleophiles[a-c]: [a] **3a** (1 mmol), **4** (1.1 mmol) in DCE (5 mL). [b] **3a** (0.3 mmol), **4d** (0.33 mmol) in DCE (1.5 mL). [c] Isolated yields.



Scheme 6 Mechanistic studies



Scheme 7 Plausible mechanism

A plausible mechanism was proposed (Scheme 7). Initially, σ-acid activation of the methoxy group as complex **A** is followed by elimination of methoxy group to afford 3-azidoindole **B**.[18]

Then, σ-activation of the azido group is followed by a release of N_2 to afford iminium ion **C**.[15,17] Next, attack of the nucleophile on **C** afford complex **D**. Finally, elimination of indium-NH_2X species from complex **E** furnish 3-substituted indoles **5**. This is the first report that 3-azidoindoles showed untapped reactivities of *ipso*-substitution of the azido group.[3e] The formation of **7** can be explained through side-pathways of intermediate **F** derived from **C** by elimination of indium complexes. The C–H insertion of **4c** with **F** would result in the formation of 3-amino-N-Ts indole **8**, thereby affording NH-indole **7** through tosyl migration from the indole nitrogen to the aniline nitrogen.[19]

In summary, we have developed 3-azido-2-methoxyindolines (AZINs), a user-friendly, bench-stable, thermally stable and reactive 3-azidoindole surrogate, which provided synthetically important 3-arylindoles through *ipso*-substitution of azido moieties in the presence of indium catalyst with a loss of N_3 moiety. This transformation features broad substrate scope, good functional group tolerance, and moderate to high yields. The important merits of AZINs are brought about by the O–Nβ bonding,[14] which was responsible for its thermal stability and generation of reactive 3-azidoindole before thermally decomposition. Of particular note, an azidoindole surrogate was for the first time exploited in organic chemistry except for click chemistry, thus opening an avenue to the development of its potency as versatile synthons for diverse transformations.

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Conflicts of interest

The authors declare no competing interests.

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