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Switchable Synthesis of 3-Aminoindolines and 2'-Aminoarylacetic Acids Using Grignard Reagents and 3-Azido-2-hydroxyindolines †

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The switchable synthesis of 3-aminoindolines and 2'-aminoaryl acetic acids from the same substrates, 3-azido-2-hydroxyindolines, was developed through denitogenative electrophilic amination of Grignard reagents. The key to success is the serendipitous discovery that reaction conditions including solvents and reaction temperature can affect the chemoselectivity. It is noteworthy that isotope-labeling experiments revealed the occurrence of the aziridine intermediate in the production of 2'-aminoaryl acetic acids.

3-Aniline-substituted indoles such as junalimycins A and B, and catellatolactam C represent a unique class of indole alkaloids (Fig.1A).[1,2] Many synthetic strategies have been developed for the synthesis of 3-aniline-substituted indoles.[3] Meanwhile, the 2-aminoaryl acetic acid scaffold is basic structural motif for the nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac having a variety of biological activities including COX-2 inhibitors (Fig. 1B).[4,5] Over the past decades, different cross-coupling reactions enabled the construction of 2-aminoaryl acetic acid scaffolds.[6] However, the controllable and differentiated synthesis of 3-aniline-substituted indoles and 2-aminoaryl acetic acids using the same substrates have not been reported so far.

Selectivity has become the important motivator for the development of protocols for the efficient synthesis of organic molecules.[7] The ability to discriminate among the multi reactive sites is referred to as "chemoselectivity". If the chemoselectivity is achieved by only a control of reaction conditions,[8] it seems very useful for organic chemist due to its time economic properties.[9]

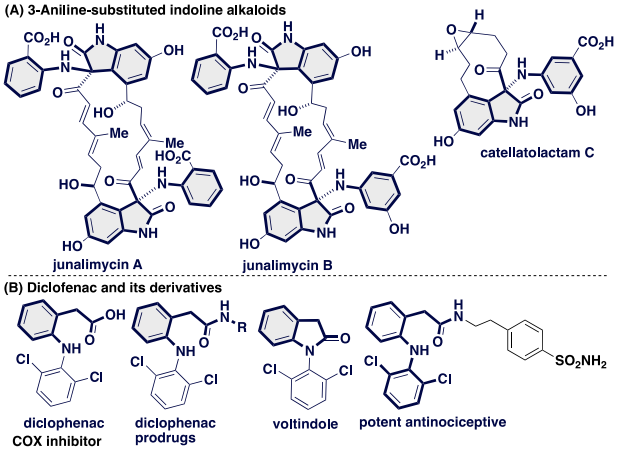

Fig. 1 Natural products and pharmaceuticals bearing aniline moiety: (A) 3-Aniline-substituted indoline alkaloids; (B) Diclofenac and its derivatives.

Azide compounds are versatile intermediates in organic chemistry due to their inherent high reactivity and easy availability.[10] Among the recent methods for forming C–N bonds through a release of N_2 from azide moieties,[11] the use of Grignard reagents is highly attractive due to their diverse reactivities against azide moieties.[12] As shown by Dimroth,[12a] Trost,[12b] and Li,[12c] the azides have been recognized as precursors to triazene-type products on the reaction of azides with Grignard reagents (Scheme 1a). On the other hand, Kumar achieved efficient synthesis of secondary amines from azides and Grignard reagents with a release of N_2 by varying the reaction conditions.[12d] Surprisingly, there is a few precedents of such secondary amine synthesis by electrophilic amination of Grignard reagents using azide compounds. More recently, extensive progress has been made in this field by Knochel and co-workers,[12f] who reported that the azide compounds have been deployed with organozinc reagents at 50 °C in the presence of 50 mol % of $FeCl_3$ to afford a variety of secondary amines. These transformations are interesting alternatives to make secondary amines but still suffer from limited applicability to the switchable synthesis.[13] Thus, more

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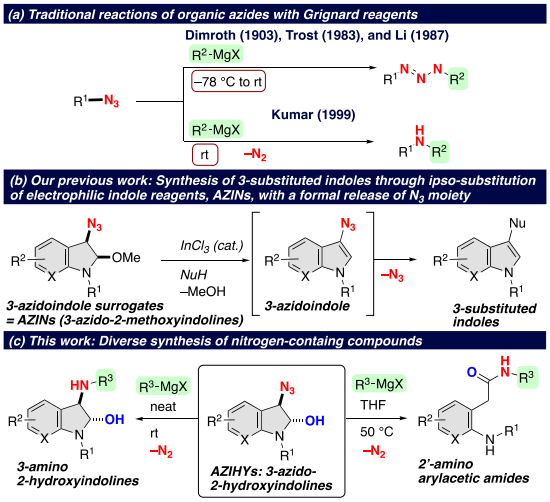
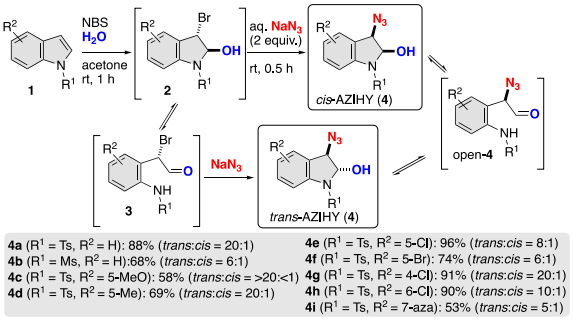
controllable reaction protocol on the reaction with azides and Grignard reagents in the absence of transition-metal catalysts is highly desirable.

In continuation of the research on the synthetic potential of 3-azido-2-methoxyindoline (AZINs, Scheme 1b),[14] we envisioned that a combination of azidoindolines and hemiaminals[15] can be a suitable precursor of a controllable coupling reaction utilizing both chameleonic character of the azido and the open-form of the cyclic hemiaminals. Herein, we present a switchable reactivity of 3-azidoindoline hemiaminals under transient tautomeric control[16] for yielding a variety of 3-aminoindolines and 2'-aminoarylacetic acids (Scheme 1c). The key to success is the serendipitous discovery that reaction conditions including solvents and reaction temperature can affect the chemoselectivity.



Scheme 1 (a) Traditional reactions of organic azides with Grignard reagents; (b) Synthesis of 3-substituted indoles using our developed 3-azidoindole equivalents; (c) This work.

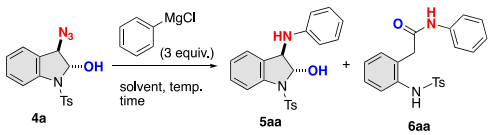


Scheme 2 Preparation of 3-azido-2-hydroxyindolines **4**.

Our newly designed 3-azido-2-hydroxyindolines (AZIHY, **4**) were prepared from N-protected indoles **1** via a two-step sequence involving bromohydroxylation of **1**/nucleophilic substitution of **2** by NaN_3 (Scheme 2). AZIHYs **4** predominantly existed in their *trans*-form, which can readily tautomerize into open-**4** and closed form (*trans*-**4** and *cis*-**4**).

Our investigation began when a AZIHY **4a** was treated with PhMgCl (2M solution in THF, 3 equiv.) at room temperature (entry 1, Table 1). After 6 h, the desired 3-anilinoindole **5aa** in 65% yield along with unexpected ring-opening amide **6aa** in 12% yield. We found that solvent-free conditions play a crucial role to operate a formation of **5aa** (entries 2–3). When the reaction conducted in THF at increasing reaction temperature, the yield of **6aa** were increased (entries 4–5). After polar solvent screening, THF afforded the best result in the formation of **6aa** (entries 6–9). Nonpolar solvent could not improve the isolated yield due to the poor solubility of the reaction components (entries 10–11). The best result was obtained, when 3 equivalents of PhMgCl was used (entries 1 vs 11—13).

Table 1 Optimization of reaction conditions.[a]

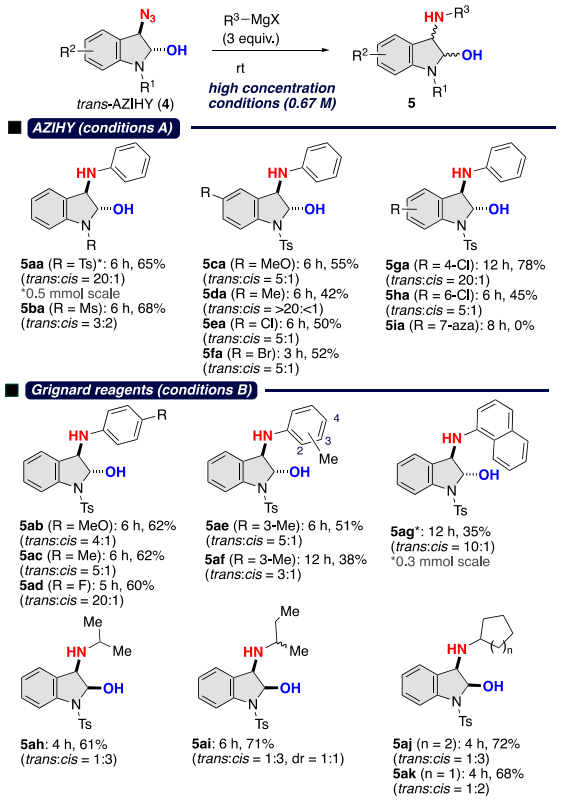


Entry	solvent	Temp. (°C)	Time (h)	Yield (%)[b] **5a**	Yield (%)[b] **6a**
1	**---**	**rt**	**6**	**65**	**12**
2	---	50	6	trace	35
3	THF	rt	6	30	18
4	**THF**	**50**	**6**	**trace**	**66**
5	THF	reflux	6	trace	65
6	1,4-dioxane	50	8	trace	37
7	iPr_2O	50	24	trace	8
8	Ph_2O	50	8	trace	48
9	2-MeTHF	50	6	trace	53
10	benzene	50	8	trace	45
11	toluene	50	8	trace	33
12[c]	---	rt	24	44	19
13[d]	---	rt	24	31	20
14[e]	---	rt	24	17	10

[a] **4a** (0.5 mmol), PhMgCl (1.5 mmol, 3 equiv.) in solvent (5 mL) under argon atmosphere. [b] Isolated yields. [c] Using PhMgCl (1.25 mmol, 2.5 equiv.). [d] Using PhMgCl (1.0 mmol, 2.0 equiv.). [e] Using PhMgCl (0.5 mmol, 1.0 equiv.).

After identifying the optimal reaction conditions (Table 1, entry 1), we next aimed to explore the substrate scope under reaction conditions A (Scheme 3). The mesyl substitution on the nitrogen atom gave 3-anilinoindolines **5ba** in 68% yield albeit with lower diastereoselectivity (*trans*:*cis* = 3:2). A series of AZIHYs containing methoxy, methyl, and halogen groups at the C5-position of the indolines gave the corresponding 3-aminoindolines **5ca–5fa** in 42–55% yields, respectively. The halogen atom at the C4- and C6-positions the indolines could also be participated in our transformation to afford **5ga** and **5ha** in 78% and 45% yields, respectively. The desired reaction did not proceed in the case of 7-aza-AZIHY (**5ia**: 0%). Next, efforts were steered to investigate the Grignard reagents under the reaction conditions B. Diverse aryl Grignard reagents bearing phenyl group with substituents at the para, metha, and ortho positions proceeded to afford 3-anilinoindolines **5ab–5ag** in 38–62% yields, respectively. The reactions are also successful with alkyl Grignard reagents including cycloalkanes afforded 3-

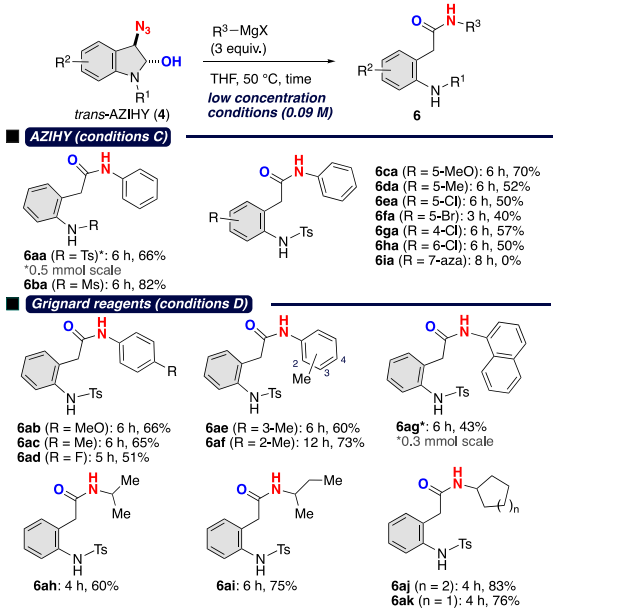
alkylaminoindolines **5ah–5ak** albeit with intrinsic *cis*-selectivities due to their neighboring-group participation of alkyl amine moieties through an intramolecular hydrogen bonding in a hemiaminal tautomerism.



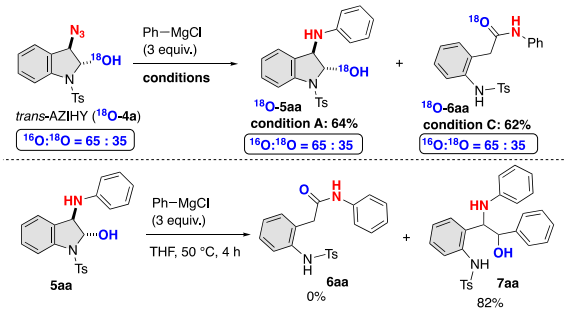
Scheme 3 Reaction of **4** with Grignard reagents (0.67 M): Reaction conditions A: **4** (0.3 mmol), PhMgCl (0.9 mmol) at rt under argon atmosphere; Reaction conditions B: **4a** (0.5 mmol), RMgBr (1.5 mmol) at rt under argon atmosphere.

Having explored the scope of the 3-aminoindolines synthesis, we turned our attention to the synthesis of 2'-aminoarylacetic amides under the optimum reaction conditions (Scheme 4). AZIHYs bearing substituents, such as N-Ms (**4b**), 5-MeO (**4c**), 5-Me (**4d**), 5-Cl (**4e**), 5-Br (**4f**), 4-Cl (**4g**), and 6-Cl (**4h**), reacted smoothly and afforded the 2'-aminoarylacetic amides **6aa–6ha** in 40–82% yields, respectively. However, when 7-aza-AZIHY was used, the reaction failed to obtain the desired product **6ia**. Various Grignard reagents including aryl, acyclic, and cyclic alkyl substituents were also suitable nucleophiles for our transformation, with the corresponding products **6ab–6ak** in 43–83% yields.

To gain additional insights into the reaction mechanism, we performed an isotope-labeling experiment (Scheme 5). ^{18}O-Labeled AZIHY **4a** (^{16}O : ^{18}O = 65:35) reacted with Grignard reagent under the reaction conditions A or B to afford the products **5aa** and **6aa** with a keeping ^{18}O-ratio (^{16}O : ^{18}O = 65:35). It is noteworthy that the hydroxy group of indoline hemiaminal was found to be the distinct source of the carbonyl oxygen atom in this transformation. Next, we investigate that aniline **5aa** can be the intermediate for the formation of **6aa**. When the reaction of **5aa** under low concentration conditions (50 °C, THF), the expected **6aa** was not produced. Instead of **6aa**, the diphenylated product **7aa** was obtained in 82% yield.

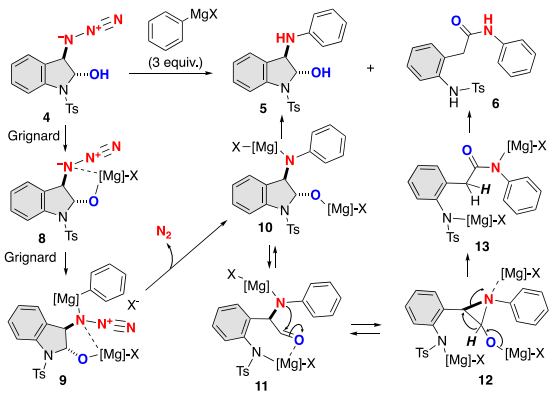


Scheme 4 Reaction of **4** with Grignard reagents in THF (0.09 M): Reaction conditions C: **4** (0.3 mmol), PhMgCl (0.9 mmol) in THF (3 mL) at 50 °C under argon atmosphere; Reaction conditions D: **4** (0.5 mmol), PhMgCl (1.5 mmol) in THF (5 mL) at 50 °C under argon atmosphere.



Scheme 5 Control experiments.

Based on the precedent[12,13,14,16] and our observations, a plausible mechanism has been proposed (Scheme 6). First, deprotonation of **4** by a Grignard reagent results in the formation of intermediate **8**, in which Mg-center could activate an electrophilicity of the azide nitrogen atom by chelating to the nitrogen atom of the azide group.[17] Then intermediate **8** undergoes addition of the Grignard reagent to produce magnesium species **9**. The magnesium species **9** is subsequently converted into intermediate **10** with a release of N_2, which is hydrolyzed to produce 3-anilinoindoline **5**. On the other hands, the tautomerism exists between the intermediate **9** and α-aminoaldehyde **11**.[16] Aziridination of **11** may be promoted by magnesium species to afford α-oxygenated aziridine **12** for which currently there is no direct structural evidence for the occurrence of α-hydroxyaziridine.[18] Finally, a ring-opening of the aziridine triggered by Heyns-type 1,2-hydride shift give the final product **6**.[19] Increasement of the isolated yield of **6aa** in the reaction with polar solvent suggests that an ionic intermediate such as **12** might be present, which would allow for the conversion of **10** into **6**.



Scheme 6 Plausible mechanism.

In conclusion, we have developed a switchable transformation of 3-aminoindolines and 2'-aminoaryl acetic acids from 3-azido-2-hydroxyindolines through denitogenative electrophilic amination of Grignard reagents. The reactions proceed smoothly to afford a series of 3-aminoindolines and 2'-aminoaryl acetic acids in good yields. The distinctive reaction condition controls the hemiaminal tautomerism to achieve high chemoselectivity.

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Conflicts of interest

The author declares no competing interests.

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