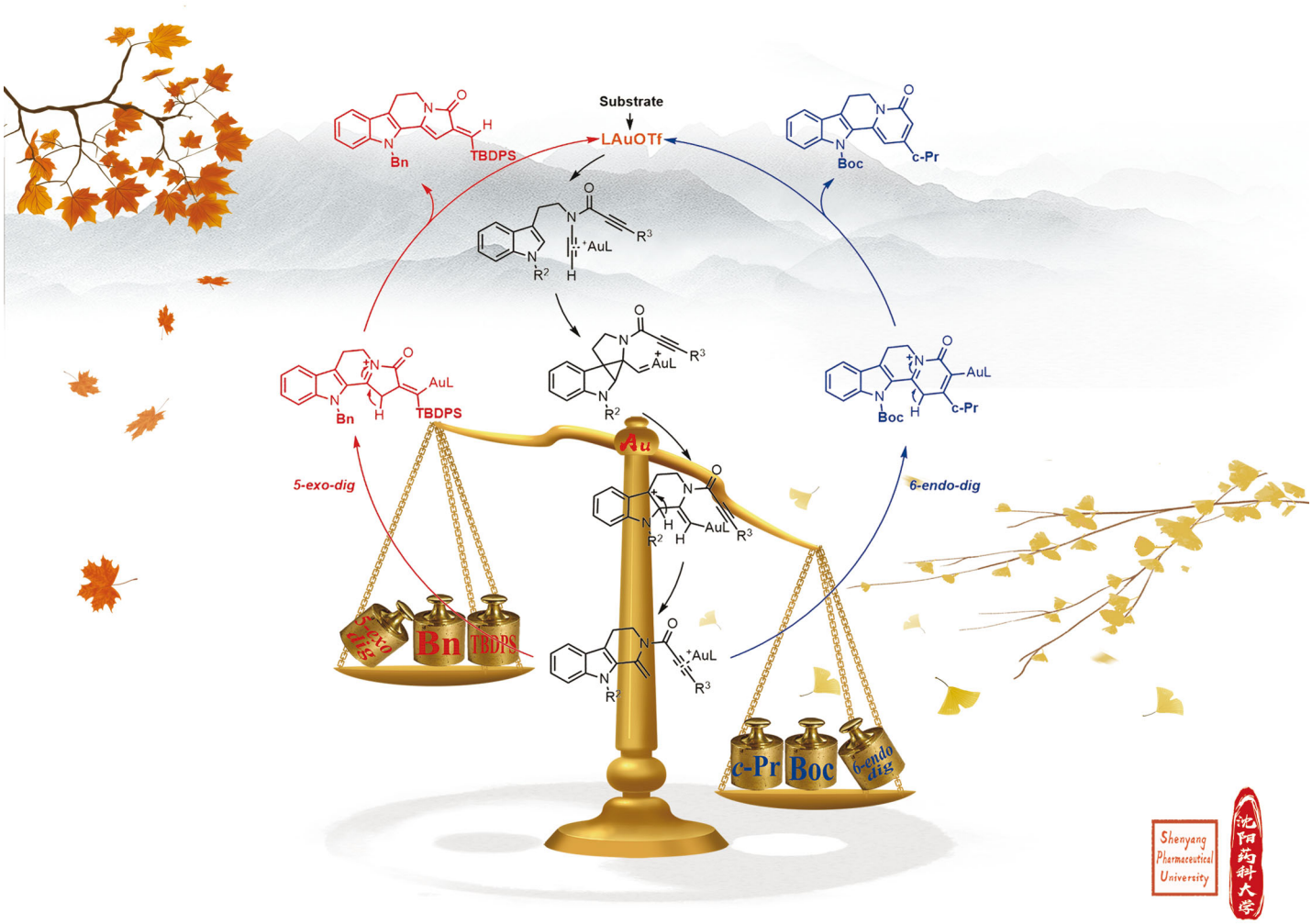

Showcasing research from the laboratory of Professor Bin Lin and Professor Yongxiang Liu, Key Laboratory of Structure-Based Drug Design and Discovery, Shenyang Pharmaceutical University, Ministry of Education, Shenyang, China. Image designed by Professor Yongxiang Liu and illustrated by Kaitong Zhuang.

Gold(I)-catalyzed pathway-switchable tandem cycloisomerizations to indolizino[8,7-*b*]indole and indolo[2,3-*a*]quinolizine derivatives

A novel synthetic method was developed to provide a common strategy to access either indolizino[8,7-*b*]indoles or indolo[2,3-*a*]-quinolizines in a switchable fashion *via* cascade cycloisomerizations of tryptamine-*N*-ethynylpropiolamide substrates. DFT calculations were performed to offer theoretical insights into the experimental observations.

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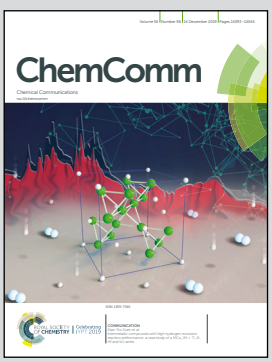

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Gold(I)-catalyzed pathway-switchable tandem cycloisomerizations to indolizino[8,7-*b*]indole and indolo[2,3-*a*]quinolizine derivatives†

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Experimental and theoretical explorations were performed on the pathways of the cascade cycloisomerizations of tryptamine-*N*-ethynylpropiolamide substrates. The methodology provided a common strategy to access either indolizino[8,7-*b*]indoles or indolo[2,3-*a*]-quinolizines in a switchable fashion.

Tetrahydro-β-carboline exists as a core skeleton in a variety of natural indole alkaloids. Among them, indolizino[8,7-*b*]indole and indolo[2,3-*a*]quinolizine are two of the representative structures (Fig. 1). Due to their diverse biological activities,[1] indole alkaloids containing these two scaffolds have drawn much attention from both academia and industry.[2] Target-oriented syntheses of these natural products have been carried out and synthetic methodologies for these two scaffolds have been developed in the few past decades.[3] So far, *N*-acyl-iminium ion or iminium ion cyclizations are the most popular strategies in constructing these two scaffolds.[3c,g,h] These strategies are primarily aimed at synthesizing the scaffold of either indolizino-[8,7-*b*]indole or indolo[2,3-*a*]quinolizine. Only a few precedents on the development of a common strategy are applicable for both of these two scaffolds.[4] Therefore, developing a method to synthesize both scaffolds in a pathway-switchable fashion is highly desired.

Recently, ynamides as versatile building blocks have shown extraordinary potential in constructing complex structures due to their predictable regioselectivity, high reactivity and relative stability.[5] In particular, tryptamine-derived ynamide represents a unique building block to prepare indoline scaffolds in the syntheses of polycyclic indole alkaloids and derivatives.[6] Previously, two tandem cyclizations based on the same type of tryptamine-derived ynamide substrates were developed in our laboratory to synthesize 1*H*-pyrrolo[2,3-*d*]carbazole and spiro[indoline-3,3′-pyrrolidin]-2-one skeletons in a pathway-switchable fashion.[6d,e] In this study, we further applied the strategy to synthesize indolizino[8,7-*b*]indole and indolo[2,3-*a*]quinolizine scaffolds from a common tryptamine-*N*-ethenylpropiolamide intermediate *via* gold-catalyzed respective 6-*endo-dig* and 5-*exo-dig* cycloisomerizations.

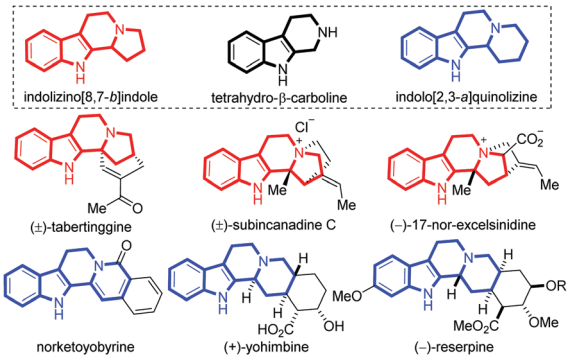

Fig. 1 Natural products containing indolizino[8,7-*b*]indole and indolo[2,3-*a*]-quinolizine scaffolds.

A number of precedent studies on the cyclization of *N*-alkenyl (aryl) alkynylamides in different manners have been reported as demonstrated in Scheme 1.[7] For example, Tanaka and coworkers developed an *in situ* formation of *N*-alkenyl alkynylamides/gold-catalyzed 5-*exo-dig* cycloisomerization/cyclopropyl gold carbene formation and rearrangement strategy to generate pyridinones.[7b] Vadola and coworkers reported a gold(I)-catalyzed 6-*endo-dig* annulation of *N*-aryl alkynamides to yield 2-quinolinones.[7g] Different from these two studies, van der Eycken and coworkers described a silver-nanoparticle-catalyzed 5-*exo-dig* cyclization of the substrates with terminal alkyne to give 3-spiroindolenines.

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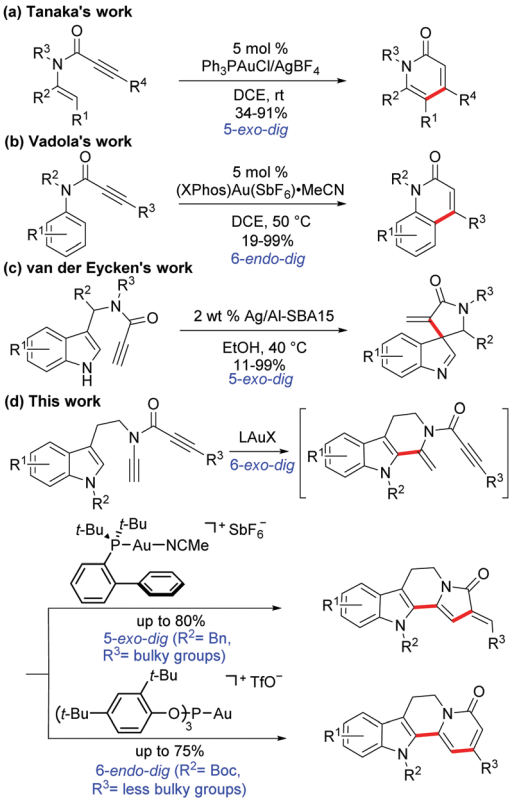
† Electronic supplementary information (ESI) available: Experimental procedures, condition screening, compound characterization data, NMR spectra and computational details. X-ray single crystal diffraction data of **2k** and **3t**. CCDC 1880231 and 1880232. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc05667j

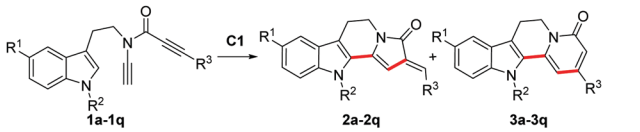


Scheme 1 Cyclization of *N*-alkenyl alkynylamides.

However, the substrates with alkyl substituted alkyne afforded a mixture of 5-*exo-dig* and 6-*endo-dig* cyclization products.[7f] These examples demonstrated that the selectivity of these ring-closing reactions was governed by several factors such as the types of substrates and the substitutions of alkyne. In this study, we showed that steric effects and electronic effects can be fine-tuned in the cycloisomerization of tryptamine-based *N*-alkenyl alkynylamide. Thus a common pathway-switchable strategy for the syntheses of both indolizino[8,7-*b*]indole and indolo[2,3-*a*]quinolizine scaffolds was developed based on a gold(I)-catalyzed cascade cyclization.

Our initial research commenced with the preparation of a model substrate followed by condition optimizations (see the ESI†). A thorough screening of catalysts, additives, solvents and catalyst loadings led to the determination of the optimal conditions as to perform the reaction in THF with the catalysis of 8 mol% JohnPhosAu(MeCN)SbF_6[8] at room temperature for 15 min (**C1**, see the ESI†). With the optimal conditions in hand, the regioselectivity of the second cyclization was first investigated by changing the substitutions on the propiolamide moieties. It was observed that the substrates with the least bulky functional groups such as methyl (Me) and cyclopropyl (c-Pr) substitutions on the alkynes of propiolamide afforded the 5-*exo-dig* and 6-*endo-dig* cyclization products with a ratio of up to 1.4 : 1 (Table 1, entries 1–3). For the substrate with more bulky *n*-propyl (*n*-Pr) substituted alkyne, the ratio of the two isomers reached up to 5.6 : 1 (Table 1, entry 4). The substrate with very bulky *t*-butyl (*t*-Bu) substitution provided the products **2e** and **3e** with a ratio of 8.2 : 1 (Table 1, entry 5). The substrates with phenyl (Ph)

Table 1 Scope of cyclization of **1a–1q** on condition 1 (**C1**)[a]



Entry	Substrate	R^1	R^2	R^3	Yield [2 + 3] (%)	Ratio [2 : 3]
1	**1a**	Cl	Bn	Me	87	1.1 : 1
2	**1b**	H	Bn	c-Pr	93	1.1 : 1
3	**1c**	H	PMB	c-Pr	76	1.4 : 1
4	**1d**	H	Bn	*n*-Pr	73	5.6 : 1
5	**1e**	H	Bn	*t*-Bu	83	8.2 : 1
6	**1f**	H	Bn	Ph	74	6.4 : 1
7	**1g**	H	Bn	*p*-FC_6H_4	86	5.1 : 1
8	**1h**	H	Bn	*p*-ClC_6H_4	90	6.5 : 1
9	**1i**	H	Bn	*p*-BrC_6H_4	84	8.9 : 1
10	**1j**	H	Bn	*p*-$CH_3C_6H_4$	78	5.5 : 1
11	**1k**	H	Bn	TBDPS	63	100 : 0
12	**1l**	F	Bn	TBDPS	72	100 : 0
13	**1m**	Cl	Bn	TBDPS	68	100 : 0
14	**1n**	OMe	Bn	TBDPS	59	100 : 0
15	**1o**	F	Bn	TIPS	78	100 : 0
16	**1p**	H	Bn	TIPS	75	100 : 0
17	**1q**	H	Boc	c-Pr	15	0 : 100

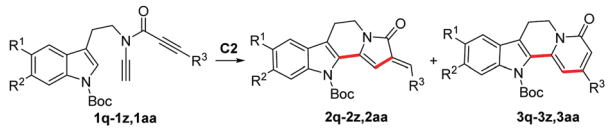
[a] The reaction was performed in THF at the catalysis of 8 mol% JohnPhosAu(MeCN)SbF_6 at room temperature for 15 min.

substitutions on the alkyne of propiolamide favored the products **2f–2j** *via* the 5-*exo-dig* process regardless of electron-rich or deficient groups on the benzene rings (Table 1, entries 7–10). To our delight, the substrates with extremely bulky *t*-butyldiphenylsilyl (TBDPS) or triisopropylsilyl (TIPS) substituted alkynes of propiolamide gave 5-*exo-dig* cyclization products **2k–2p** exclusively (Table 1, entries 11–16).

Next, the protective groups on the indole nitrogen were investigated. It was observed that when the electron-donating functional groups (Bn and PMB) were switched to the electron-withdrawing group *t*-butyloxycarbonyl (Boc), the 6-*endo-dig* cyclization product **2l** was obtained exclusively, although in a relatively low yield (Table 1, entry 17). The result indicated that the electron density on the indole nitrogen could determine the pathway of the second cyclization. Efforts were therefore made to improve the yields of the 6-*endo-dig* cyclization products. In the end, the optimal conditions were obtained as to perform the reaction under the catalysis of [tris(2,4-di-*tert*-butylphenyl) phosphite]gold chloride[9] and AgOTf in THF at room temperature for 1.5 h (**C2**, see the ESI†).

We further examined the influence of the substitutions of alkyne of propiolamide moieties on the regioselectivity by utilizing *N*-Boc substituted substrates under the optimized reaction conditions (**C2**). It was found that when the substrates had c-Pr and Me substitution, 6-*endo-dig* cyclization products were obtained exclusively (Table 2, entries 1–7). When *n*-Pr was used, the 6-*endo-dig* cyclization products were also the major products (Table 2, entries 8 and 9). For the substrate with more bulky phenyl substitution, the ratio of 5-*exo-dig* cyclization increased dramatically (Table 2, entry 10). Moreover, when the very bulky *t*-Bu group was introduced to the alkyne of propiolamide, the regioselectivity was reversed leading to a 4.3 : 1 ratio of 5-*exo-dig*

Table 2 Scope of cyclization of **1q–1z**, and **1aa** on condition 2 (**C2**)[a]



Entry	Substrate	R^1	R^2	R^3	Yield [2 + 3] (%)	Ratio [2 : 3]
1	**1q**	H	H	c-Pr	70	0 : 100
2	**1r**	H	Me	c-Pr	68	0 : 100
3	**1s**	H	Me	Me	66	0 : 100
4	**1t**	H	H	Me	72	0 : 100
5	**1u**	Me	H	Me	63	0 : 100
6	**1v**	F	H	Me	60	0 : 100
7	**1w**	Cl	H	Me	71	0 : 100
8	**1x**	H	H	*n*-Pr	87	1 : 6.3
9	**1y**	H	Me	*n*-Pr	80	1 : 5.7
10	**1z**	H	H	Ph	91	1 : 1.8
11	**1aa**	H	H	*t*-Bu	74	4.3 : 1

[a] The reaction was performed under the catalysis of [tris(2,4-di-*tert*-butylphenyl)phosphite]gold chloride and AgOTf in THF at room temperature for 1.5 h.

and 6-*endo-dig* cyclization (Table 2, entry 11). Finally, both structures of the 5-*exo-dig* cyclization product **2k** and 6-*endo-dig* cyclization product **3t** were confirmed by X-ray crystallographic analysis (Fig. 2).

Based on precedent studies[5,6] and control experimental results (see the ESI†), a plausible mechanism was proposed for the gold(I)-catalyzed ynamide-based pathway-switchable tandem cyclizations to the syntheses of indolizino[8,7-*b*]indole and indolo[2,3-*a*]quinolizine derivatives as depicted in Scheme 2. A selective activation of alkyne in ynamide **1k** (**1q**) promoted the formation of a gold(I)–ynamide complex **1k-1** (**1q-1**), which underwent the first cyclization to furnish a cyclopropyl gold carbene intermediate **1k-2** (**1q-2**). An instantaneous rearrangement occurred to give intermediate **1k-3** (**1q-3**), followed by an aromatization and protodeauration to form the intermediate **1k-4** (**1q-4**). The substrates with *N*-Bn substituted indole and bulky substitutions on the alkyne of propiolamide preferred a 5-*exo-dig* pathway leading to the formation of indolizino[8,7-*b*]indole derivatives (pathway a). The substrates with *N*-Boc substituted indole and less bulky substitutions on the alkyne of propiolamide favored 6-*endo-dig* cyclization yielding indolo[2,3-*a*]quinolizine derivatives (pathway b).

In order to gain insight into the regioselectivity of the cyclizations, density functional theory (DFT) calculations were performed by employing the M11-L method[10] to calculate the energy profiles for the competing pathways. The results are shown in Fig. 3. Bn and Boc functional groups on the nitrogen of indole were considered for the electronic effects when the

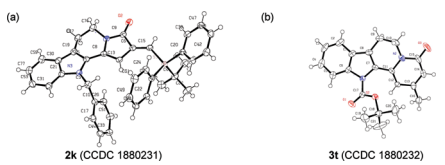
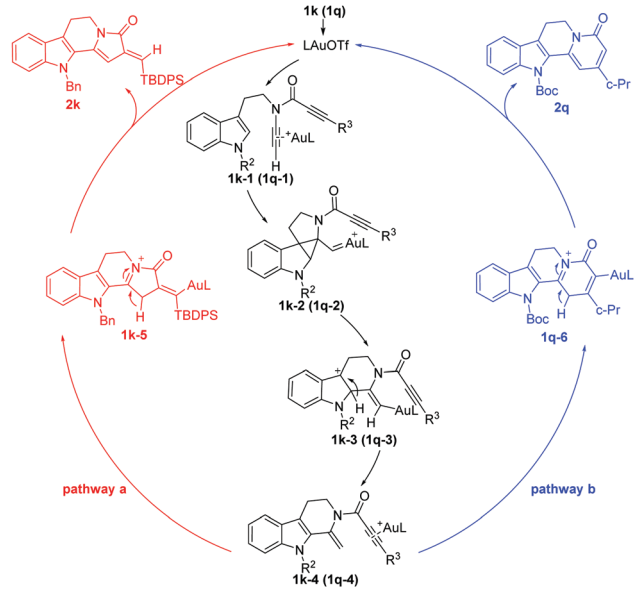


Fig. 2 ORTEP diagrams of **2k** (a) and **3t** (b). The ellipsoid probability is 50%.



Scheme 2 The proposed mechanism.

functional group on the propiolamide was fixed as c-Pr. The less bulky c-Pr and the more bulky TBDPS functional groups on the propiolamide moieties were considered for the steric effects for the *N*-Bn substrates. The energy barrier was 4.6 kcal mol^{-1} for the transition state of the *N*-Boc substrate (**1q-6-ts**) compared to 6.8 kcal mol^{-1} for the transition state of the *N*-Bn substrate (**1q-5-ts**). The energy barrier for the 6-*endo-dig* pathway was 2.2 kcal mol^{-1} lower than that of the 5-*exo-dig* pathway and the reaction proceeded by following the latter to yield indolo[2,3-*a*]quinolizine products. This was consistent with the experimental observations, explaining the electronic effects. As for the steric effects, it was found that the transition state energy barrier was 9.0 kcal mol^{-1} lower for the 5-*exo-dig* pathway (**1k-5-ts**) than the 6-*endo-dig* pathway (**1k-6-ts**) for the TBDPS substrate, explaining why the 6-*endo-dig* product was favored. Such a significantly large energy barrier difference was

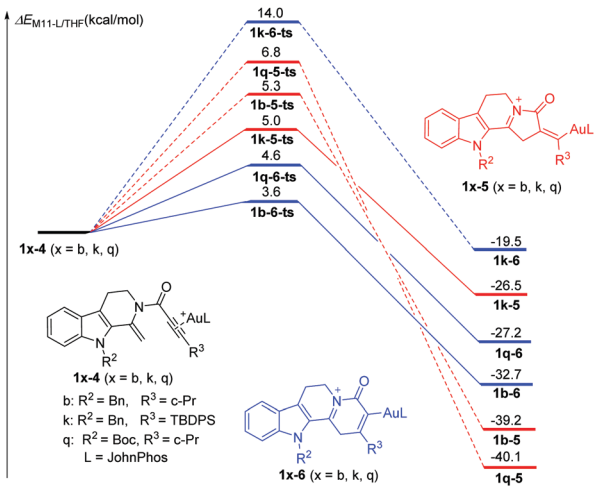


Fig. 3 The energy profiles of the proposed mechanism.

due to the enormous steric hindrance between the extremely bulky TBDPS group and the neighboring ring for the 6-*endo-dig* pathway. It came as no surprise that the 5-*exo-dig* product was obtained exclusively because of its significantly lower energy barrier. When a Bn functional group was on the nitrogen of indole and a c-Pr functional group was on the propiolamide moiety, neither the electronic effect nor the steric effect played a dominant role. The transition state energy barrier (**1b-5-ts** *vs.* **1b-6-ts**) came in between 1.7 kcal mol^{-1} and a mixture of 5-*exo-dig* cyclization product and *6-endo-dig* cyclization product was obtained.

In conclusion, a common strategy for the pathway-switchable syntheses of both indolizino[8,7-*b*]indole and indolo[2,3-*a*]-quinolizine scaffolds has been developed based on the cascade 6-*exo-dig*/5-*exo-dig* and 6-*exo-dig*/6-*endo-dig* cyclosiomerization of tryptamine *N*-ethynylpropiolamide substrates. The substitutions on the nitrogen of indole and the alkyne of propiolamide have a great influence on the selectivity of the products. A DFT calculation provided a theoretical insight into the regioselectivity in the formation of these two scaffolds. This study offered a reliable and predictable method to access both indolizino[8,7-*b*]indole and indolo[2,3-*a*]quinolizine derivatives in a switchable fashion.

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Conflicts of interest

There are no conflicts to declare.

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